Pulmonary veins are considered to be the most common origin of the focal activity that triggers the onset of atrial fibrillation (AF). However, little is known about the importance of ectopic activity located outside the pulmonary veins. This study included 45 patients (8 women and 37 men, mean age 55 ± 12 years) with paroxysmal (n = 25) and persistent (n = 20) AF in whom multisite mapping of the right and left atria was performed using a 64-electrode basket catheter (n = 21) or a noncontact mapping system (n = 24). Spontaneous or orciprenaline-line-induced atrial premature complexes (APCs) were mapped. In all, 94 AF onsets from 38 distinct foci in 30 patients were observed and analyzed. Of these foci, 20 (53%) were located in pulmonary veins and 18 (47%) were located outside the pulmonary veins in other parts of the atria. In 22 patients (73%), AF was reproducibly induced by APCs from a single focus (59 episodes). In 8 patients (27%), AF originated from 2 distinct foci (35 episodes). Additionally, 20 of 30 patients (67%) who developed AF had APCs in different locations not inducing AF. APCs inducing AF had shorter coupling intervals than APCs not inducing AF (307 ± 54 vs 409 ± 76 ms, p <0.001). This study showed that 47% of ectopic foci triggering the onset of AF were located outside the pulmonary veins in extravenous parts of the left atrium and the right atrium, and 27% of patients had AF onsets of bifocal origin. These data challenge the current opinion that extrapulmonary foci play a minor role in inducing AF.

METHODS

Patient group: The study group consisted of 45 patients (mean age was 55 ± 12 years) with documented AF enrolled consecutively in the study. Twenty-five patients had paroxysmal AF (>2 episodes within the last month), and 20 had persistent AF (lasting ≥3 months). Structural heart disease was present in 28 patients (coronary artery disease in 10, arterial hypertension in 18, and no detectable structural heart disease in 17 patients). All patients included in the study had poor results with ≥2 antiarrhythmic drugs. All antiarrhythmic drugs were discontinued for ≥5 half-lives before the study and no patient had received amiodarone within the preceding 6 months. No patient with overt or concealed preexcitation was included in this study. The left and right atrial echocardiographic diameters were 53 ± 9 × 40 ± 8 mm and 50 ± 7 × 39 ± 6 mm, respectively. The presence of atrial thrombi was excluded by transesophageal echocardiography.

Characteristics of the mapping systems and deployment: All patients gave written, informed consent. Two global mapping systems were used: a 64-electrode basket catheter (Constellation, EP Technologies, San Jose, California) was used in 21 patients, and a
noncontact mapping system (EnSite, Endocardial Solutions Inc., St. Paul, Minnesota) was used in 24 patients. Details of deployment of the basket catheter and the noncontact mapping system in the right and the left atria have recently been reported by our group7,8 and other investigators.9,10 Mapping with a basket catheter was performed by obtaining 56 bipolar electrograms. The relation between basket catheter electrodes and the right and left atrial regions was defined by using radiopaque markers mounted on the splines (Figure 1A).

With use of the noncontact mapping system, the 3-dimensional geometry of the atria was constructed by maneuvering a steerable catheter into the chamber and by sampling location points over the endocardium. The sampled data were recorded on a Silicon Graphics workstation (Silicon Graphics Inc., Mountain View, California) at which >3,000 electrograms were reconstructed.

FIGURE 1. A, fluoroscopic view of basket catheters placed in the right and left atria in the left anterior oblique position (LAO 45°) and angiography of left upper pulmonary vein (LUPV). A and B mark the splines with a fluoroscopic identifier on the electrodes 8 (A) and 7 (B) in the right atrium (RA). The remaining splines are oriented in a clockwise direction with the basket as seen from the proximal aspect. For the left atrial basket, electrode pair G5–G6, which is located in the midposterior area of the left atrium (LA), marks the location of a focus that induced an AF episode (B). Angiography of the left upper pulmonary vein showed a close basket-tissue contact at the ostial region of this vein. B, spontaneous onset of an AF episode. Simultaneous recordings from 5 surface electrocardiographic leads, 2 intracardiac electrograms from the mapping catheter placed in the left upper pulmonary vein, and 128 bipolar electrograms from the right and left atria are presented. Annotations on the right side of the figure denote the anatomic position of the splines. The first beat is a sinus rhythm beat. The second beat is an APC inducing an AF episode. Earliest electrical activity is displayed in the electrode pair G5–G6, which corresponds to the position shown in A. Electrical activity recorded in the mapping catheter is late compared with the earliest spot of activation. ICV = internal cardioversion catheter; MV = mitral valve; TV = tricuspid valve.
Three-dimensional localization was enabled by selected emission of a low-amplitude 5.68-kHz current (locator signal) through the tip of a conventional ablation catheter. Anatomic positions of interest (e.g., pulmonary vein ostia, ablation sites) were labeled on the virtual geometry model (Figures 2 and 3).

**Biatrial mapping and provocative maneuvers:** As a first step, the basket catheter and the noncontact mapping balloon were deployed into the right atrium through 11Fr sheaths inserted from 1 of the femoral veins under local anesthesia. A 16-polar catheter (Pathfinder, Cardima, Fremont, California) was inserted into the coronary sinus. After deployment of the catheters in the right atrium and the coronary sinus, internal defibrillation was performed in patients with persistent AF using a single-lead system (Alert, EP MedSystems, West Berlin, New Jersey). In all patients in sinus rhythm, the right atrium and the coronary sinus recordings were continuously monitored and screened for spontaneous APCs. If APCs were of right atrial origin, the earliest activity spot was defined either in the basket catheter or noncontact mapping recordings.

As a second step, irrespective of the yield of right atrial mapping, the basket catheter and the noncontact mapping balloon were collapsed within the right atrium and deployed in the left atrium after a transseptal puncture. A quadripolar catheter with a 4-mm tip was inserted transseptally and used to map all pulmonary veins for local potentials and to perform radiofrequency ablation. Angiography of all 4 pulmonary veins was performed by injecting contrast medium via a catheter placed within the veins, and the ostial regions were marked.

If APCs occurred spontaneously, the earliest activation spot was defined in basket catheter recordings or virtual geometry maps, and a roving catheter was steered to this point under the fluoroscopic guidance or the locator signal. During mapping in the left atrium, an APC was considered as having a pulmonary vein origin if the earliest activity emerged from the respective ostial regions and the mapping catheter within the vein revealed a 2-component electrogram with a leading sharp potential. In this case, electrical activity in the pulmonary vein preceded any atrial electrograms in both atria. In contrast, an APC was
considered of extravenous origin if earliest activity was recorded or emerged from regions outside the pulmonary veins. In this case, the quadripolar mapping catheter was placed in the nearest vein to the observed extravenous onset, and the local potential recorded from this vein was late and had a proximal-to-distal activation sequence in the mapping catheter. If APCs did not occur spontaneously, provocative pacing and orciprenaline (at a starting dose of 0.5 \( \mu \text{g/min} \), with dose increments until the heart rate increased by 30\%) were used to provoke atrial ectopic activity.

Simultaneous 12-lead electrocardiograms and intracardiac electrograms were continuously acquired with a filter bandwidth of 30 to 500 Hz, digitized (1,000 samples/s) and displayed on a high-resolution monitor at a speed of 100 to 200 mm/s. Data were stored on an optical disk for retrieval and off-line analysis. In patients studied with the noncontact mapping system, all intervals containing APCs and onsets of AF were recorded. By following the spreading isopotential wave fronts, APCs were traced back to their origin or breakthrough site and labeled on virtual geometry. Anticoagulation was performed by a bolus administration of 5,000 IU of heparin, followed by continuous intravenous heparin infusion to maintain an activated clotting time at approximately 300 seconds.

**Radiofrequency ablation:** A focus-oriented approach was used for radiofrequency ablation. APCs triggering AF were primarily targeted. In patients with no inducible AF, all reproducibly monomorphic APCs were also targeted. Local potentials in the pulmonary veins were ablated in patients with no ectopic activity. In all other patients, no efforts were made to ablate "silent" pulmonary veins. For locations within the pulmonary veins, a preset temperature of 50°C and a maximal power of 20 to 25 W were used. For extravenous locations, the preset temperature and maximal power were 60°C and 30 W, respectively. Criteria for successful ablation were abolition of the spontaneous or orciprenaline-induced APCs emerging from the targeted focus, disappearance of the local potentials within the pulmonary veins during sinus rhythm and left atrial pacing, and the lack of provocation of APC-induced AF after provocative pacing and orciprenaline infusion. After discharge, patients were contacted by phone monthly, and whenever they reported palpitations, they were revisited. Twenty-four-hour Holter monitoring was performed at 1, 3, 6, and 12 months after discharge. Electrocardiographic documentation of AF during repeat visits or occurrence of AF episodes lasting >30 seconds in Holter recordings were considered as a recurrence.

**Statistical analysis:** Data are presented as mean ± SD, percentage, or range. For continuous data, a 2-tailed unpaired Student’s \( t \) test was used to test statistical difference. Discrete variables were compared by chi-square test or Fisher’s exact test. Differences were considered significant at a \( p \) value <0.05.

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**FIGURE 3.** Documentation of the ectopic focus inducing an AF episode in the region of the left upper pulmonary vein. Five electrocardiographic leads, intracardiac electrograms recorded from the mapping catheter (Map d and Map p), coronary sinus (Cs d and Cs p), right atrium (Cr d and Cr p), and 3 virtual electrograms are shown. Earliest spot of activation was observed in the region of the left upper pulmonary vein ostium. White arrow in the lower panel indicates the earliest activity during APC that induced the fibrillation episode. Abbreviations as in Figure 2.
RESULTS

At the time of electrophysiologic study, 20 patients had AF. Sinus rhythm was restored by internal defibrillation in all. During all procedures, 94 AF onsets were observed and analyzed. Internal cardioversion was used to terminate 63 episodes of AF (mean 9.5 ± 4 J), whereas 31 episodes converted spontaneously to sinus rhythm.

Anatomic location of APCs: After restoring sinus rhythm, a total of 96 foci in 42 patients fired spontaneously or after provocative pacing or orciprenaline infusion. AF episodes were triggered repeatedly by 38 foci (40%) in 30 patients. The remaining 58 foci did not trigger AF. Anatomic distribution of all mapped foci is shown in Table 1 and Figure 4. Of 96 foci, 77 (80%) emerged from the left atrium and 19 (20%) emerged from the right atrium. Thirty-one of 77 left atrial foci (40%) and 7 of 19 right atrial foci (37%) emerged from the right atrium. Thirty-one of 77 left atrial foci (40%) in 30 patients. The remaining 58 foci did not trigger AF. Anatomic distribution of all mapped foci is shown in Table 1 and Figure 4. Of 96 foci, 77 (80%) emerged from the left atrium and 19 (20%) emerged from the right atrium. Thirty-one of 77 left atrial foci (40%) and 7 of 19 right atrial foci (37%) emerged from the right atrium. Thirty-one of 77 left atrial foci (40%) were localized with a basket catheter. Of the foci located outside pulmonary veins, 31 (52%) were found in other parts of the left atrium. A total of 18 of 38 foci (47%) that triggered onset of AF had an origin outside the pulmonary veins (Table 1).

Examples of APCs of extravenous origin inducing AF are shown in Figures 1B and 2.

Fifty foci (52%) were mapped with the noncontact mapping, and 46 foci (48%) were mapped with a basket catheter. Of the foci located outside pulmonary veins, 31 (53%) were localized with noncontact mapping and 28 (47%) were localized with a basket catheter.

Relation between anatomic location and AF induction: Fifty-nine foci (61%) were located in atrial regions outside the pulmonary veins, and 37 (39%) were located inside the pulmonary veins (Figure 3). Foci located inside the pulmonary veins (20 of 37, 54%) induced AF more frequently than foci that had an extravenous origin (18 of 59, 30%; p = 0.037). When the left atrium was considered separately, again, a significantly higher proportion of the venous foci triggered onset of AF (20 of 37, 54%) than extravenous foci (11 of 40 foci, 27%; p = 0.03).

In 3 patients, after restoration of sinus rhythm, no APCs occurred spontaneously or after orciprenaline infusion or provocative pacing. Furthermore, 12 patients developed APCs in different locations, but none of them triggered the onset of AF episodes.

Coupling intervals of APCs: In total, APCs that induced AF had a shorter coupling interval than those that did not induce AF (307 ± 53 vs 409 ± 76 ms, p <0.001). A statistically significant difference between APCs inducing and not inducing AF was also observed for ectopic foci located in extravenous areas of the right and left atria (292 ± 49 vs 420 ± 78 ms, p <0.001) and the pulmonary veins (315 ± 54 vs 361 ± 61 ms, p <0.001). Coupling intervals of all APCs are shown in Figure 5.

Monomorphic and polymorphic origin of AF: A total of 94 AF onsets in 30 patients were studied. In 22 patients (73%), AF was induced reproducibly by APCs originated by a single focus (59 AF episodes). In the remaining 8 patients (27%), AF was induced by firing from 2 distinct foci, accounting for 35 AF episodes. Foci responsible for AF episodes of bifocal origin were located in 2 pulmonary veins (1 patient), in pulmonary veins and extrapulmonary areas (3 patients), and 2 extrapulmonary areas (4 patients). Patients having 2 different foci-inducing AF had significantly more overall ectopic foci (4.9 ± 1 vs 1.8 ± 1, p <0.001) than patients having a single focus-inducing AF. In 13 of 22 patients (59%) with unifocal origin of AF and in 7 of 8 patients (88%) with a bifocal origin of AF, additional APCs not inducing AF in different locations were observed. In 15 patients, no AF episodes were observed during electrophysiologic study.

Radiofrequency ablation: Radiofrequency ablation of foci-inducing AF was attempted in 28 patients (all 22 patients with a single focus and 6 of 8 patients with 2 foci-inducing AF). In 2 patients with bifocal origin of AF, radiofrequency ablation was not performed. With a mean of 18 ± 17 radiofrequency applications, suppression of the APCs that triggered AF was achieved in 18 of 22 patients with a single focus (81%) and in 4 of 6 patients with 2 foci (67%). Thus, an acute success rate of 79% was achieved. In 9 of 12 patients (75%) with no inducible AF, APCs could be suppressed successfully by radiofrequency ablation. In 2 of the remaining 3 patients, atrial flutter degenerating into AF was induced by burst pacing. In these patients, an isthmus ablation was performed. Mean fluoroscopy time and procedure durations were 73 ± 25 and 445 ± 100 minutes, respectively. In 3 patients with no ectopic activity after internal cardioversion, local potentials in pulmonary veins were ablated. No complication occurred during mapping or ablation procedures.

Follow-up data: Patients were followed for a mean of 371 ± 181 days. At the end of the follow-up period, 8 patients (32%) with paroxysmal AF were in stable sinus rhythm. Of them, 4 had a recurrence within 24 hours after the ablation procedure and underwent a second ablation before discharge. All patients with persistent AF developed recurrences during follow-up.

DISCUSSION

Main findings: The most important finding of this study was that 47% of discharging foci that induced AF were located outside the pulmonary veins. Our data are supported by several studies that have provided indisputable evidence on the existence of structures with auto-

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**TABLE 1 Biatrial Distribution of APCs**

<table>
<thead>
<tr>
<th></th>
<th>RUPV</th>
<th>LUPV</th>
<th>RLPV</th>
<th>LLPV</th>
<th>LA*</th>
<th>RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All foci (n = 96)</td>
<td>16 (17%)</td>
<td>11 (11%)</td>
<td>5 (5%)</td>
<td>5 (5%)</td>
<td>40 (42%)</td>
<td>19 (20%)</td>
</tr>
<tr>
<td>Foci-inducing AF (n = 38)</td>
<td>7 (18%)</td>
<td>5 (13%)</td>
<td>5 (13%)</td>
<td>3 (8%)</td>
<td>11 (29%)</td>
<td>7 (18%)</td>
</tr>
</tbody>
</table>

*LA* = denotes extravenous parts of the left atrium.

RUPV, LUPV, RLPV, LLPV = right upper, left upper, right lower, and left lower pulmonary veins, respectively; RA = right atrium; LA = left atrium.
matic function in the right and the left atria.\textsuperscript{11–14} Experimental and clinical studies have demonstrated that, besides pulmonary veins, other cardiac structures such as the ligament of Marshall,\textsuperscript{11,12} crista terminalis,\textsuperscript{13} and superior vena cava\textsuperscript{14} are electrically active and could generate impulses that could initiate atrial arrhythmias including AF. Furthermore, our study showed that in 27% of patients, onsets of AF were of bifocal origin.
This high incidence of multiple foci-inducing AF is supported by 2 recent studies.15,16 Hindricks and Kottlapp,15 using a noncontact mapping system, found that 8 of 17 patients with paroxysmal AF (47%) had from 2 to 4 foci per patient inducing AF. Kolb et al.16 using a 12-lead Holter monitoring system in patients with paroxysmal AF, found that 30% of patients with paroxysmal AF had AF episodes induced by APCs of different P-wave morphologies, suggesting a multifocal origin.

Another important finding of this study refers to the characteristics of APCs that trigger AF. A location preferably in the pulmonary veins and a shorter coupling interval appear to be important factors underlying the power of APCs to induce AF compared with APCs that did not induce AF. The exact factors that favor initiation of AF from impulses emerging from the pulmonary veins compared with other locations are unclear. However, the architecture of the posterior wall is complex, with intertwining and overlapping of fibers17,18 that could provide areas of conduction block, creating anatomically preferred circuits for reentry.

Previous studies have suggested that prematurity of APCs is critical to AF onset.19,20 In a recent study, Sakse et al.21 reported that APCs that induced AF had coupling intervals >100 ms shorter than APCs that did not induce AF. Our data confirm these findings and reaffirm that the degree of prematurity of APCs parallels aggressiveness of APCs to induce AF.

Implications: First, our data showed that an important fraction of foci capable of inducing AF are located outside the pulmonary veins. According to our data, extraneous foci contribute significantly to the induction of AF. Probably, if ignored by the mapping/ablation approach, they could explain, at least in part, the high recurrence rates reported by recent studies concentrating primarily on the pulmonary vein ablation approaches. Second, the finding that in more than one fourth of the patients, AF could have a multifocal origin may have implications for mapping/ablation approaches. Global mapping systems, such as those used in this study, could be particularly advantageous for patients with multifocal onsets.

Study limitations: Although extraneous foci were located anatomically within the atria, a direct connection between these foci and distinct extraneous anatomic structures, such as the ligament of Marshall or crista terminals could not be documented in this study. Because basket catheters are relatively bulk structures, one could raise the question that some extraneous foci could be mechanically induced by these devices. However, no differences in the number of APCs of extraneous origin were observed between patients studied with a basket catheter and those studied with a noncontact mapping system. A noncontact mapping balloon is not considered arrhythmogenic if properly placed. In prior studies with basket catheters in the atrium or in ventricles with more vigorous contraction and, as a consequence with a more pronounced basket-tissue friction,22 mechanically induced APCs were not reported. At the time of conception of this study, only the pulmonary veins disclosing automatic foci (mostly 1 vein) were targeted by radiofrequency ablation. This may explain the high recurrence rate of AF after ablation attempts targeting initiating triggers. In a recent study, Gerstenfeld et al.23 reported a 68% recurrence rate of AF by ablating the initiating triggers mainly in one of the pulmonary veins.