Heart Rhythm Disorders

Sites of Focal Atrial Activity Characterized by Endocardial Mapping During Atrial Fibrillation

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OBJECTIVES
The aim of the present study was to assess the feasibility of identifying sites of focal atrial activity by localized high-density endocardial mapping during atrial fibrillation (AF).

BACKGROUND
Sites of focal activity in the left atrium have been demonstrated by epicardial mapping during AF. Twenty-four patients (15 with paroxysmal, 3 with persistent, and 6 with permanent AF) underwent endocardial mapping during AF. A 20-pole catheter with five radiating spines was used to map both atria for 30 s in each of 10 pre-determined segments. A focal activity was defined as ≥3 atrial cycles with activation spreading from center to periphery of the mapping catheter. Catheter ablation was performed independent of the mapping results.

RESULTS
Spontaneous focal activities were observed in 13 sites in the left atrium (9%; anterior 1, roof 2, posterior 6, inferior 4) in 12 patients (9 paroxysmal, 3 persistent). Focal activity was observed continuously (two sites) or intermittently (11 sites, median 5 episodes), and associated with shortening of the cycle length (from 183 ± 33 ms to 172 ± 29 ms; p < 0.05). The mean duration of an intermittent episode was 1.5 s (range 0.4 to 7.1 s). Atrial fibrillation terminated without ablation at the foci in all of 12 patients, but in 2 of them, re-initiated arrhythmia was successfully ablated at these foci. Nine of these 12 patients (75%) were arrhythmia-free without antiarrhythmic drugs during a follow-up period of 7.0 ± 3.1 months.

CONCLUSIONS
Termination of AF without ablation at the sites of atrial focal activity suggests that this activity may be triggered by impulses originating from other regions, such as the pulmonary veins. (J Am Coll Cardiol 2006;47:2005–12) © 2006 by the American College of Cardiology Foundation

The importance of the pulmonary veins (PVs) in catheter ablation of atrial fibrillation (AF) is well recognized (1–5). Although the efficacy of catheter ablation is improved by additional modification of the atrial substrate (4–9), the mechanisms by which this is achieved are incompletely understood. Using epicardial activation mapping, Cox et al. (10) have demonstrated macro–re-entry during atrial fibrillation, interruption of which contributes to the efficacy of the Maze procedure. More recently, rapid focal activity in the left atrium (LA) and PVs has been demonstrated by epicardial mapping, implying a potential role for focal atrial activity in the maintenance of AF (11–14); however, the use of endocardial mapping to identify atrial foci during AF has not been reported. Additionally, the impact of PV isolation alone on such activity is unknown.

The aim of the present study, therefore, was to identify and characterize atrial focal activity during AF, using a newly developed multispine catheter, and to investigate the relationship between the presence of focal atrial activity and the procedural and clinical outcomes of AF ablation.

METHODS

Study population. The present study comprised 24 patients with drug-refractory AF. Atrial fibrillation was paroxysmal in 15, persistent in 3, and permanent in 6. All antiarrhythmic drugs except amiodarone were discontinued at least five half-lives before ablation. Four patients with paroxysmal AF and two with permanent AF were taking amiodarone. Baseline characteristics of patients are shown in Table 1. All patients gave written informed consent.

Electrophysiological study. All patients had effective anticoagulation for at least one month, and transesophageal echocardiography was performed no more than 48 h before ablation to exclude thrombus in the LA. For the ablation procedure, a 6-F quadripolar catheter (Xtrem, ELA Medical, Montrouge, France) was positioned in the coronary sinus. Surface electrocardiogram and intracardiac electrograms were measured at a paper speed of 100 mm/s utilizing a digital amplifier/recording system (Bard Electrophysiology, Lowell, Massachusetts). A single bolus of 50 IU/kg of
heparin was administered after the trans-septal puncture and repeated only for procedures lasting more than 4 h.

**Study protocol.** A 20-pole multispine catheter (PentaRay, Biosense Webster, Diamond Bar, California) was utilized for endocardial two-dimensional mapping (Fig. 1). This catheter has five spines, with four electrodes on each spine. Each electrode measures 1 mm, with an interelectrode spacing of 2-6-2 mm. A mapping area has a diameter of 35 mm if all spines are optimally applied to the atrial endocardium. Using this catheter, high-density mapping was performed within the LA and the right atrium (RA) during spontaneous or induced AF in each of the following sites for 30 s: anterior LA, LA roof, posterior LA, inferior LA, lateral LA, LA septum, anterior RA, lateral RA, posterior RA, and RA septum. For patients with a diagnosis of paroxysmal AF who were in sinus rhythm at the beginning of the procedure, AF was induced before commencement of mapping by burst pacing from the coronary sinus, LA, or RA.

Wave front propagation was categorized as follows: 1) passive activation—consistent propagation of a single wave front sweeping across the mapping area during three or more consecutive beats (Fig. 2); 2) chaotic activation—beat-to-beat variable activation pattern, or highly fragmented or split potentials without a consistent activation sequence (Fig. 3); and 3) centrifugal activation—a single wave front emanating from the center of a mapping area during three or more consecutive beats. Centrifugal activation was defined as the earliest endocardial activation occurring on the innermost bipole of all spines and propagating simultaneously to the outermost bipole of all spines of the mapping catheter (Fig. 4). This activation pattern was considered to demonstrate focal activity originating from within the area encompassed by the catheter spines.

The dominant activation pattern was defined as the pattern occupying the greatest proportion of the 30-s mapping window. In those regions showing intermittent centrifugal activation, the duration of centrifugal activation and cycle length during the episode were determined. In addition, the duration of activity in the mapping area, defined as the interval from the onset of earliest activity to the end of the latest activity among bipoles of the mapping catheter, was determined during centrifugal activation. If no atrial electrograms could be recorded on three or more bipoles, the activation pattern was not evaluated at that site and the mapping catheter was moved to the next recording site. All endocardial mapping data were analyzed offline by a single investigator who was blinded to ablation outcomes.

**Catheter ablation.** After two-dimensional mapping of six sites in the LA, all patients underwent catheter ablation during ongoing AF with use of a 3.5-mm, irrigated-tip catheter (Biosense Webster). Ablation was performed independent of the mapping results.

For paroxysmal AF, isolation of each pulmonary vein was first performed guided by a 10-pole circumferential catheter. Radiofrequency (RF) energy was delivered at 1 cm proximal to the PV ostium or at the rim of the ostium with a delivered power of 30 or 25 W, respectively. If ipsilateral PVs were located closely or a common ostium was observed, RF lesions for each PV were connected and these two PVs were isolated en bloc. The ablation catheter was dragged every 30 to 60 s with continuous RF energy delivery. The end point was circumferential elimination or dissociation of PV potential. Inducibility of AF was tested after completion of PV isolation by burst pacing from the LA, RA, and coronary sinus. If AF was inducible or persisting ≥10 min, modification of the atrial substrate was performed, including linear ablation (connecting both superior PVs [roof line] and/or from the postero-lateral mitral annulus to the left inferior PV [mitral isthmus line]), ablation targeting fractionated or short cycle-length activity in the LA (atrial ablation), and disconnection of the superior vena cava (SVC) (9). The end point of linear lesions was bi-directional block confirmed during sinus rhythm.

**Table 1. Patients’ Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF (n = 15)</th>
<th>Persistent/Permanent AF (n = 9)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>54 ± 11</td>
<td>52 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/3</td>
<td>8/1</td>
<td>NS</td>
</tr>
<tr>
<td>AF duration (months)</td>
<td>66 ± 62</td>
<td>92 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Persistent AF duration (months)</td>
<td>—</td>
<td>16 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Structural heart disease</td>
<td>0</td>
<td>2 (LV hypertrophy 1, ischemic heart disease 1)</td>
<td>NS</td>
</tr>
<tr>
<td>LA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasternal (mm)</td>
<td>37 ± 7</td>
<td>46 ± 5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Longitudinal (mm)</td>
<td>53 ± 9</td>
<td>61 ± 10</td>
<td>0.06</td>
</tr>
<tr>
<td>Transverse (mm)</td>
<td>39 ± 5</td>
<td>43 ± 7</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>70 ± 8</td>
<td>69 ± 13</td>
<td>NS</td>
</tr>
</tbody>
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AF = atrial fibrillation; LA = left atrium; LV = left ventricle; LVEF = left ventricular ejection fraction.
For persistent or permanent AF, PV isolation and atrial substrate modification were performed in an attempt to convert arrhythmia into sinus rhythm (9).

**Follow-up.** Patients were hospitalized for one day at one, three, and six months after the last procedure for clinical review and ambulatory monitoring. If patients maintained sinus rhythm for three months, cessation of anticoagulation was considered. A successful outcome was defined as the absence of all documented arrhythmia beyond the second month after ablation without antiarrhythmic medication.

**Statistical analysis.** Continuous variables are presented as mean ± SD or proportions, and categorical variables are presented as number and percentage. Analysis was performed by Student t test or Fisher exact test. A two-sided p < 0.05 was considered statistically significant.

**Figure 1.** (A) A 20-pole multispine catheter. The spine A and B being recognized by radio-opaque markers (circled) for visualization with fluoroscopy. The marker on spine A is proximal to the external two electrodes, and on spine B distal to the internal two electrodes. (B) A multispine catheter deployed in the inferior left atrium. Quadrupolar catheters are deployed in the left atrium and coronary sinus.

**Figure 2.** Passive activation demonstrated by two-dimensional mapping. The earliest activation was recorded on the external bipole of spine C (+) and the latest activation on the external bipole on spines A and E. A single wave front enters into the mapping area from spine C (+) and exits from spines A and E (right). This activation sequence was observed in three consecutive beats.
RESULTS

Endocardial two-dimensional mapping. Mapping was performed in 17 patients (8 with paroxysmal AF, 3 with persistent AF, and 6 with permanent AF) during spontaneous AF, and in 7 patients (all with paroxysmal AF) during induced AF. Mapping in the LA and RA were performed in all and in 15 patients (paroxysmal 11, persistent 2, permanent 2), respectively. A total of 144 and 54 sites were mapped in the LA and RA, respectively. In 32 sites (19%: anterior LA 6, LA roof 1, posterior LA 1, inferior LA 1, lateral LA 12, LA septum 7, anterior RA 1, lateral RA 1, posterior RA 1, and RA septum 1), the activation pattern could not be determined because of poor catheter contact with the endocardial surface. Of the remaining 116 and 50 sites (anterior LA 18, LA roof 23, posterior LA 23, inferior LA 23, lateral LA 12, and LA septum 17; anterior RA 10, lateral RA 14, posterior RA 13, and RA septum 13), the dominant activation pattern in the LA and RA was passive activation in 63 (54%) and 20 (40%) sites, chaotic activation in 51 (44%) and 30 (60%) sites, and centrifugal activation in 2 (2%) and 0 (0%) sites, respectively. Centrifugal activation was observed continuously throughout the 30-s mapping period at the anterior LA in one patient with persistent AF and at the LA roof in one patient with paroxysmal AF (Fig. 5). In the LA, chaotic activation was determined as dominant most commonly in the septum (65%) and least commonly in the lateral LA (8%) (Fig. 6). In the RA, chaotic activation was determined most commonly in the septum and posterior RA (85%) and least in the anterior RA (20%).

Continuous or intermittent centrifugal activation, indicating focal activity within the mapping area, was observed in a total of 13 mapping sites (anterior LA 1, LA roof 2, posterior LA 6, and inferior LA 4) (Fig. 7) in 12 patients (paroxysmal AF 9, persistent AF 3, perma-

Figure 3. Chaotic activation demonstrated by two-dimensional mapping. The activation sequence changes beat-to-beat. The analysis of wave front propagation was prevented by the presence of double potentials and fractionated potentials.

Figure 4. Centrifugal activation demonstrated by two-dimensional mapping. Activity on the internal bipole precedes that on the external bipole in each spine, indicating focal activity in the center of the mapping area. This activation sequence is observed in four consecutive beats.
nent AF). No sites showed centrifugal activation in the RA. Although more than one-half of paroxysmal or persistent AF patients demonstrated areas of focal activity, endocardial mapping in patients with permanent AF failed to reveal such activity, presumably owing to the complexity of local electrograms.

In 11 mapping sites, intermittent focal activity was observed during the 30-s recording period, with a median of five episodes (range 1 to 11) and a mean episode duration of 1.5 s (range 0.4 to 7.1 s) (Fig. 8). During periods of focal activity, the mean cycle length was $172 \pm 29$ ms, and the variation of cycle length during an episode was $29 \pm 20$ ms. The cycle length of focal activity was significantly shorter than the five cycles preceding the onset of focal activity ($183 \pm 33$ ms, $p < 0.05$) (Fig. 8). The duration of activity in the mapping area during focal activity occupied $\leq 50\%$ of tachycardia cycle length in all episodes, indicating that re-entry is unlikely to be the mechanism.

Figure 5. Episode of continuous centrifugal activation.

Figure 6. The regional incidence of chaotic activation for the six areas mapped in each patient. LA = left atrium.

Figure 7. Schema demonstrating the location of atrial focal activity. Blue dots indicate the site of continuous activity, and red dots indicate the sites where additional ablation was performed.
Catheter ablation. PAROXYSMAL AF. All 15 patients with paroxysmal AF underwent PV isolation, and 3 patients (20%) underwent additional atrial substrate modification (Table 2). Atrial fibrillation was terminated by PV isolation in 14 of 15 patients (93%), including one patient who showed continuous centrifugal activation, and by substrate modification in the remaining patient. Atrial fibrillation was rendered non-inducible in all patients but one (93%).

In all of nine patients who showed atrial focal activity, AF was terminated without ablation at the region where focal activity was identified: eight patients during PV isolation, one patient during SVC disconnection. In these patients, focal activity had been identified in the LA roof (two), posterior LA (three), and inferior LA (four). In seven of nine patients (78%), AF was non-inducible after termination of AF.

After termination of AF, AF or focal atrial tachycardia was inducible in two of nine patients (22%). At the region where the focus had been identified by endocardial mapping before ablation in these two patients, one patient showed rapid activity with a cycle length of 110 ms in the posterior LA during AF, and the other showed the focus of atrial tachycardia in the inferior LA. Additional ablation at each site terminated the arrhythmia in both patients (Fig. 7).

PERSISTENT/PERMANENT AF. All of nine patients underwent PV isolation and atrial substrate modification (Table 2). Atrial substrate modification included a roof line and atrial ablation in all patients, mitral isthmus ablation in six patients (67%), and disconnection of the SVC in five patients (56%). In eight of nine patients (89%), including one patient who showed continuous centrifugal activation, AF was terminated by ablation alone.

Atrial focal activity was identified in three patients with persistent AF before ablation. Atrial fibrillation was terminated in all of these patients without ablation at the region where focal activity was identified.

Clinical outcome. Six of 24 patients (25%; paroxysmal AF 3, persistent AF 1, permanent AF 2) underwent a repeat

<table>
<thead>
<tr>
<th>Table 2. Mapping and Ablation Results</th>
<th>Paroxysmal AF (n = 15)</th>
<th>Persistent/Permanent AF (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who showed atrial focal activity</td>
<td>9 (60%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Conversion of AF during PV isolation</td>
<td>14 (93%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>Atrial substrate modification</td>
<td>3 (20%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Repeat procedure</td>
<td>3 (20%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Follow-up period since the last procedure (months)</td>
<td>7.9 ± 2.8</td>
<td>8.2 ± 3.4</td>
</tr>
<tr>
<td>Overall success without use of antiarrhythmic drugs</td>
<td>13 (87%)</td>
<td>7 (78%)</td>
</tr>
</tbody>
</table>

AF = atrial fibrillation; PV = pulmonary vein.
procedure, in which recurrence of focal activity was not observed (Table 2). Twenty of 24 patients (83%; paroxysmal AF 13, persistent AF 2, permanent AF 5) were free from arrhythmia without antiarrhythmic drugs during a follow-up of 8.0 ± 2.9 months since the last procedure.

PATIENTS WITH ATRIAL FOCI. Among 12 patients in whom focal activity had been identified, 1 patient with persistent AF underwent a repeat procedure. This patient was free from arrhythmia after the repeat procedure, in which re-isolation of the PVs and ablation at the mitral isthmus were performed without targeting the posterior LA, where the focus had been identified.

Recurrent arrhythmia was controlled by class I antiarrhythmic drugs without a repeat procedure in three patients (two paroxysmal AF and one persistent AF), and none of them had undergone ablation at the area of focal activity in the index procedure. Nine of 12 patients (75%) were free of arrhythmia without antiarrhythmic drugs during a follow-up of 7.0 ± 3.1 months.

DISCUSSION

The new findings of this study are: 1) endocardial mapping with a multispine catheter demonstrated sites of continuous or intermittent focal atrial activity during AF; and 2) AF was terminated by catheter ablation without targeting at regions harboring focal activity, although some patients required ablation at the foci to promote non-inducibility of arrhythmia.

Atrial focal activity. Atrial focal activity has been demonstrated by high-density epicardial mapping (11–13), but to date this has not been feasible by endocardial mapping with conventional catheters. Using a novel multispine mapping catheter applied to the atrial endocardium, we have been able to map both the direction of wave front propagation and the site of earliest local atrial activation during AF. A centrifugal activation pattern is described by activation spreading from center to periphery in all five spines of this mapping catheter, excluding any entry of wave fronts from outside the mapping area; under such circumstances, the center of the mapping area most likely represents a focal source of activity. This has been confirmed in patients with focal atrial tachycardia where sites demonstrating an identical pattern of centrifugal activation were successful targets for catheter ablation (15). Although a centrifugal activation pattern may reflect endocardial breakthrough from the epicardium (for example, if heterogeneous activation pattern may reflect endocardial breakthrough from the epicardium, this hypothesis is not supported by the wide anatomical distribution of focal sites mapped in the present study, notably the absence of this phenomenon in the trabeculated RA.

Some studies reported focal sites of centrifugal activity during epicardial mapping (11–13). Continuous or intermittent focal activity in the posterior LA or near the PV and left atrial appendage were demonstrated in patients with permanent AF, but the mechanisms of these focal activities could not be specified. In the present study, activity recorded on the mapping catheter covered only a limited period of the tachycardia cycle length, suggesting therefore triggered activity or abnormal automaticity as the mechanism. In contrast, activity spanning the entire tachycardia cycle length was identified within the mapping area of the multispine catheter, thus recognizing small re-entrant circuits confirmed by entrainment technique (15).

The present study demonstrated that most patients with focal atrial activities had restoration of sinus rhythm without ablation at the areas of these activities. This suggests that atrial foci may represent secondary drivers triggered by impulses originating from the PVs or other regions, thereby offering an additional explanation for the efficacy of PV isolation in the treatment of AF (3,4). On the other hand, two patients required ablation at the focus to promote non-inducibility of arrhythmia, suggesting that such activities may potentially drive the atria in some circumstances. Further investigation is required to distinguish the primary driving foci from secondary ones.

Chaotic activation pattern. Chaotic activation may represent the entry of multiple wave fronts into the mapping area, conduction block, and/or slow conduction within the area. The lateral LA showed the lowest incidence of chaotic activation in the present study, which may be due to a limited number of wave fronts entering this region surrounded by anatomical obstacles, including the PVs and mitral annulus. In contrast, the LA septum showed the highest incidence of chaotic activation. This region is connected to other regions of the LA and also to the RA, thus being likely to be activated by a greater number of wave fronts.

Study limitations. In the present study, atrial focal activity was identified in patients with paroxysmal and persistent AF, but none was found in patients with permanent AF. Considering the role of atrial substrate and the limited efficacy of PV isolation in permanent AF (9), it is likely that the mapping technique has failed to detect rather than demonstrated the absence of foci in this type of AF. The following are possible explanations: 1) the interaction of multiple foci or very short cycle-length activity makes electrograms too chaotic or fragmented for analysis, or 2) the critical site was not captured in the mapping area.

The ostia of the PVs and LA appendage, which have been reported as major sources of focal activity (16), were not investigated, because the multispine catheter could not be appropriately deployed on the distorted endocardial surface in these regions.

Conclusions. Endocardial mapping using a multispine catheter demonstrated sites of continuous or intermittent focal activity in the LA during AF in patients with paroxysmal and persistent AF. Atrial fibrillation was terminated by PV isolation and/or atrial substrate modification without targeting sites of focal activity. This suggests that atrial focal activities may be the secondary phenomenon triggered by impulses originating from other regions, such as the PV.
REFERENCES