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# Difference in the maintenance mechanism of atrial fibrillation perpetuated after pulmonary vein isolation between paroxysmal and persistent atrial fibrillation: Effects of subsequent stepwise ablation☆

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ABSTRACT

*Background:* Neither the atrial fibrillation (AF) maintenance mechanism after pulmonary vein isolation (PVI) nor the mechanism of AF termination via stepwise ablation is clearly understood.
*Methods:* Among 226 consecutive AF patients (154 paroxysmal (P-AF) and 72 persistent AF (Per-AF) patients), left atrial endocardial non-contact mapping was performed after PVI in the initial 10 P-AF and 16 Per-AF patients to define the AF maintenance mechanism. Subsequently, effect of stepwise catheter ablation (linear roof lesion and complex fractionated atrial electrogram (CFAE) following PVI) was evaluated in all patients.
*Results:* After PVI, AF was maintained by the activation around isolated PV/mitral annulus, focal discharge and disorganized activations mostly observed over residual CFAE region (pivoting activation, wave break and fusion). CFAE region in P-AF was smaller than Per-AF after PVI ($1.6 \pm 2.1$ vs. $7.7 \pm 2.5$ cm$^2$, $p < 0.0001$). The frequency of pivoting activation, wave break and fusion in P-AF were lower than those in Per-AF ($1.9 \pm 2.0$ vs. $11.8 \pm 5.0$ times/s; $p < 0.0001$, $0.1 \pm 0.3$ vs. $3.6 \pm 2.5$ times/s; $p < 0.001$, $5.8 \pm 3.6$ vs. $9.8 \pm 3.2$ times/s; $p < 0.01$). AF termination was more frequent in P-AF than Per-AF (94.8% vs 81.9%, $p = 0.0019$). AF termination by PVI alone was more frequent in P-AF than Per-AF (85.6% vs. 18.6%, $p < 0.0001$). However, AF termination via roof line and/or CFAE ablation was less frequent in P-AF than Per-AF (14.4 vs. 81.4%, $p < 0.0001$).
*Conclusions:* Disorganized activations after PVI, more prominent in Per-AF, were associated with residual CFAE region. Most P-AF was terminated by PVI alone, however additional roof line lesion and CFAE ablation were necessary to terminate Per-AF, consistent with mapping results.



## 1. Introduction

Pulmonary vein (PV) isolation (PVI) has become a widely accepted strategy for catheter ablation of atrial fibrillation (AF) [1,2]. PVI has resulted in high procedural success rates for paroxysmal AF (P-AF) [3,4], but success rates for PVI alone are often lower in patients with persistent AF (Per-AF) [5]. Thus, various ablation strategies, such as those targeting complex fractionated atrial electrogram (CFAE) region, linear roof lines or mitral lines and their combinations, have been performed [6–8]. However, the precise mechanisms of disorganized activation perpetuated after PVI have not yet been well clarified; moreover, the mechanism of AF termination via stepwise ablation remains to be elucidated.

The purpose of this study was to define the mechanism of AF perpetuation after PVI and clarify its difference between patients with P-AF and Per-AF. We also examined how stepwise ablation terminates AF. Previously, we demonstrated that CFAE region plays an important role for the initiation and maintenance of AF before ablation [9,10]. We therefore hypothesized that CFAE region also plays important roles even after PVI. Thus we initially examined the mechanisms of AF perpetuation after PVI, especially in relation to the respective CFAE region. Then, we elucidated the usefulness of stepwise ablation, including PVI, roof line lesion and CFAE ablation on the termination of AF and maintenance of sinus rhythm.

## 2. Methods

### 2.1. Patients

The study subjects were 226 consecutive patients with AF who were referred for radiofrequency catheter ablation of AF (162 men and 64 women; mean age, $62.4 \pm 9.4$ years, range, 27–79 years). There were 154 patients with P-AF (P-AF group) and 72 patients with Per-AF (Per-AF group) (Table 1). The mean age of the P-AF group was older

*Abbreviations:* AF, atrial fibrillation; AFL, atrial flutter; AT, atrial tachycardia; CFAE, complex fractionated atrial electrogram; FIRM, focal impulse and rotor modulation; LA, left atrium; P-AF, paroxysmal AF; Per-AF, persistent AF; PV, pulmonary vein; PVI, pulmonary vein isolation.

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**Table 1**
Patient characteristics.

| | Paroxysmal AF group (n = 154) | Persistent AF group (n = 72) | p value |
|---|---|---|---|
| Age (year) | 63.5 ± 8.6 | 60.2 ± 10.5 | p < 0.05 |
| Sex | 100 male | 62 male | p < 0.01 |
| History of AF (month) | 41.5 ± 36.1 | 70.4 ± 47.8 | p < 0.0001 |
| Long-standing persistent AF | (−) | 18 (25%) | p < 0.0001 |
| No. AADs before ablation | 1.1 ± 0.2 | 1.0 ± 0.2 | NS |
| Amiodarone, n (%) | 0 | 0 | NS |
| Hypertension, n (%) | 99 (64.3%) | 43 (59.7%) | NS |
| Diabetes mellitus, n (%) | 16 (10.4%) | 2 (2.8%) | p < 0.05 |
| Structural heart disease | | | |
| CAD, n (%) | 4 (2.6%) | 3 (4.2%) | NS |
| Cardiomyopathy/valvular HD, n (%) | 0 | 0 | NS |
| LVEF (%) | 64.2 ± 4.9 | 60.6 ± 6.6 | p < 0.0001 |
| LAd (mm) | 35.9 ± 5.1 | 40.8 ± 4.6 | p < 0.0001 |
| CHADS2 score | 1.1 ± 1.0 | 1.0 ± 1.0 | NS |

AF = atrial fibrillation, AAD = antiarrhythmic drug, CAD = coronary artery disease, HD = heart disease, LAd = left atrial dimension, LVEF = left ventricular ejection fraction.

than that of the Per-AF group. Male gender was less frequent in the P-AF group. The AF history in the P-AF group was shorter than that in Per-AF group (Table 1). Eighteen long-standing AF patients are included in the Per-AF group (Table 1). There was no significant difference in the number of anti-arrhythmic drugs used before ablation between the P-AF and Per-AF groups (Table 1). Amiodarone was not used in any of the patients. Prevalence of hypertension was not different between the P-AF and Per-AF groups (Table 1). Diabetes mellitus was observed more often in the P-AF group, but no difference was found as regards structural heart disease (Table 1). The echocardiographic left ventricular ejection fraction in P-AF group was higher than that in the Per-AF group. The left atrial dimension in the P-AF group was smaller than that in the Per-AF group (Table 1). There was no difference in the CHADS2 score between the 2 groups (Table 1). Written informed consent was obtained from each patient. The protocol was approved by the Kumamoto University Hospital Human Research Committee.

### 2.2. Electrophysiological study

All antiarrhythmic agents were discontinued 5 half-life periods before the procedures. In total, 6-Fr 20-pole and 6-Fr quadripolar electrode catheters (St. Jude Medical, MN) were percutaneously inserted from the right jugular and left femoral veins and positioned in the coronary sinus and right ventricular apex, respectively. Two to three 8-Fr long sheaths (St. Jude Medical) were inserted from the right femoral vein and advanced into the left atrium (LA). After a transseptal puncture was achieved, systemic anticoagulation was achieved utilizing intravenous heparin to maintain an activated clotting time of between 300 and 350 s. After left atriography, a 7-Fr 20-pole circular mapping catheter (Inquir Optima; St. Jude Medical) was positioned in either the left or right superior PV and a 7-Fr large-tip (3.5 mm in length) irrigated ablation catheter (Cool Path Duo; St. Jude Medical) was used for ipsilateral PVI. Bipolar electrograms were filtered between 50 and 600 Hz and recorded along with the surface electrocardiograms using polygraph (EP-workmate; EP Med. Systems, Inc., Mt. Arlington, NJ). Pacing was performed using a cardiac stimulator (SEC-4103; Nihon Kohden, Tokyo).

### 2.3. Study protocol

#### 2.3.1. Non-contact mapping of the LA

In the initial 26 patients (P-AF; 10 patients, Per-AF; 16 patients), non-contact mapping of the LA was performed. In these 26 patients, one 8-Fr long sheath in the right femoral vein was exchanged for a 10-Fr sheath. A 9-Fr multi-electrode array catheter (EnSite 3000; St. Jude Medical, MN) was introduced into the LA via a 10-Fr sheath, deployed on a 0.032-inch guide wire with its distal tip fixed in the left superior PV. Endocardial mapping of the LA was performed using a non-contact mapping system (EnSite 3000; St. Jude Medical, MN). The details of the EnSite 3000 System have been described previously [9].

The location of the CFAE region was identified before and after PVI by contact and/or non-contact virtual unipolar and the virtual Laplacian bipolar electrograms [9,10]. The CFAE was defined with the following criteria [6]: 1) atrial electrograms with fractionated electrograms composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-second recording period; and, 2) atrial electrograms with a very short cycle length (<120 msec) averaged over a 10-second recording period. The location of the CFAE region was agreed upon by two independent observers.

Activation mapping of the LA was performed after PVI utilizing the above non-contact mapping system. The location and frequency of focal discharge, pivoting activation, where waves turned around at the end of arcs of the functional block, wave break and fusion were analyzed, especially in relation to the CFAE region. Activation from a focal discrete source, with radial dispersion of activation, was identified as a focal discharge [9,10]. Wave break was defined when the wave front split into different independent wave fronts [9,10]. Wave fusion was defined when different independent wave fronts were fused into a new wave front [9,10]. Pivoting activation was defined as wave propagation when the wave front changed its direction over 90° [9,10]. These parameters were compared between the P-AF and Per-AF groups.

#### 2.3.2. Catheter ablation

Radiofrequency catheter ablation was performed in a stepwise fashion using AF termination as a procedural endpoint in all patients. First, the ipsilateral PV antrum was isolated during AF. If this failed to terminate AF, a linear roof line lesion, joining the right and left superior PVs, was created, and then CFAE-targeted ablation was performed in a stepwise fashion. If the AF was not terminated by CFAE ablation in the LA, CFAE ablation in the coronary sinus was then performed in some patients. Mitral isthmus ablation was not performed because achieving a complete bidirectional conduction block is often difficult and an incomplete ablation line increases the risk of recurrence of atrial flutter [11]. AF termination was defined when the AF directly converted to a sinus rhythm or regular atrial tachycardia (AT) occurred. If AF converted to regular AT or failed to terminate, external electrical cardioversion was used to restore a sinus rhythm. Radiofrequency energy (20 to 40 W for 30 to 120 s) was delivered with a temperature limit of 40 °C, using a cardiac ablation generator (IBI-1500 T12; St. Jude Medical) in combination with a 7-Fr large-tip (3.5 mm in length) irrigated ablation catheter with a flow rate set at 16 ml/min (Cool Path Duo; St. Jude Medical).