Multiple Arrhythmogenic Foci Associated With the Development of Perpetuation of Atrial Fibrillation

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Background—The presence of multiple arrhythmogenic sources may be associated with the perpetuation of atrial fibrillation (AF). In this study, we investigated the hypothesis that multiple foci might be involved in the development of AF persistency.

Methods and Results—Two hundred fourteen consecutive patients with AF undergoing catheter ablation were enrolled in this study. The location of the arrhythmogenic foci was determined using simultaneous recordings from multipolar catheters before and after pulmonary vein isolation during an isoproterenol administration. We detected 500 arrhythmogenic foci (263 foci as AF initiators, and 237 foci as non-AF initiators). High-dose isoproterenol infusions (ranging from 2 to 20 μg/min) revealed potential arrhythmogenic foci, especially non–pulmonary vein foci (55%). Persistent AF was more highly associated with an incidence of multiple (>2) foci than paroxysmal AF (88% versus 65%, P=0.002), and a multivariate analysis demonstrated that multiple foci (>2) were an independent contributing factor for persistent AF (odds ratio; 95% confidence interval, 4.69; 1.82 to 12.09, P<0.001). In paroxysmal AF, the number of foci was higher in patients with long-term AF (>24 hours) than in those with short-lasting AF (2.64±0.14 versus 1.77±0.16, P=0.001). In the persistent AF group, the patients with short-lasting AF (<12 months) had a greater number of foci than did those with long-term AF (>12 months) (3.62±0.15 versus 1.92±0.16, P=0.04).

Conclusions—Multiple foci were likely to be involved in the development of persistent AF. However, if AF persisted for >12 months, they may not have had a significant effect on the AF perpetuation. (Circ Arrhythm Electrophysiol. 2010; 3:39-45.)

Key Words: ablation ■ arrhythmia ■ cardioversion ■ catheter ablation ■ nervous system ■ sympathetic

In patients with atrial fibrillation (AF), some cases remain in a paroxysmal state long-term, whereas other cases easily develop persistent AF. Electric and structural changes due to AF perpetuation could help to promote its persistency; however, the mechanism of how AF transforms from paroxysmal to persistent AF remains unknown. It is possible that other unknown factors may also be associated with the development of AF persistency.

AF may be triggered by ectopy from the pulmonary veins (PVs) and/or non-PV foci.1-2 The mechanisms underlying the rapid activity from the PVs and non-PV foci may include enhanced automaticity, triggered activity, and localized microreentry, which may be involved in both the initiation and maintenance of AF.3-5 The presence of multiple triggers may facilitate the development of AF persistency because their presence may provide a greater chance of reintiating AF after spontaneous termination in patients with paroxysmal AF. Further, the site of the arrhythmogenic foci could also exhibit a more frequent activation during AF,6 and its triggered activity may become exaggerated under conditions of tachycardia remodeling due to rapid activation,7 which may imply the possibility of multiple arrhythmogenic foci as promoters of AF perpetuation. In this study, we investigated the hypothesis that the presence of latent multiple foci were associated with the development of AF persistency.

Study Population
The study population consisted of 214 consecutive patients with drug-refractory AF episodes who underwent radiofrequency catheter ablation (CA). The patients’ mean age was 61 years, 152 (71%) were male, and 44 (21%) had persistent AF. Persistent AF was defined as that lasting longer than 7 days, not self-terminating, and usually requiring medical intervention.5 Permanent AF, which was refractory to cardioversion or persisted for greater than 1 year, was also included in the persistent AF group. The patients were considered for ablation based on the presence of symptomatic AF resistant to ≥1 antiarrhythmic agents (AAAs). All AAAs were generally discontinu-
used for at least 3 days before the CA. Amiodarone was withdrawn at least 2 months before the procedure. The AF duration was defined as the longest-lasting AF episode assessed from the medical records, Holter ECG, and patient complaints if the episodes were symptomatic in the clinical setting. All patients provided written informed consent for the electrophysiological study and CA. This study was approved by our institutional review board.

Electrophysiological Study and Catheter Ablation

Transesophageal echocardiography was performed to exclude any left atrial (LA) thrombi. A 10-pole or 20-pole diagnostic catheter was positioned in the CS for pacing and recording. A 20-pole catheter was placed in the right atrium to cover the area along the crista terminalis or superior vena cava (SVC). The LA and PVs were accessed by a transeptal approach. We introduced 3 steerable catheters, including 2 spiral curve catheters, into the left atrium through a single transseptal puncture site. The PVs were mapped with a circumferential 10-pole or 20-pole catheter (IBI, Irvine, Calif). The surface ECG and intracardiac electrograms filtered between 30 to 500 Hz were recorded simultaneously with a polygraph (DUO EP Laboratory; Bard Electrophysiology, Lowell, Mass). A single 150 IU/kg bolus of heparin was administered after the transseptal puncture and repeated to maintain an activated clotting time of >300 seconds.

After the initial AF induction protocol, a PV isolation procedure was performed using a double circular mapping catheter technique. We confirmed the success of the electric PV isolation by monitoring the circumferential electric isation at the antrum level: approximately 1 cm from the ostium of both the right and left PVs. The complete disappearance of the potentials from all 4 PVs was confirmed in all patients. In the case of burst-inducible AF after the PV isolation procedure, an additional roof line was created. Then, additional radiofrequency (RF) energy applications were appropriately applied for any mitral isthmus–induced atrial tachycardia circuits and complex fractionated electric activity.

RF energy was delivered for 30 to 60 seconds at each site using an 8-mm tip catheter. The RF energy was delivered with the power limited to 35 W. The temperature was limited to 55°C (Japan Life Line Co, Ltd, Fantasista, Tokyo, Japan).

Protocol for Induction and Detection of the Arrhythmogenic Foci

At first, spontaneous arrhythmogenic foci in both atria were carefully mapped before the PV isolation procedure during an intravenous infusion of isoproterenol (ISP) without sedation. In the case of sinus rhythm, ISP was initially administered at 1 to 2 μg/min for at least 5 minutes, and then the dose was gradually increased to 20 μg/min while blood pressure was carefully monitored. If the blood pressure fell below 70 mm Hg, the increased dose of ISP was reversed to the g/min basal level. If AF persisted or spontaneously occurred under ISP, we attempted to cardiovert the AF up to 3 times. The DC induction maneuvers as in the initial protocol (up to 20 g/min) were repeated.

During the ablation procedure, the ISP administration was maintained at 1 to 2 μg/min basal level. If AF persisted or spontaneously occurred under ISP, we attempted to cardiovert the AF up to 3 times. The DC energy was delivered with an external biphasic waveform up to 270 J, and hence sinus rhythm was temporarily or successfully restored in all patients including permanent AF.

To detect the location of the arrhythmogenic foci, we simultaneously used 5 multipolar catheters to record the electrograms from the PVs and outside the PVs to search for any arrhythmogenic foci. A 20-pole catheter (2-mm interelectrode spacing) covered the area from the SVC to the crista terminalis, coronary sinus, and ostium of the left PVs. A roving catheter was located at the right superior PV ostium (Figure 1). If the arrhythmogenic foci were suspected to have originated from a non-PV area uncovered by the catheters, we attempted to search the location with a roving catheter followed by the previous mapping technique.2 Arrhythmogenic foci were defined as direct AF triggers or spontaneous reproducible atrial premature beats with coupling intervals of <350 ms or frequent repetitive firings (Figure 2).

Follow-Up

All patients were discharged home 3 days after the CA procedure and were seen in our hospital at 1- to 2-month intervals. The AF episodes after discharge were adequately assessed by the patients’ complaints, 12-lead ECG, and 24-hour Holter ECG recordings. AF recurrence was defined as the occurrence of atrial tachyarrhythmias after a 2-month blanking period after the CA procedure. After the CA, AAAs were given for 3 to 6 months to patients with long-lasting persistent AF or to those with paroxysmal AF and easily inducible residual AF. The mean follow-up period after the CA was 563 days (355 to 1052 days).

Statistical Analysis

The continuous variables with a normal distribution are expressed as mean±SD; data were compared by a Student t test. The number of foci were expressed as mean±SEM; percentage of the variables or the distribution was compared by a χ2 test. The variables without a normal distribution are expressed as the median (25th percentile, 75th percentile); data were compared by a Mann-Whitney U test, which was used for the nonparametric analysis. A logistic multivariate analysis was used to assess the relationship between the predictor variables and persistent AF, and backward selection using P<0.05 (Wald test) to stay was used to detect significant independent factors related to persistent AF. The possible confounding clinical factors (age, male sex, structural heart disease, hypertension, AF duration, atrial flutter, number of AAAs used, left ventricular ejection fraction, and left atrial diameter) related to the development of persistent AF and multiple (>2) foci were incorporated into the multivariate model. The relationship between multiple (>2) foci and AF recurrence was assessed by a log-rank analysis. A Cox proportional hazards analysis was used to assess the relationship between multiple (>2) foci and AF recurrence as multivariate analysis. P<0.05 was considered statistically significant. All
analyses were performed using SPSS 10.0 statistical software (SPSS, Inc, Chicago, Ill).

Results

Patient Characteristics

Patient characteristics are shown in Table 1. There were no significant differences in the mean age, structural heart disease, mean AF duration, clinical coexistence of atrial flutter, or number of prior AAAs between the paroxysmal and persistent AF groups. Male sex was significantly higher for persistent AF than paroxysmal AF. The left atrial diameter was significantly larger and left ventricular ejection fraction was significantly lower in patients with non-PV foci compared to those without non-PV foci.

Features of the Arrhythmogenic Foci

Table 2 demonstrates the clinical and electrophysiological characteristics of the arrhythmogenic foci. Five hundred arrhythmogenic foci were found. PV and/or non-PV foci were revealed in 210 of 217 (93.9%) patients, 263 foci (52.6%) in 174 patients (81.3%) were confirmed as direct AF triggers, and 237 foci (47.4%) in 150 patients (70.1%) exhibited reproducible prema-

ture atrial contractions with an interval of <350 ms or frequent repetitive firings. PV foci were detected in 195 of 214 patients (91.1%) and non-PV foci in 107 of 214 (50%), which accounted for one third of all the arrhythmogenic foci (164 of 500 foci). Foci from only PVs were detected in 95 of 214 patients (44.4%), both PVs and non-PV origins in 98 of 214 (45.8%), and only non-PV origins in 8 of 214 (3.7%). The locations of 142 non-PV foci included the left atrial posterior wall (31, 14%), superior vena cava (41, 21%), crista terminalis (16, 7.4%), lateral mitral area (15, 6.9%), left atrial roof (12, 4.6%), interatrial septum (7, 3.7%), coronary sinus (16, 7.4%), and other sites (4, 1.5%). Non-PV foci were documented before the PV isolation in 55 of 109 foci (50%) [left atrial posterior wall (13%, left atrial roof (24%), superior vena cava (77%), crista terminalis (38%), lateral mitral area (20%), interatrial septum (39%), and coronary sinus (38%)], and hence the roving catheter had to be relocated to search for the foci uncovered by the catheters in 58 of 214 patients (27%). The coupling interval of the PV foci was shorter than that of the non-PV foci (196 ± 68 versus 255 ± 90 ms, *P* < 0.001). The PV foci were significantly more associated with the occurrence of AF than non-PV foci (PV foci, 61% versus non-PV foci, 28%, *P* < 0.001). The total number of induced foci was higher in patients with non-PV foci than in those without (3.1 ± 1.7 versus 1.5 ± 1.4, *P* < 0.001).

Table 3 shows a comparison of the clinical characteristics between the patients with and without direct AF triggers. The AF patients with structural heart disease included a significantly lower incidence of foci related to the AF initiation than those without structural heart disease (22% versus 38%, *P* = 0.039). There was no significant impact of the mean age, male sex, mean AF duration, number of prior AAAs, left atrial diameter, or left ventricular ejection fraction on direct AF triggers.

Figure 3 demonstrates the association between the inducibility of PV/non-PV foci and the ISP dose. Non-PV foci were induced 15% of the time with no ISP, 30% with 1 to 2 µg/min, and 55% with 2 to 20 µg/min. PV foci were revealed 25% of the time with no ISP, 43% with 1 to 2 µg/min, and 32% with 2 to 20 µg/min. The distribution of the inducibility according to the ISP dose significantly differed between PV foci and non-PV foci (*P* < 0.001).
Comparison of the Arrhythmogenic Foci Between Paroxysmal and Persistent AF

Table 4 shows the comparison of the arrhythmogenic foci features between paroxysmal and persistent AF. The incidence of PV foci and foci from the left atrium did not significantly differ between paroxysmal and persistent AF. The incidence of non-PV foci, total number of foci, number of non-PV foci, incidence of foci in the right atrium, and incidence of multiple foci was significantly higher in the persistent AF than paroxysmal AF patients. A multivariate analysis demonstrated that multiple foci were one of the independent factors to persistent AF as well as the left atrial diameter (Table 5).

Number of Foci and AF Duration

Figure 4 shows the comparison of the number of induced foci between paroxysmal and persistent AF. The number of induced foci was significantly higher after >24 hours than <24 hours (1.77±0.16 versus 2.64±0.14, P=0.001) in the patients with paroxysmal AF and significantly higher after 1 year than >1 year (3.62±0.15 versus 1.92±0.16, P=0.038) in those with persistent AF. As a result of comparing the incidence of AF arising from PVs and non-PV foci between paroxysmal and persistent AF, PV foci were observed in 86% after >24 hours, in 94% within <24 hours in the patients with paroxysmal AF, in 96% within <1 year, and in 86% after >1 year in the patients with persistent AF. Non-PV foci were observed in 32% after >24 hours, in 58% within <24 hours in the paroxysmal AF patients, in 66% after <1 year, and in 59% after >1 year in the persistent AF patients.

Procedural Outcome

All foci from the PVs were successfully delineated by the PV electric isolation procedure, and 109 of 146 (75%) non-PV foci could be delineated at the end of the CA (Table 2). AAAs...
were administered in 32% of the patients after the CA. The use of AAAs was significantly higher in patients with non-PV foci than in those without (42% versus 26%, \( P<0.001 \)). AF recurrence was observed in 22% of the patients with PV foci and in 28% with non-PV foci. AF recurrence was significantly higher in patients with multiple (>2) foci than in those without (total; 26% versus 11%, \( P=0.024, [22\% \text{ versus } 14\%], \ P=0.16 \) in paroxysmal AF, 26% versus 19%, \( P=0.630 \text{ in persistent AF} \)). After adjusting for persistent AF and the duration of the AF episodes, the hazard ratio of multiple foci being related to AF recurrence revealed that those foci were not a significant related factor for AF recurrence (2.03 [0.92 to 3.76], \( P=0.106 \)).

**Discussion**

In this study, we examined the features of the induced arrhythmogenic foci and assessed the implications of multiple foci in AF persistency. We detected PV foci in 195 of 214 patients (91.1%), and non-PV foci were highly revealed in 107 of 214 patients (50%); which accounted for one third of all the inducible foci. The number of foci was significantly higher in the persistent than paroxysmal AF patients, and multiple foci were an independent related factor for persistent AF. The duration of the longest AF episodes was determined by the patient statements or medical records. The number of foci was significantly higher after >24 hours than within <24 hours (1.77±0.16 vs 2.64±0.14, \( P<0.001 \)) in the patients with paroxysmal AF and significantly higher within <1 year than after >1 year (3.62±0.15 vs 1.92±0.16, \( P=0.038 \)) in the patients with persistent AF. These findings may suggest that the presence of multiple foci may facilitate the progression from paroxysmal to persistent AF, and long-lasting AF might reduce the significance of the arrhythmogenic foci in the perpetuation of AF. Number of foci is expressed as mean±SEM.

AF. Increased foci were associated with foci from non-PV lesions, which could be revealed by using a high dose ISP administration. An increased number of foci was significantly associated with a longer AF duration in the patients with paroxysmal AF, whereas it was significantly associated with a shorter AF duration in the patients with persistent AF. Thus, these findings may suggest the possibility that transient increased foci may facilitate the development of a transition from paroxysmal to persistent AF; however, the significance of that may gradually become reduced as long-lasting AF develops.

**Multiple Triggers and AF Persistency**

The presence of multiple triggers may provide a greater chance of reinitiating AF after the spontaneous termination and may help the AF persistency progress from a paroxysmal to persistent state. Meanwhile, the increased triggered activity from multiple sites as the cause of AF persistency may beget AF perpetuation by creating new wavelets and decreasing the likelihood of AF termination.

Dispersion of the atrial refractoriness is also an essential element for AF persistency. The increased atrial dispersion is likely to be associated with the progression from paroxysmal to persistent AF, and a reversal of the atrial dispersion by biatrial resynchronized pacing may prevent the development of AF persistency. Ventricular premature beats could promote an increased dispersion of the ventricular refractoriness, and polymorphic premature beats exhibiting multiple origins may increase the risk of ventricular fibrillation with remodeled heart disease. These observations may provide a clue as to why multiple triggers are associated with the development of the fibrillatory process in AF persistency.

**PV/Non-PV Foci as AF Triggers and Involvement in the Perpetuation of AF**

AF is mainly initiated by PV triggers, and a rapidly firing source located within the PVs could be responsible for...
initiating, and in some cases, maintaining arrhythmias in patients with AF. The mechanism underlying such rapid discharges from PVs, including enhanced automaticity or triggered activity mechanisms may be involved in the initiation of AF. Further, the PV circumference is also most likely important for sustaining the reentry for maintaining AF and may also provide a substrate that is suitable for a possible reentrant mechanism, which could potentially promote a condition for persistent AF.

Non-PV foci could arise from the superior vena cava, left atrial posterior free wall, crista terminalis, ostium of the coronary sinus, interatrial septum, or Marshall bundle with an incidence of those ranging from 3.2% to 47%. The predominant non-PV triggering sites have a slow diastolic depolarization that enhances spontaneous depolarization, and the triggered activity of the non-PV triggers could also be involved in the onset and perpetuation of AF. Previous studies have reported that triggered activity with delayed afterdepolarizations has been documented in the superior vena cava, coronary sinus, ligament of Marshall continuous with the muscular sleeve around the coronary sinus, atrial muscle that extends into the mitral valve, and working muscle.

Because triggered activity is likely to occur in the presence of underlying disease such as cardiomyopathy, the development of the atrial remodeling process may enhance the triggered activity of PV/non-PV lesions. A previous study reported that multiple PV arrhythmogenic foci may be associated with an older age, longer AF duration and larger atrial dimensions. LA enlargement predisposes the atrium to LA posterior wall triggers, and persistent AF is more frequently triggered by foci from the LA side of the LA-PV junction than is paroxysmal AF.

**Induction of Arrhythmogenic Foci**

The incidence of PV/non-PV foci may be influenced by the induction maneuvers. PV arrhythmogenicity is enhanced by neurohumoral stimulation with acetylcholine or isoproterenol. The relationship between the precise ISP dose and arrhythmogenic inducibility remains unknown; however, the majority of PV/non-PV foci may be revealed during a high dose isoproterenol administration of up to 20 μg/min or after cardioversion of AF. High-dose ISP often invokes vagally mediated nerve reflex bradycardia, which appears to cause an increased arrhythmogenicity due to autonomic nerve competition.

In this study, non-PV foci could be induced in 55% of the patients and PV foci in 32% when the ISP dose ranged from 2 to 20 μg/min. Non-PV foci were detected in half the patients and accounted for one third of all arrhythmogenic foci. Although high-dose ISP could increase the ratio of detection of both PV and non-PV foci, the dose of the ISP was significantly higher for the non-PV foci than the PV foci. The predominant non-PV trigger sites appeared to be associated with anatomic structures such as the crista terminalis or ligament of Marshall, which are known to be catecholamine sensitive structures, which may explain why the a relatively high dose of ISP was required to induce non-PV foci.

**Comparison of the Pathogenesis Between Paroxysmal and Persistent AF**

Because PVs are major sites of AF initiation and maintenance in patients with paroxysmal AF, PV isolation is the cornerstone of the treatment of paroxysmal AF, with a 65% to 85% success rate. Compared with paroxysmal AF, the mechanisms underlying persistent AF are more complex and multifactorial. Although PVs remain as the dominant source of the maintenance of persistent AF, macroreentrant and microreentrant mechanisms are involved in AF perpetuation. The development of a remodeled atrium due to AF perpetuation could promote the multifactorial evidence for maintaining AF.

A recent study demonstrated that rapid focal activity in the LA and PVs, demonstrated by epicardial mapping, implied the potential role of focal atrial activity in the maintenance of AF, and the localized fibrillating sources that demonstrated an identical pattern of centrifugal activation were successful targets for catheter ablation. These continuous or intermittent focal activities were commonly demonstrated in patients with paroxysmal and persistent AF, and, although the mechanisms of these focal activities could not be specified, triggered activity or abnormal automaticity may be the cause of the mechanism. Whether or not the location of the arrhythmogenic foci is related to those sites with focal activity remains unknown; however, there is the possibility that the mechanism of enhanced triggered activity due to AF persistency may promote the sustainability of AF.

Long-lasting AF perpetuation eventually leads to structural changes within the atria, and the structural changes, including left atrial dilation, further increase the fibrotic process with the deposition of increased amounts of connective tissue that promote the consistency and prolongation of the atrial conduction, which maintains macroreentrant AF. The data from our study support that process as a result of long-lasting AF perpetuation, because the significance of the arrhythmogenic foci on the AF perpetuation was less in the patients with long-lasting AF (>1 year) than in those without (<1 year).

**Study Limitations**

The AF duration was determined according to the patient’s symptoms. Therefore, we could not evaluate the asymptomatic AF episodes in this study.

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**Disclosures**

None.

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CLINICAL PERSPECTIVE

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