Spatiotemporal Organization of the Left Atrial Substrate After Circumferential Pulmonary Vein Isolation of Atrial Fibrillation

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Background—There is a paucity of data regarding the mechanism of maintaining atrial fibrillation (AF) after pulmonary vein isolation (PVI) in patients with AF. The aim of this study was to examine the impact of circumferential PVI on the left atrial (LA) substrate characteristics.

Methods and Results—Seventy-two AF patients (age, 53±11 years) underwent mapping and catheter ablation using an NavX system. The biatrial characteristics such as the complex fractionated atrial electrograms (CFEs; based on fractionated intervals) and frequency analysis (based on dominant frequencies) were mapped before and after PVI. PVI with electric isolation was performed in all patients. In the 45 patients who did not respond to PVI, the continuous CFEs (>8 seconds, 18±18% and 12±17% of the LA sites, before and after PVI, respectively, P=0.02), degree of LA fractionation (mean fractionated interval: 75.6±14.3 msec versus 87.3±16.7 msec, P=0.001), and mean LA dominant frequencies (6.92±0.88 Hz versus 6.58±0.91 Hz, P=0.001) decreased after PVI. Complete PVI altered the distribution of the CFEs toward the LA anteroseptum, mitral annulus, and LA appendage regions. A persistent presence of continuous CFEs in the vicinity of the dominant frequencies sites (observed in 53% patients) correlated with a higher procedural AF termination rate for the CFE ablation (63% versus 23%, P<0.05).

Conclusions—Complete PVI eliminated some CFEs in the LA and altered the distribution of the CFEs. The persistent presence of CFEs before and after PVI in the vicinity of the high frequency sites is important for AF maintenance after PVI. (Circ Arrhythmia Electrophysiol. 2009;2:233-241.)

Key Words: atrial fibrillation ■ electrogram frequency analysis ■ left atrium

Atrial fibrillation (AF) is the most common type of tachyarrhythmia encountered in clinical practice.1 Pulmonary vein isolation (PVI) has become the mainstream catheter ablation technique for AF.2,3 In the consensus of the catheter ablation therapy for AF, substrate modification is considered to be necessary in patients with nonparoxysmal AF.4 A previous study showed that substrate modification with left atrial (LA) linear ablation or complex fractionated electrogram (CFE) ablation in patients with nonparoxysmal AF improved the clinical outcome.5-7,8 However, there is a paucity of data regarding the mechanism of AF maintenance in patients who did not respond to PVI. The atrial substrate characteristics before and after PVI may provide important information for these patients. The purposes of this study were (1) to investigate the impact of circumferential PVI with electric isolation on the LA substrate characteristics, and (2) to understand the spatiotemporal organization of the LA substrate after PVI.

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Methods

Patient Characteristics
This study enrolled 72 patients with symptomatic, drug-refractory AF who received radiofrequency ablation guided by an NavX system (NavX, with CFE software, St. Jude Medical Inc., St. Paul, Minn). These patients manifested incessant AF at the onset of the procedure (not pacing or isoproterenol induced AF) and included 33 patients (46%) with paroxysmal AF, 9 (13%) with persistent AF (duration of patient characteristics).

Received August 4, 2008; accepted February 20, 2009.

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Circ Arrhythmia Electrophysiol is available at http://circep.ahajournals.org DOI: 10.1161/CIRCEP.108.812024

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Electrophysiological Study
Each patient underwent an electrophysiological study and catheter ablation in the fasting state, after informed consent was obtained. All antiarrhythmic drugs except for amiodarone were discontinued for at least 5 half-lives before the procedure. Overall, 31% of the patients received amiodarone before the procedure. No patient received amiodarone therapy during electrophysiological procedure to terminate AF. The method of 3D electroanatomic mapping has been described previously.9,10 Mapping was performed with an irrigated 4-mm-tip deflectable catheter (EPT, Boston Scientific Corporation, Natick, Mass) inserted into the LA alongside the transseptal sheath without the need for an additional puncture site. A 3D geometry of the LA was then created using the NavX system.

We attempted to find the spontaneous onset of atrial ectopic beats or repetitive episodes of short runs or sustained AF and predict the location of the initiating foci at the baseline, after restoration of SR after the procedure, or after an algorithm designed for facilitating the initiation of AF.2,11 The methods used to provoke spontaneous AF were attempted at least twice to ensure reproducibility.2,11

Signal Recording
After acquiring the LA geometry, a 4-mm-tip catheter was selected as the “roving” catheter for sequential contact mapping. Regarding the protocol for sampling in the right atrium (RA) and LA, first, we divided the LA into 7 parts and RA into 7 parts according to previous study.12 In each region, at least 10 points were determined. The points in each region were similar in number and were nearly equally distributed. The points designated at the PVs were obtained from the PV ostium and antrum regions outside the PV lines. The points within the veins were excluded for comparison of the organization of the fibrillation waves before and after PVI to investigate the change in the substrate property rather than the local effect of radiofrequency application. Second, to avoid a too-high density in some regions, any mapping site with a distance of <0.5 mm to any of the other nearest sites was deleted by off-line software. The averaged mean distance between any 2 mapping sites in the LA and RA was 5.4±0.9 and 6.2±0.9 mm, respectively. A previous study showed that the microreentrant circuits of the high frequency AF drivers were approximately 10 mm in diameter.13 The density of the mapping points in this study may provide sufficient spatial resolution for detecting the dominant frequency (DF) sites.

Signal Analysis
The NavX mapping parameters were set to “CFE-mean,” which was an interval-analysis algorithm that measures the average index of the fractionation at each site and produces a color map representative of the CFE distribution. Previously, we demonstrated that the continuous CFEs (>8 seconds) were defined by an averaged fractionated interval (FI) of ≤50 ms over 5 seconds. The continuous CFEs represent the continuous fractionated activity of over 1 minute.14 The parameters of the automatic algorithm for CFEs have been described previously.14 Variable CFEs were defined as having a mean FI between 50 and 120 ms. The non-CFEs were defined as having an FI of >120 ms. We performed CFE mapping both before and after PVI. The method of the fast Fourier transform (FFT) has been described previously.15 A 6.82-second segment of data was exported to an external computer program. The FFT analysis (sampling rate, 1200 Hz; resolution, 0.14 Hz, with a Hanning window function) was performed from all recording sites. The largest peak frequency of the resulting spectrum was identified as the DF. The RA and LA substrate characteristics were compared quantitatively and qualitatively to investigate the difference in the atrial substrate before and after PVI.

Catheter Ablation
The stepwise procedure of the catheter ablation of AF involved the following steps:

- **Step 1 (isolation of the PVs):** After a successful transseptal procedure, continuous circumferential lesions were created encircling the right and left PV ostia guided by the NavX system using an irrigated-tip 4-mm ablation catheter. Radiofrequency energy was applied continuously while repositioning the catheter tip every 40 seconds with a target temperature of 35° to 40°C and maximum power of 25 to 30 W in the power control mode. When the ablation line was near the posterior LA near the esophagus, a 4-mm-tip catheter was applied with a target temperature of 45° to 50°C and maximum power of 45 to 50 W in the temperature control mode. The intention was to place the radiofrequency (RF) lesions at least 1 to 2 cm away from the angiographically defined ostia. After completion of the circumferential lesion set, the ipsilateral superior and inferior PVs were mapped carefully by a circular catheter recording. Successful circumferential PVI was demonstrated by the absence of any PV activity or dissociated PV activity during AF. After restoration to SR by procedural AF termination or electric cardioversion, PV-LA conduction block was confirmed once again. Additional ablation at the sites of the residual PV potentials was applied from the atrial side of the PV antrum using the electrogram-guided approach to obtain entrance block.

- **Step 2 (linear ablation by the anatomic approach):** After successful isolation of all 4 PVs, additional linear ablation was performed at both the anterior roof and lateral mitral isthmus. Linear ablation was guided by the NavX system with the creation of split potentials or an electrogram voltage reduction of >50% after each application of radiofrequency energy. The RA, cavo-tricuspid isthmus (CTI) ablation was performed with an 8-mm-tip ablation catheter with a maximum power of 70 W, temperature of 70°C, and duration of 120 seconds. Bidirectional conduction block of the CTI was confirmed after restoration to SR.

- **Step 3 (continuous CFE site ablation):** If AF did not stop after steps 1 to 2 of the ablation procedure, an additional CFE-guided substrate ablation was performed sequentially, based on the post-PVI CFE maps. The CFE ablation was confined to the continuous CFEs in the LA and CS.16,17 Considering the possible complications caused by the long procedure time and efficacy of the RA substrate modification,18 we did not routinely ablate the CFEs in the RA. The end point of the CFE site ablation was to obtain a prolongation of the cycle length, eliminate the CFEs (thus, FI >120 ms), or abolish the local fractionated potentials (bipolar voltage <0.05 mV). The end point of the step 3 procedure was elimination of all continuous CFEs in the LA and CS. If AF terminated during the linear ablation through the CFE sites, complete linear ablation to an anatomic obstacle or nearest ablation line was performed to prevent proarrhythmias.

- **Step 4 (non-PV ectopies):** After SR was restored from AF either by procedural AF termination or electric cardioversion, the mapping and ablation was only applied to spontaneously initiating focal atrial tachycardias and non-PV ectopies that initiated AF.11 If any non-PV ectopies initiating AF from superior vena cava (SVC) were identified, isolation of the SVC was guided by the circular catheter recordings from the SVC-atrial junction. An AF inducibility test was not performed in the patients with persistent AF or long-lasting persistent AF.

In this study, if AF became organized during the step 1 to 3 procedures, electroanatomic mapping and ablation were performed to terminate the organized tachycardia. The procedural AF termination was defined as AF restored to SR during the ablation in steps 1 to 3. AF induction was not performed in any patients with persistent AF or long-lasting persistent AF.
Follow-Up of AF Recurrence

After discharge, the patients underwent follow-up (2 weeks after the catheter ablation, then every 1 to 3 months thereafter) at our cardiology clinic or with the referring physicians where routine ECGs were obtained during each follow-up, and antiarrhythmic drugs were prescribed for 8 weeks to prevent any early recurrence of AF. When the patients had symptoms suggestive of a tachycardia after the ablation, 24-hour Holter monitoring and/or cardiac event recording with a recording duration of 1 week were performed to define the cause of the clinical symptoms.4 AF recurrence was defined as an episode lasting more than 1 minute and that was confirmed by ECGs 2 months after the ablation (blanking period). The end point for the follow-up was clinically documented recurrence of atrial arrhythmias or repeat ablation procedures.

Statistical Analysis

All continuous data were presented as mean value±SD. A χ² test with Fisher exact test was used for the categorical data. The means of continuous data of 2 groups were compared with the Student t test. Comparisons of more than 2 groups were performed with a 1-way ANOVA. A paired t test was used for comparison of the substrate properties before and after PVI. Statistical significance was considered when the 2-sided probability value was <0.05.

Results

Stepwise Catheter Ablation Results

In the initial ablation step, PVI was performed successfully and electric isolation was confirmed in all 72 patients. PVI terminated AF, and SR was restored in 20 of 33 patients (61%) with paroxysmal AF, in 5 of 9 patients (56%) with persistent AF, and in 2 of 30 patients (6.7%) with long-lasting persistent AF. The second step involving linear ablation in the remaining 45 patients (63%) resulted in termination of AF in 5 patients (7%). The subsequent step of continuous CFE ablation in the patients with ongoing AF resulted in AF termination in 13 patients (18%). The cumulative rate of procedural AF termination with the stepwise procedure (without antiarrhythmic medications during the procedure) is shown in Figure 1.

The total procedural time in the patients with paroxysmal AF, persistent AF, and long-lasting AF was 111±42, 102±22, and 165±55 minutes, respectively (P<0.001). The mean procedural time for the step 1 to 3 procedures was

![Figure 1. Cumulative percentage of patients in whom AF terminated with each step of ablation.](image_url)

Table 1. Patient Characteristics and Substrate Properties in Patients Who Responded to PVI and Those Who Did Not in Terms of Termination

<table>
<thead>
<tr>
<th>Clinical and Substrate Factors</th>
<th>AF Did Not Terminate With PVI</th>
<th>AF Terminated With PVI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male/female</td>
<td>33/12</td>
<td>17/10</td>
<td>0.43</td>
</tr>
<tr>
<td>Age, y</td>
<td>50.5 ± 11.1</td>
<td>55.4 ± 10.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Paroxysmal AF/persistent AF/long-lasting persistent AF</td>
<td>13/7/25</td>
<td>20/2/5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Underlying disease (heart failure, CAD, or VHD)</td>
<td>11/34</td>
<td>3/24</td>
<td>0.34</td>
</tr>
<tr>
<td>Nonpulmonary vein ectopy, n (%)</td>
<td>22 (42%)</td>
<td>5 (28%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA diameter, mm</td>
<td>40.6 ± 6.67</td>
<td>39.3 ± 6.02</td>
<td>0.435</td>
</tr>
<tr>
<td>LV ejection fraction, mm</td>
<td>53.9 ± 9.45</td>
<td>60.5 ± 5.98</td>
<td>0.002</td>
</tr>
<tr>
<td>LV end-diastolic dimension, mm</td>
<td>52.0 ± 6.64</td>
<td>48.4 ± 4.96</td>
<td>0.018</td>
</tr>
<tr>
<td>LV end-systolic dimension, mm</td>
<td>34.0 ± 8.41</td>
<td>29.2 ± 4.38</td>
<td>0.008</td>
</tr>
<tr>
<td>Fractionation analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean degree of fractionation in the LA, mean FI, ms</td>
<td>77.1 ± 15.1</td>
<td>93.1 ± 24.3</td>
<td>0.002</td>
</tr>
<tr>
<td>FI of the maximal CFE, ms</td>
<td>40.3 ± 7.69</td>
<td>47.1 ± 7.91</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean degree of fractionation in the RA, mean FI, ms</td>
<td>79.8 ± 13.6</td>
<td>107.3 ± 27.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Proportion of continuous CFEs (FI &lt;50 ms) in the LA, %</td>
<td>17.7 ± 14.6</td>
<td>3.8 ± 7.3</td>
<td>0.008</td>
</tr>
<tr>
<td>Proportion of variable CFEs (FI=50–120 ms) in the LA, %</td>
<td>57.6 ± 16.4</td>
<td>64.4 ± 14.0</td>
<td>0.258</td>
</tr>
<tr>
<td>Frequency analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DF of LA, Hz</td>
<td>6.92 ± 0.88</td>
<td>6.01 ± 0.71</td>
<td>0.005</td>
</tr>
<tr>
<td>Highest DF of LA, Hz</td>
<td>10.9 ± 2.06</td>
<td>9.59 ± 2.05</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean DF of RA, Hz</td>
<td>6.60 ± 1.00</td>
<td>5.46 ± 0.58</td>
<td>0.001</td>
</tr>
<tr>
<td>Highest DF of RA, Hz</td>
<td>8.64 ± 1.37</td>
<td>7.83 ± 1.97</td>
<td>0.282</td>
</tr>
<tr>
<td>Mean LA-RA DF gradient, Hz</td>
<td>0.45 ± 0.85</td>
<td>0.95 ± 0.51</td>
<td>0.162</td>
</tr>
</tbody>
</table>

AFL indicates atrial flutter; CAD, coronary artery disease; VHD, valvular heart disease.
Fractionation analysis in the LA in terms of the procedural AF termination. Patients with a longer AF duration, lower LV ejection fraction, and larger LV dimension were less likely to respond to PVI. In those patients, both the LA and RA substrate were more fractionated in terms of the maximal magnitude of the CFEs (P<0.001), mean degree of the CFEs (P=0.002), and proportion of the continuous CFEs in the LA (P=0.008), compared with the patients who responded to PVI. The frequency analysis showed that the mean DF value in both the LA and RA was higher (P<0.001), and the LA-to-RA DF gradients were less evident.

**LA Substrate Before and After PVI in Patients Who Did Not Respond to PVI**

In 45 patients (13 patients with paroxysmal AF, 7 with persistent AF, and 25 with long-lasting persistent AF) who did not respond to PVI in terms of AF termination, the LA substrate characteristics were assessed before and after PVI. As shown in Table 2 and Figure 2, the LA substrate was less fractionated in terms of the maximal magnitude of the CFEs (shortest FI, P=0.033), mean degree of the CFEs (P=0.001), and proportion of the continuous CFEs (P=0.02) after PVI. The spatial distribution of the continuous CFEs in the LA also differed after PVI (Figure 3). The frequency analysis showed that the mean DF value in the LA was lower with less intra-LA.

### Table 2. Substrate Properties Before and After PV Isolation

<table>
<thead>
<tr>
<th>Substrate Factors</th>
<th>Before PVI</th>
<th>After PVI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Degree of fractionation</strong> (mean FI, ms)</td>
<td>75.6 ± 14.3</td>
<td>87.3 ± 16.7</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Variation of the fractionation</strong> (SD of FI), ms</td>
<td>39.1 ± 10.3</td>
<td>40.2 ± 11.6</td>
<td>0.626</td>
</tr>
<tr>
<td><strong>Fl of the most fractionation site, ms</strong></td>
<td>44.3 ± 4.46</td>
<td>48.4 ± 7.45</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>Proportion of continuous CFEs, %</strong></td>
<td>17.7 ± 14.6</td>
<td>11.6 ± 16.9</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Proportion of variable CFEs, %</strong></td>
<td>57.5 ± 16.4</td>
<td>58.6 ± 18.4</td>
<td>0.806</td>
</tr>
<tr>
<td><strong>Frequency analysis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean DF of the LA, Hz</td>
<td>6.92 ± 0.88</td>
<td>6.58 ± 0.91</td>
<td>0.001</td>
</tr>
<tr>
<td>Variation of DF in LA, SD of DF, Hz</td>
<td>1.32 ± 0.60</td>
<td>1.00 ± 0.42</td>
<td>0.032</td>
</tr>
<tr>
<td>Mean DF of RA, Hz</td>
<td>6.60 ± 1.00</td>
<td>6.27 ± 1.02</td>
<td>0.132</td>
</tr>
<tr>
<td>Variation of DF in RA, SD of DF, Hz</td>
<td>1.11 ± 0.60</td>
<td>1.01 ± 0.49</td>
<td>0.626</td>
</tr>
<tr>
<td>Highest DF of the LA, Hz</td>
<td>10.5 ± 1.62</td>
<td>9.06 ± 1.58</td>
<td>0.012</td>
</tr>
<tr>
<td>Highest DF of RA, Hz</td>
<td>8.64 ± 1.37</td>
<td>8.34 ± 1.54</td>
<td>0.575</td>
</tr>
</tbody>
</table>

**Table 1 shows the comparison of the substrate characteristics in patients who responded to PVI and in those who did not in terms of the procedural AF termination. Patients with a** longer AF duration, lower LV ejection fraction, and larger LV dimension were less likely to respond to PVI. In those patients, both the LA and RA substrate were more fractionated in terms of the maximal magnitude of the CFEs (P<0.001), mean degree of the CFEs (P=0.002), and proportion of the continuous CFEs in the LA (P=0.008), compared with the patients who responded to PVI. The frequency analysis showed that the mean DF value in both the LA and RA was higher (P<0.001), and the LA-to-RA DF gradients were less evident.

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In 45 patients (13 patients with paroxysmal AF, 7 with persistent AF, and 25 with long-lasting persistent AF) who did not respond to PVI in terms of AF termination, the LA substrate characteristics were assessed before and after PVI. As shown in Table 2 and Figure 2, the LA substrate was less fractionated in terms of the maximal magnitude of the CFEs (shortest FI, P=0.033), mean degree of the CFEs (P=0.001), and proportion of the continuous CFEs (P=0.02) after PVI. The spatial distribution of the continuous CFEs in the LA also differed after PVI (Figure 3). The frequency analysis showed that the mean DF value in the LA was lower with less intra-LA.

**Figure 2. Regional distribution of the FI, representing complex fractionated electrograms in the LA before and after circumferential PVI and the corresponding bipolar electrograms during AF. CFE mapping exhibited multiple CFE sites, including the LA lower septum, LA appendage base, and near the mitral annulus region, where fractionated electrograms were observed. After circumferential PVI, the fibrillatory electrograms became organized with an increased FI, whereas the CFE sites near the mitral annulus region remained fractionated and radiofrequency ablation successfully terminated AF.**

**Figure 3. Regional distribution of continuous CFE (>8 seconds, with averaged FI <50 ms) before and after PVI in patients who did not respond to PVI in terms of the AF procedural AF termination. A complete PVI altered the distribution of the CFE toward the LA anteroseptum, mitral annulus, and LA appendage regions.**
variation of the DF after PVI ($P<0.05$, Figure 4). The highest DF in the LA was also lower ($P=0.012$). On the other hand, the highest DF and mean DF of the RA were similar before and after PVI ($P=NS$).

**Distribution of Continuous CFEs After PVI**

In the 45 patients who did not respond to PVI, 53% of the continuous CFE sites in the LA/CS were eliminated by complete PVI. The remaining 47% of the continuous CFE sites could be classified depending on the spatial relationship to the highest DF sites after PVI (Figures 5 and 6).

In 24 of the 45 patients (53%), some CFE regions were compatible with the highest DF sites in the LA/CS after PVI. Overall, 25 regions of this type of CFEs (32% of all 84 CFEs after PVI) were identified with an average of 0.6 regions per patient. The mean distance from the highest DF site to the shortest FI sites (center-to-center) was $1.1 \pm 0.53$ cm (range 0 to 2 cm, Figure 5). Elimination of those CFEs resulted in procedural AF termination in 15 of 24 (63%) patients.

In 31 of the 45 patients (69%), some CFE regions were observed within homogenous DF substrate or in the periphery of the highest DF sites in the LA/CS (center-to-center distance >2 cm). Overall, 53 regions (76% of all 84 CFEs) of this type of CFEs were identified with an average of 1.3 regions per patient (Figures 5 and 6). Elimination of those CFEs was associated with a lower rate of termination in 7/31 (23%) of the patients ($P<0.05$, compared with the CFEs near the highest DF sites).

**Long-Term Follow-Up**

With a mean follow-up of $14 \pm 7$ months, the rate of SR maintenance with and without drugs was 88%, 78%, and 70% in the patients with paroxysmal AF, persistent AF, and long-lasting persistent AF, respectively ($P=0.217$). SR was maintained in 87%, 88%, and 80% patients in the patients who underwent the step 1, step 1 to 2, and step 1 to 3 procedures with procedural AF termination. In patients without procedural AF termination and who received cardioversion after the step 1 to 3 procedures, the SR maintenance rate was lower (42%, $P<0.01$, compared with the other patients).

**Discussion**

**Main Findings**

This study demonstrated that patients with a less fractionated LA and RA were more likely to respond to PVI in terms of the procedural AF termination. The mean DF values of both
atria were lower with evident LA-to-RA gradients of the DF value. The LA substrate after PVI was characterized by a lower mean DF value, lower intra-LA DF gradients, and fewer continuous CFEs. The remaining continuous CFEs after PVI represented the high-frequency sources in the vicinity and could be observed in the homogeneous DF substrate. The continuous CFEs that persisted both before and after PVI in the vicinity of the high DF sites correlated with a higher rate of AF termination during CFE ablation.

**Maintenance of AF After PVI**

Previous studies demonstrated that AF was maintained by the high-frequency sites in the arrhythmogenic veins and that elimination of those sites could treat most patients with paroxysmal AF.15,19–20 This study demonstrated that patients who responded to PVI had limited continuous CFEs within the LA. On the other hand, patients who did not respond to PVI and required substrate modification had more continuous CFEs in the LA. Further, a high efficacy of procedural AF termination and long-term AF-free survival was observed when achieving procedural AF termination by targeting the continuous CFEs. These results indicate that the continuous CFEs were important for the maintenance of AF after PVI.

In this study, the patients who did not respond to PVI were predominately nonparoxysmal AF in nature with a lower LV ejection fraction and larger LV dimension. Substrate mapping showed that both atria had higher DF values before PVI with limited left-to-right DF gradients. The remodeled and heterogeneous atrial substrate in these patients may facilitate multiple mechanisms and multiple AF drivers for AF maintenance. Complete PVI eliminated some continuous CFEs in the LA, indicating that those CFEs were secondary to the PV activities. This could be also explained by the adrenergic and cholinergic nerves in the ganglionated plexi in the PV vicinity. Complete PVI may interrupt their autonomic input and interconnections with PV sleeves. After PVI, the remaining continuous CFEs in the LA and CS may drive AF with or without the presence of the high frequency AF sites in the LA.

**Mechanism of Fractionation After PVI**

Substrate mapping and catheter ablation of AF has recently incorporated the analysis of the DF and CFEs. However, the relationships between the DF and fractionation and spatiotemporal organization of the fibrillation waves after PVI remain unclear. This study demonstrated that a complete PVI reduced some continuous CFEs in the LA. The remaining continuous CFEs after PVI were observed at the high-frequency sites and at the boundaries of the high-frequency sites. A recent study by Stiles et al also had similar finding in human AF. They demonstrated clusters of high DF sites, mostly in the LA, with fractionation observed at or adjacent
to these DF sites. This could be explained by the recent observation from a computer stimulation model that showed that increased meandering of AF rotors increased the fractionation. The fractionation may also be observed at the boundaries of the fixed high-frequency sources or within the inhomogeneous atrial substrate without the high-frequency sources in the vicinity. Those results and the present study indicated that both the stability of the rapid AF sources and inhomogeneous LA substrate contribute to the fractionated electrograms.

Clinical Implications
This study demonstrated that the intra-atrial DF gradients in the LA before PVI partly resulted from the PV activity. The continuous CFEs after PVI were more localized compared with those observed in the previous studies. These findings indicate that a complete PVI should be performed before CFE ablation to avoid any unnecessary substrate modification. This study also demonstrated that the frequency analysis may not be enough to identify the different sites of interest in the atrial substrate in patients with nonparoxysmal AF after PVI. Sites with fractionation provide potential targets for selective LA substrate modification in addition to frequency mapping. Fractionated sites in the vicinity of high DF sites were more frequently associated with AF termination compared with other CFE sites, suggesting that ablation of these may be beneficial. These data showed that individualized knowledge of the spatial organization of the fibrillation waves, including the fractionation and frequency analysis, may help in the identification of the different mechanisms of AF.

Limitations
First, the density of the mapping sites may not have been high enough. A higher density of mapping sites may provide incremental information, particularly on the relationship between the DF sites and continuous CFEs. Second, oral amiodarone was not discontinued before the electrophysiological study because these patients had frequent episodes of AF attacks. This may have affected the results of the DF and CFE mapping. However, in this study, each patient served as his or her own control, and the change in the DF and FI after PVI could not be influenced by the amiodarone. Third, the results of this study are in part based on the effect of the ablation of the linear lines and continuous CFEs.

Figure 6. Comparison of the regional distribution of the FI and DF (left panels) in a patient with nonparoxysmal AF after PVI. The intracardiac bipolar electrogram and corresponding frequency spectra during AF are shown in right panels. The most fractionated areas (shortest FI, site E) in the LA low posterior wall are in the periphery of the high-frequency sites of AF (highest DF site, site C) near the lateral mitral isthmus. CFE ablation did not terminate AF; however, linear ablation in the lateral mitral annulus crossing the highest DF site successfully terminated AF.
after PVI; therefore, the cumulative effects may have led to restoration of SR. Last, we did not systemically assess the CFE distribution after the LA linear ablation because the aim of this study was to investigate the effect of complete PVI on the CFEs in the LA.

Conclusions

The atrial substrate characteristics differed in patients who responded and those who did not respond to a complete PVI. The fibrillatory activity in the LA was more organized and frequency distribution more homogeneous after a complete PVI. A complete PVI eliminated some CFEs in the LA and altered the distribution of the CFEs toward the LA anteroseptum, mitral annulus, and LA appendage regions. A persistent presence of continuous CFEs before and after PVI in the vicinity of the high frequency Sites was important for the maintenance of AF post PVI.

Sources of Funding

This study was supported by research grants from the Taipei Veterans General Hospital (97DHA0100216), National Scientific Council (NSC96-2314-B-010-006, NSC96-2628-B-010-036), and the Research Foundation of Cardiovascular Medicine (RFCM 96-02-018).

Disclosures

None.

References


CLINICAL PERSPECTIVE

Pulmonary vein isolation (PVI) has become the main catheter ablation technique for atrial fibrillation. For persistent atrial fibrillation, additional substrate modification with complex fractionated electrogram (CFE) ablation is considered in patients who did not respond to PVI. However, the mechanisms of atrial fibrillation maintenance after PVI remain unclear, and CFEs are usually observed in many regions of the atria, making identification of a critical atrial substrate difficult. This study focused on the spatiotemporal organization of fibrillation waves before and after PVI. We found that variation of activation frequency and fractionation before PVI were partly related to PV activity. After PVI, regional activation frequencies and the degree of fractionation in the left atrial substrate were diminished. These findings suggest that identification of critical substrate areas in the left atrium would be difficult without PVI isolation and that PVI should be performed before additional CFE-guided substrate modification to avoid unnecessary substrate modification. Furthermore, zones of continuous CFEs that persisted both before and after PVI appeared to be critical CFEs. Ablation at fractionated sites in the vicinity of high dominant frequency sites more frequently terminated atrial fibrillation termination compared with ablation at other CFE sites. Therefore, a combined analysis of both fractionation and frequency may allow a more targeted approach to identifying critical atrial substrate that remains after PVI.
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Circ Arrhythm Electrophysiol. 2009;2:233-241; originally published online March 6, 2009;
doi: 10.1161/CIRCEP.108.812024

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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