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# Post-shock sinus node recovery time is an independent predictor of recurrence after catheter ablation of longstanding persistent atrial fibrillation

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ABSTRACT

*Background:* Electro-anatomical remodeling of the atria has been reported to be associated with sinus node dysfunction in patients with atrial fibrillation (AF). We hypothesized that post-shock sinus node recovery time (PS-SNRT: the time from cardioversion to the earliest sinus node activation) is related to the degree of left atrial (LA) remodeling and the clinical outcome of radiofrequency catheter ablation (RFCA) in patients with longstanding persistent AF (L-PeAF).

*Methods and results:* We included 117 patients with L-PeAF (82.0% males, $55.4 \pm 10.7$ years old) who underwent RFCA. PS-SNRTs were measured after internal cardioversion (serial shocks 2, 3, 5, 7, 10, and 15 J) before RFCA. All patients underwent the same ablation design, and we compared regional LA volume (3D-CT imaging) and LA voltage (NavX). Results: 1. During the $13.5 \pm 5.8$-month follow-up period, it was noted that the patients with recurrent AF 3 months after RFCA ($n = 31$) had longer PS-SNRTs ($1622.90 \pm 1196.92$ ms vs. $1112.53 \pm 690.68$ ms, $p = 0.005$) and greater anterior LA volume ($p = 0.032$) than those who remained in sinus rhythm. 2. The patients with PS-SNRT $\geq 1100$ ms showed lower AF-free rates (58.3%) compared to those with PS-SNRT $<1100$ ms (89.5%, $p<0.001$). However, shock energy, number of cardioversion, and LA volume were not different between two groups. 3. Multivariate Cox regression analysis demonstrated PS-SNRT $\geq 1100$ ms was a significant predictor of clinical recurrence of AF (HR 5.426, 95% CI 2.099–14.028, $p<0.001$).

*Conclusion:* In patients with L-PeAF, prolonged PS-SNRT is an independent predictor of clinical recurrence of AF after RFCA, but not closely associated with electro-anatomical remodeling of LA.



## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice and is associated with high morbidity and mortality [1]. Radiofrequency catheter ablation (RFCA) of AF is known to be more effective in maintaining sinus rhythm compared to anti-arrhythmic drugs (AAD), but the recurrence rate of AF after RFCA during long-term follow-up is substantial [2,3]. The persistence of AF is associated with electro-anatomical remodeling [4,5] and sinus node dysfunction [6], and the degree of atrial remodeling has been reported to be a predictor of clinical recurrence of AF after catheter ablation [7]. As electro-anatomical remodeling progresses, atrial chambers expand, endocardial voltage decreases, and conduction time lengthens [8].

The left atrial (LA) volume index is highest in patients with longstanding persistent AF (L-PeAF) compared to those with paroxysmal AF (PAF) or controls [9]. We previously noted that enlargement of the volume of the anterior portion of the LA and low endocardial voltages was associated with AF recurrence after RFCA [7]. Additionally, right atrial volume has incremental and additive prognostic power with regard to AF recurrence after catheter ablation [10]. However, the association between sinus node dysfunction, the degree of LA remodeling, and clinical outcomes after AF ablation have not yet been determined. We hypothesized that the degree of sinus node dysfunction measured by post-shock sinus node recovery time (PS-SNRT) might be associated with the degree of electro-anatomical remodeling of the LA and could also predict clinical recurrence after catheter ablation of AF in patients with L-PeAF.

## 2. Methods

### 2.1. Study population

The study protocol was approved by the Institutional Review Board of Yonsei University Health System. All patients provided written informed consent. We included 117 patients with L-PeAF (82.0% males, $55.4 \pm 10.7$ years old) who underwent RFCA. L-PeAF was defined as electrocardiographically documented AF episodes lasting longer than 1 year that required cardioversion [11]. All those patients recurred to AF within 2 weeks after electrical cardioversion in spite of concomitant anti-arrhythmic drug. All patients had drug-refractory, recurrent AF after external electrical cardioversion, and the study's exclusion criteria were as follows: 1) AF refractory to electrical cardioversion; 2) PAF or sinus rhythm at the beginning of the procedure; 3) LA size >55 mm as measured by echocardiography; 4) AF with rheumatic valvular disease; and 5) prior

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AF ablation. All patients stopped anti-arrhythmic drugs (AAD) and digoxin for a period corresponding to at least five half-lives prior to catheter ablation. In total, 45 patients (38.5%) were taking amiodarone, which was discontinued for at least four weeks prior to the procedure. Anticoagulation therapy was maintained before catheter ablation, and β-blocker therapy was continued in 26/117 patients (22.2%) with associated coronary artery disease or heart failure (Table 1).

### 2.2. Electrophysiologic mapping and post-shock sinus node recovery time

Intracardiac electrograms were recorded using the Prucka CardioLab™ electrophysiology system (General Electric Health Care Systems Inc., Milwaukee, WI, USA), and catheter ablation was performed in all patients using 3-D electro-anatomical mapping (St. Jude Medical Inc., Minnetonka, MN, USA) merged with 3-D spiral computed tomography (CT). Before starting RF ablation, AF was terminated with internal cardioversion utilizing a biphasic shock with R wave synchronization (Lifepak12, Physiocontrol Ltd.).An anodal decapolar catheter (WOVEN diagnostic catheter, Bard Electrophysiology, Lowell, MA, USA) was placed in the right atrium and a cathodal duo-decapolar catheter (St. Jude Medical Inc., Minnetonka, MN, USA) was placed inside the coronary sinus (CS; Fig. 1A). We initiated shock energy from 2 J to 15 J (serial shocks 2, 3, 5, 7, 10, and 15 J), and waited for 5 min before increasing the shock energy due to failed cardioversion. We then evaluated post-shock sinus node recovery time (PS-SNRT), defined as the time interval between the internal electrical cardioversion and the earliest sinus node activation time (Fig. 1B).

### 2.3. Radiofrequency catheter ablation

All patients initially underwent bilateral circumferential antral ablation with electrical pulmonary vein (PV) isolation (circumferential PV isolation; CPVI) with an open irrigation deflectable catheter with a 3.5-mm tip (Celsius, Johnson & Johnson Inc., Diamond Bar, CA, USA; irrigation flow rate 20 to 30 mL/min; 25–35 W; 47 °C). If the sinus rhythm was maintained after CPVI, then we generated a LA 3-D electro-anatomical voltage map by obtaining contact bipolar electrograms from 350 to 400 points on the LA endocardium during high right atrial pacing with a cycle length of 500 ms, as previously described by Park et al. [12]. We conducted CPVI, cavo-tricuspid isthmus (CTI) block, roof line, and posterior inferior line as a routine lesion set in all patients (Fig. 1C). If AF is reinitiated after routine linear ablation, then we generated an anterior line [12,13] and performed complex fractionated atrial electrogram (CFAE) ablation (Fig. 1D). If AF persisted after the aforementioned ablation protocol, then we stopped the procedure after internal cardioversion. The end point of our procedure was to get to the point of no immediate recurrence of AF after cardioversion with isoproterenol infusion (5–10 μg/min). If there were non-PV foci under isoproterenol, then we ablated them all.

### 2.4. Post-ablation follow-up

Patients visited the outpatient clinic regularly at 1, 3, 6, 9 and 12 months after RFCA, and then every 6 months thereafter or whenever symptoms occurred after RFCA. All patients underwent electrocardiography (ECG) at every visit, and 24- to 48-hour Holter recording and/or event recorder monitoring was performed at the 3, 6, and 12 month visits after RFCA. All patients discontinued their AADs after RFCA, but AADs were prescribed again to patients whose atrial arrhythmias recurred or who experienced highly symptomatic, frequent atrial premature beats. After the third month post-RFCA, AADs were maintained in 26/117 patients (22%). Clinical recurrence was defined as AF documented on ECG, or atrial tachycardia of at least 30 s in duration after the 3-month blanking period during follow-up [14]. The mean follow-up duration was 13.5 ± 5.8 months.

### 2.5. Off-line volumetric analysis of 3D spiral CT imaging and voltage maps

3D spiral CT images of the LA were analyzed on an image processing workstation (Aquarius, Terarecon Inc., USA). Each LA image was divided into three portions: the venous LA (posterior LA including the antrum and posterior wall), the anterior LA (excluding the LA appendage [LAA] and venous LA), and the LAA [15]. The absolute volumes of each portion were calculated, standardized by dividing by body surface area (BSA, ml/m$^2$), and compared. We analyzed the color-coded voltage maps of both the anterior–posterior (AP) and posterior–anterior (PA) views that had been converted to image files. The percent area occupied by each color area was calculated using customized software, and referenced to color scale bars. PVs were not included in the analysis [12].

### 2.6. Data analyses

The normally distributed continuous variables were expressed as a mean ± standard deviation (SD). We compared the mean LA volume/BSA (ml/m$^2$), which included the anterior LA/BSA (ml/m$^2$), venous LA/BSA (ml/m$^2$) and LAA/BSA (ml/m$^2$), to the mean LA voltage (mV), conduction velocity (m/s), and PS-SNRT (ms) between patients with clinical recurrence and those without using an independent two sample *t*-test for normally distributed continuous variables, and $\chi^2$ testing for categorical variables. Statistical significance was defined as a p-value <0.05. Cox regression analysis was used to determine the predictive value of each variable with regard to AF recurrence. Variables selected for multivariate analysis were those with p-value <0.2 on univariate analysis or with having association with AF recurrence clinically. And if there was significant correlation between selected variables (R > 0.5), only one variable was used to avoid multicolinearity for multivariate regression analysis. The AF-free rate was determined by the log-rank test using the Kaplan–Meier method. The cut off values for PN-SNRT and anterior LA/BSA, which best differentiate recurrence and no recurrence, were determined by an algorithm of maximization of hazard ratio [16].

**Table 1**
Baseline characteristics of patients with PS-SNRT ≥ 1100 ms and <1100 ms.

| | PS-SNRT ≥ 1100 ms (n = 60) | PS-SNRT < 1100 ms (n = 57) | p-Value |
|---|---|---|---|
| Age (years) | 55.8 ± 10.2 | 55.0 ± 11.2 | 0.693 |
| Male (n, %) | 47 (78.3%) | 49 (86%) | 0.282 |
| Body mass index (kg/m$^2$) | 25.08 ± 2.81 | 25.19 ± 2.56 | 0.816 |
| CHADS2 score | 0.92 ± 1.11 | 0.95 ± 1.03 | 0.877 |
| Heart failure (n, %) | 3 (5.0%) | 1 (1.8%) | 0.334 |
| Hypertension (n, %) | 28 (46.7%) | 31 (54%) | 0.404 |
| Age > 75 years (n, %) | 2 (3.3%) | 0 | 0.164 |
| Diabetes (n, %) | 8 (13.6%) | 7 (12.3%) | 0.837 |
| Stroke/TIA (n, %) | 5 (8.3%) | 7 (12.3%) | 0.482 |
| Medication before RFCA | | | |
| ARB or ACEi (n, %) | 12 (20.0%) | 21 (36.8%) | 0.043 |
| β-Blocker (n, %) | 16 (26.7%) | 10 (17.5%) | 0.235 |
| Statin (n, %) | 11 (18.3%) | 9 (16.1%) | 0.747 |
| Echocardiographic findings | | | |
| LA size (mm) | 44.13 ± 5.32 | 43.32 ± 5.91 | 0.433 |
| EF (%) | 62.08 ± 8.96 | 62.86 ± 7.17 | 0.607 |
| E/E′ | 10.68 ± 4.56 | 10.10 ± 3.28 | 0.456 |
| CT LA volume/BSA (ml/m$^2$) | | | |
| LA/BSA | 73.36 ± 19.49 | 73.74 ± 21.66 | 0.919 |
| VA/BSA | 22.83 ± 7.93 | 22.78 ± 7.67 | 0.975 |
| LAA/BSA | 5.41 ± 2.48 | 5.55 ± 2.54 | 0.782 |
| ALA/BSA | 45.29 ± 13.67 | 45.51 ± 15.31 | 0.934 |
| Mean LA voltage (mV; n = 30/37) | 0.94 ± 0.40 | 0.90 ± 0.53 | 0.755 |
| Shock energy (J) | 7.00 ± 3.32 | 7.39 ± 3.61 | 0.548 |
| Number of CV | 3.68 ± 1.44 | 3.81 ± 1.44 | 0.644 |
| Cumulative CV energy (J) | 17.17 ± 10.56 | 18.30 ± 11.15 | 0.579 |
| Ablation time (sec) | 6560.57 ± 1883.86 | 5740.94 ± 1531.30 | 0.013 |
| Fluoroscope time (min) | 59.09 ± 21.78 | 50.67 ± 15.74 | 0.022 |
| Procedure time (min) | 228.57 ± 68.30 | 205.94 ± 36.72 | 0.028 |
| Early recurrence rate (n, %) | 28 (46.7%) | 21 (36.8%) | 0.282 |
| Clinical recurrence rate (n, %) | 25 (41.7%) | 6 (10.5%) | <0.001 |
| AAD after RFCA (n, %) | 14 (23.3%) | 12 (21.4%) | 0.806 |

TIA: transient ischemic attack, ARB: angiotensin II receptor blocker, ACEi: angiotensin converting enzyme inhibitor, EF: ejection fraction, CT: computed tomography, LA: left atrium, VA: venous atrium, LAA: left atrial appendage, ALA: anterior left atrium, BSA: body surface area, PS-SNRT: post-shock sinus node recovery time, CV: cardioversion, AAD: anti-arrhythmic drug.

## 3. Results

### 3.1. Characteristics of patients with L-PeAF and prolonged PS-SNRT

We compared the clinical and electro-anatomical characteristics and ablation outcomes in terms of the initial PS-SNRT. The cutoff value (PS-SNRT; 1100 ms) was determined by an algorithm of maximization of hazard ratio (Table 1) [16]. Although there were no significant differences in terms of clinical characteristics, medications, image analysis findings, or the shock number and shock energy required for successful cardioversion, the total procedure time (p = 0.028) and ablation time (p = 0.013) were longer in patients with PS-SNRT ≥ 1100 ms than in those with PS-SNRT < 1100 ms. In contrast the early recurrence rates (within 3 months) were not different (p = 0.282), clinical recurrence rate of AF was higher in patients with long PS-SNRT ≥ 1100 ms (41.7% vs. 10.5%, p < 0.001). Notably, the proportion of patients taking AADs after RFCA was not different between the two groups (p = 0.806). The degree of LA remodeling determined by LA volume (p = 0.919) and LA voltage (p = 0.755) was not significantly different between the two groups.