Prolonged Sinus Pauses upon Termination of Paroxysmal Atrial Fibrillation:

Abnormal Right Atrial Electrophysiologic and Electroanatomic Findings

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The efficacy of pulmonary vein antral isolation for patients with prolonged sinus pauses (PSP) on termination of atrial fibrillation has been reported. We studied the right atrial (RA) electrophysiologic and electroanatomic characteristics in such patients.

Forty patients underwent electroanatomic mapping of the RA: 13 had PSP (group A), 13 had no PSP (group B), and 14 had paroxysmal supraventricular tachycardia (control group C). Group A had longer P-wave durations in lead II than did groups B and C (115.5 ± 15.4 vs 99.5 ± 10.9 vs 96.5 ± 10.4 ms; P=0.001), and RA activation times (106.8 ± 13.8 vs 99 ± 8.7 vs 94.5 ± 9.1 s; P=0.02). Group A's PP intervals were longer during adenosine triphosphate testing before ablation (4.6 ± 2.3 vs 1.7 ± 0.6 vs 1.5 ± 1 s; P <0.001) and after ablation (4.7 ± 2.5 vs 2.2 ± 1.4 vs 1.6 ± 0.8 s; P <0.001), and group A had more complex electrograms (11.4% ± 5.4% vs 9.3% ± 1.6% vs 5.8% ± 1.6%; P <0.001). Compared with group C, group A had significantly longer corrected sinus node recovery times at a 400-ms pacing cycle length after ablation, larger RA volumes (100.1 ± 23.1 vs 83 ± 22.1 mL; P=0.04), and lower conduction velocities in the high posterior (0.87 ± 0.13 vs 1.02 ± 0.21 mm/ms; P=0.02) and high lateral RA (0.89 ± 0.2 vs 1.1 ± 0.35 mm/ms; P=0.04).

We found that patients with PSP upon termination of atrial fibrillation have RA electrophysiologic and electroanatomic abnormalities that warrant post-ablation monitoring. **(Tex Heart Inst J 2017;44(2):107-14)**

Paroxysmal atrial fibrillation (PAF) might result in sinus node dysfunction (sick sinus syndrome) upon termination,[1] manifesting itself as weakness, presyncope, or syncope that originates from prolonged sinus pauses (PSP). Such conditions can necessitate pacemaker implantation. Investigators have reported good short- and midterm follow-up outcomes of ablation for PAF with PSP.[2-7] The abnormal anatomic and electrophysiologic characteristics of both atria in PAF patients have been described.[8] However, the substrate of the right atrium (RA) in PAF patients with PSP has not been fully elucidated. We hypothesized that PAF patients with PSP have sinus node dysfunction and abnormal RA substrates in comparison with patients who do not have PSP. To evaluate the RA substrate predisposing patients to such a condition, we prospectively evaluated the electrophysiologic and electroanatomic characteristics of the sinus region and RA substrate in 40 patients.

Patients and Methods

This study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. We excluded patients diagnosed with atrial fibrillation (AF) within a week before ablation,[8] or with paroxysmal supraventricular tachycardia (SVT) or AF during mapping.

Forty patients were ultimately enrolled (mean age, 62.8 ± 6.7 yr; age range, 46–75 yr; 20 men). All provided written informed consent.

We divided the 40 patients into 3 groups: 13 patients in whom PSP developed when PAF was terminated (group A), 13 without PSP when PAF was terminated (group B), and 14 who had paroxysmal SVT (control group C). In group C, 11 patients had

atrioventricular nodal reentrant tachycardia (AVNRT) and 3 had left-side accessory pathway tachycardia; none had structural heart disease.

Table I shows the patients' baseline clinical characteristics. Twelve had hypertension (30%), and 5 had coronary artery disease (12.5%). The mean duration of PSP in group A was 5.2 ± 1.9 s (range, 3.1–7.2 s). Left atrial dimension in group A was larger than that in groups B and C (P=0.03). The use of antiarrhythmic drugs was most prevalent in group B (P=0.001). No other baseline clinical characteristics among the 3 groups differed significantly.

Electrophysiologic Procedures

The patients' antiarrhythmic drugs were discontinued for at least 5 half-lives before the procedure. All patients with PAF took an anticoagulant for at least one month before the procedure, and transesophageal echocardiography was performed to exclude intracardiac thrombi. The electrophysiologic study was performed with patients in the fasting state and under conscious sedation with intravenous fentanyl. A 6F decapolar catheter (St. Jude Medical, Inc.; St. Paul, Minn) was positioned in the coronary sinus through the left subclavian vein, and a 6F quadripolar catheter (St. Jude Medical) was positioned in the right ventricle through the left femoral vein. An 8F, 65-cm SL1™ sheath (St. Jude Medical) was advanced to the RA; and a deflectable, irrigated, quadripolar NaviStar® ThermoCool® catheter (Biosense Webster, a Johnson & Johnson company; Diamond Bar, Calif) was inserted in the RA for mapping before ablation and was guided by the CARTO® 3 mapping system (Biosense Webster). Intracardiac electrograms were recorded with use of a CardioLab® digital electrophysiologic recording system (GE Healthcare; Milwaukee, Wisc) and were filtered at 32 to 300 Hz.

Electroanatomic Mapping

Before ablation, electroanatomic maps of the RA were created during sinus rhythm with use of the CARTO 3 system and a roving irrigated catheter. The roving catheter was guided by fluoroscopy and the CARTO 3 system and was used to detect local voltage and activation time through contact with the atrial wall. Points were acquired if the criteria for stability, local activation time (<5 ms), and space (<6 mm) were met.[8] Editing of points was performed offline. The constructed RA geometry was divided into 6 parts[4]: high posterior RA (HPRA), low posterior RA (LPRA), high lateral RA (HLRA), low lateral RA (LLRA), high septal RA (HSRA), and low septal RA (LSRA) (Fig. 1).

Right Atrial Substrate and Voltage Analysis

Bipolar voltages were obtained from more than 230 points within the RA. The difference between HLRA and global RA voltages was analyzed offline. Low-voltage zones were defined as areas with a bipolar voltage ≤0.5 mV; electrically silent areas (scar) were defined as areas with an absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV (the level of baseline noise in the system).

Right Atrial Conduction Velocity Analysis

Local activation times were manually annotated to the peak of the largest amplitude deflection. When there were double potentials, we used the larger value. When

TABLE I. Clinical Characteristics of the Study Population

Variable	Group A—PSP (n=13)	Group B—No PSP (n=13)	Group C—Control (n=14)	*P* Value
Age (yr)	64 ± 6.8	61.3 ± 6.1	63.1 ± 7.1	0.59
Male	6 (46)	7 (54)	7 (50)	0.93
PSP (s)	5.2 ± 1.9	NA	NA	—
Presyncope or syncope	8	0	0	—
Previous pacemaker	0	0	0	—
Antiarrhythmic drugs	0.4 ± 0.7	1.3 ± 0.8	0.4 ± 0.5	0.001
Left atrial dimension (mm)	38.6 ± 4.2	35.8 ± 4.2	34.1 ± 4.1	0.03
LVEF	0.64 ± 0.03	0.63 ± 0.3	0.64 ± 0.02	0.73
Hypertension	5 (38)	3 (23)	4 (29)	0.68
Coronary artery disease	2 (15)	2 (15)	1 (7)	0.75
Diabetes mellitus	2 (15)	1 (8)	1 (7)	0.73
CHADS$_2$ score	0.6 ± 0.6	0.5 ± 0.6	0.4 ± 0.5	0.5

CHADS$_2$ = chronic heart failure, hypertension, age >75 yr, diabetes mellitus, prior stroke and transient ischemic attack; LVEF = left ventricular ejection fraction; NA = not applicable; PSP = prolonged sinus pauses

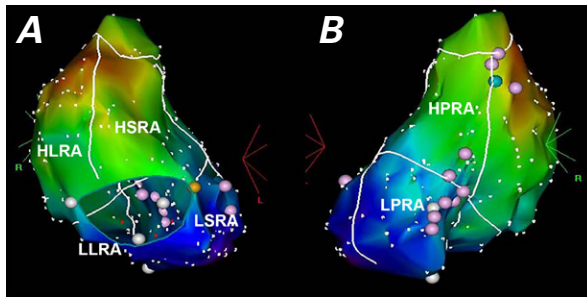Data are presented as mean ± SD or as number and percentage. *P* <0.05 was considered statistically significant.

Fig. 1 *Electroanatomic maps, obtained during sinus rhythm with use of the CARTO 3 mapping system, show the 6 right atrial segments in **A**) left anterior oblique and **B**) posteroanterior views. The earliest activation area was the HLRA.*

HLRA = high lateral right atrium; HPRA = high posterior right atrium; HSRA = high septal right atrium; LLRA = low lateral right atrium; LPRA = low posterior right atrium; LSRA = low septal right atrium

there were fragmental electrograms, we used the auto-freeze mode, wherein the mapping system records the activation time. Regional RA conduction velocity was analyzed as previously described.[9] The RA total activation time was defined as the time elapsed between the earliest and latest activation at any site within the RA. Isochronal maps were created at 5-ms intervals in local activation times to determine the regional conduction velocity. An approximation of conduction velocity was determined by dividing the linear distance between 2 points by the difference in local activation time. Conduction velocity for each region was determined as the mean of the conduction velocity between 5 pairs of points through regions of isochronal crowding in each of the RA regions. P-wave duration on lead II (P_{II}) was measured and averaged over 10 beats as a marker of RA conduction time.[10]

Double Potentials and Fragmented Electrograms

Double-potential electrograms were defined as having potentials separated by an isoelectric interval with a total duration ≥50 ms. Fragmented electrograms were defined as having complex activity with a duration ≥50 ms.

Sinus Node Function

After RA mapping was completed, the mapping catheter was advanced to the earliest activation area. Then, the sinus node recovery time (SNRT) and corrected SNRT (CSNRT) were evaluated before and after ablation. Pacing was performed at cycle lengths (CL) of 600, 500, and 400 ms for 30-s trains, and times from the last stimulus signal to the earliest activation area were measured. The SNRT and CSNRT measurements were repeated 3 times for each CL and were averaged.

Adenosine Triphosphate Testing

Adenosine triphosphate (ATP) was administered after the SNRT evaluation, before and after ablation. The test consisted of an intravenous 20-mg bolus of ATP followed by a rapid 20-mL flush of 5% dextrose solution.[11,12] An ATP injection characteristically causes the following 5-phase sequence: slowing of sinus rhythm, a short episode of first- or 2nd-degree atrioventricular block, 3rd-degree atrioventricular block, resumption of normal atrioventricular conduction, and reflex sinus tachycardia. A positive response included a phase-III cardiac pause of longer than 10 s, regardless of symptoms or any consecutive ventricular conduction interval.[12]

Catheter Ablation

After completion of the electrophysiologic test, 2 long sheaths were advanced to the left atrium through standard transseptal puncture in the patients who had PAF. Intravenous heparin was used to maintain an activated clotting time of 250 to 300 s. A deflectable, decapolar, circular LASSO® catheter (Biosense Webster) was advanced through the pulmonary vein (PV) sheath for mapping, and an irrigated catheter was inserted into the left atrium for mapping and ablation. Before the ablation procedure, a detailed map of the left atrium was created, and the anatomic locations of the PV ostia were tagged on the electroanatomic maps in accordance with the selective PV angiography. Pulmonary vein antral isolation was performed around the 2 ipsilateral PVs; a single circular catheter was used to evaluate PV potentials.[6] Catheter ablation was performed with use of irrigated radiofrequency energy delivered at a maximum cutoff temperature of 45 °C, a maximum power of 35 W, and an infusion rate of 17 mL/min. The endpoint was electrical isolation of all PVs with the disappearance or dissociation of the PV potentials from the left atrium. In AVNRT patients, slow-pathway modification was performed. The endpoint was noninducibility or no more than a single echo beat after ablation. For left-side accessory pathways, radiofrequency ablation was delivered through the transseptal approach.

Post-Ablation Follow-Up Evaluation

No patient took antiarrhythmic drugs after the procedure. A surface electrocardiogram and a 24-hour Holter recording were obtained on postprocedural day 3; at 1, 3, and 6 months; and every 6 months thereafter. In addition, electrocardiography was performed whenever a patient had relevant symptoms.

Statistical Analysis

Differences among groups were analyzed by means of Student *t* tests or analysis of variance. All analyses were performed with use of SPSS software version 13.0 (IBM Corporation; Armonk, NY). We expressed continuous

variables as mean ± SD. Reported *P* values were 2-sided, and *P* <0.05 was considered statistically significant.

Results

Right Atrial Amplitude and Conduction

We found a significant difference (*P* <0.001) in the P_{II}-wave duration in group A (115.5 ± 15.4 ms) versus group B (99.5 ± 10.9 ms) and group C (96.5 ± 10.4 ms) (Fig. 2). The P_{II}-wave amplitude did not differ significantly among the groups (group A, 0.1 ± 0.01; group B, 0.11 ± 0.02; and group C, 0.12 ± 0.03 mV; *P*=0.08); however, the voltage in group A was lower than in group C (*P*=0.02).

Sinus Node Function

At baseline, sinus-node CL did not differ significantly among groups A, B, and C (871.8 ± 161.4 vs 817.4 ± 71.1 vs 791.5 ± 129.9 ms, respectively; *P*=0.3). Figure 3 shows the CSNRT among the 3 groups before and after ablation. There was no significant difference before ablation among the 3 groups at a CL of 600 ms (*P*=0.08). However, the CSNRTs in group A versus group C were significantly different (*P*=0.03). The CSNRT was significantly different before ablation among the 3 groups at a CL of 500 ms (*P*=0.005); at 400 ms, group A had a longer CSNRT than did group C (*P*=0.02) (Fig. 3A). There was no significant difference immediately after ablation among the 3 groups at CLs of 600 (*P*=0.9) and 500 ms (*P*=0.5). However, the CSNRT was longer at a CL of 400 ms in group A than in groups B (*P*=0.03) and C (*P*=0.01) (Fig. 3B).

Pre- and Postprocedural ATP Test Results

Figure 4 shows the results of ATP testing. There was no significant difference in the longest PP interval before or after ablation in group A (4.6 ± 2.3 vs 4.7 ± 2.5 s; *P*=0.96), group B (1.7 ± 0.6 vs 2.2 ± 1.4 s; *P*=0.27), or group C (1.5 ± 1 vs 1.6 ± 0.8 s; *P*=0.69). Before ablation, group A had a longer PP interval than did group B and group C (*P* <0.001); however, groups B and C did not (*P*=0.63). The same result was observed after ablation in the longest PP interval among the 3 groups (*P* <0.001), and in the longest RR interval before and after ablation in group A (6.3 ± 2.9 vs 7.9 ± 3.6 ms; *P*=0.41), group B (4.3 ± 3.6 vs 5.7 ± 3.5 ms; *P*=0.08), and group C (5.8 ± 3.3 vs 5.5 ± 2.9 ms; *P*=0.42), respectively. The longest RR interval was not significantly different before and after ablation among the 3 groups (*P*=0.32 before; *P*=0.15 after).
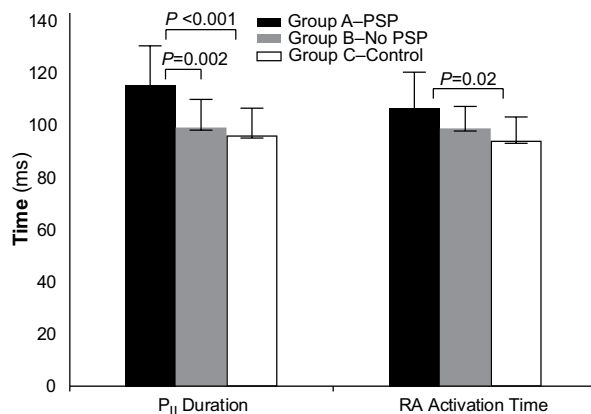
Fig. 2 Graph shows comparative P-wave durations on lead II and right atrial (RA) global activation times among the 3 groups. The P-wave duration on lead II was significantly different in group A in comparison with groups B and C (P <0.001); however, RA activation time differed significantly only between groups A and C (P=0.02).

PSP = prolonged sinus pauses
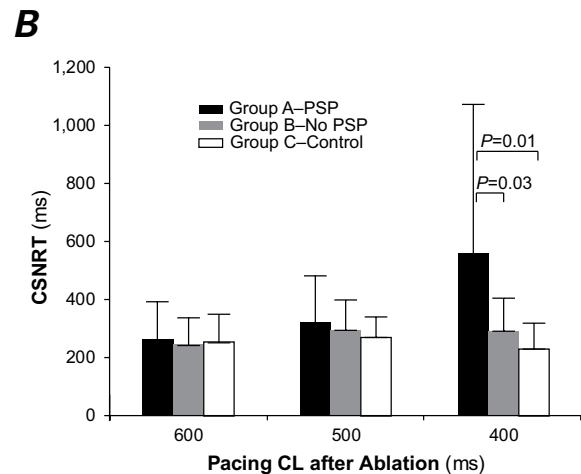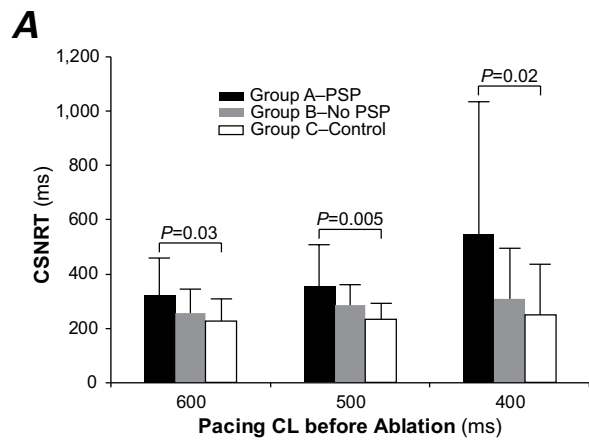
P <0.05 was considered statistically significant.

Fig. 3 Graphs show corrected sinus node recovery time (CSNRT) at different pacing cycle lengths (CL) **A)** before and **B)** after ablation. Group A had significantly longer recovery time before ablation at different pacing CLs than did group C; however, after ablation, a significant difference among the 3 groups was found at a CL of 400 ms.

PSP = prolonged sinus pauses
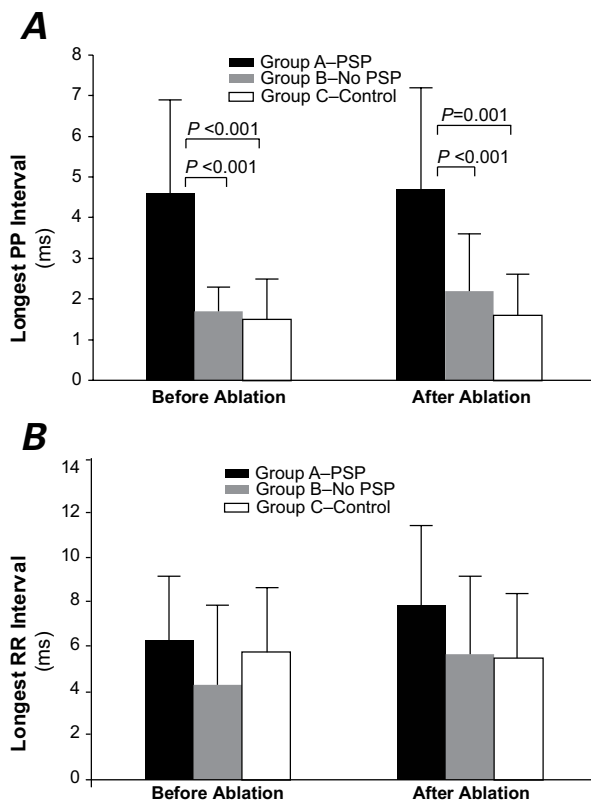
P <0.05 was considered statistically significant.

A

B

Fig. 4 Graph shows **A**) longest PP interval and **B**) longest RR interval during adenosine triphosphate (ATP) testing, before and after ablation. Group A had a longer PP interval than did groups B and C before and after ablation; however, there was no difference in longest RR interval among the 3 groups.

PSP = prolonged sinus pauses
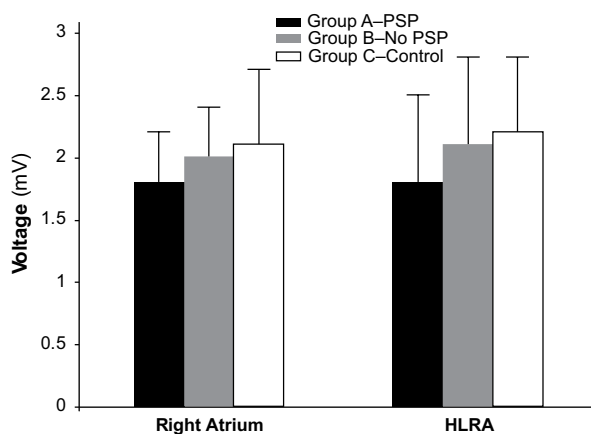
P <0.05 was considered statistically significant.

Fig. 5 Graph shows no significant difference in the mean voltage of the entire right atrium and high lateral right atrium (HLRA) among the 3 groups; however, the mean voltages of those regions were lowest in group C and highest in group A.

PSP = prolonged sinus pauses

Electroanatomic Mapping

In total, 252 ± 44 (group A), 264 ± 30 (group B), and 275 ± 35 (group C) points per patient were analyzed in the RA. Patients in group A had a longer RA global activation time than did groups B and C (106.8 ± 13.8 vs 99 ± 8.7 vs 94.5 ± 9.1 ms; $P=0.02$) (Fig. 2); however, comparisons between groups B and C ($P=0.2$) and between groups A and B ($P=0.1$) were not significantly different. Measurements of RA volume were higher in group A than in group C (100.1 ± 23.1 vs 83 ± 22.1 mL; $P=0.04$). There was no significant difference of RA mean bipolar voltage among the 3 groups; nevertheless, the mean RA voltage was somewhat higher in group C than in groups B and A (2.1 ± 0.6 vs 2 ± 0.4 vs 1.8 ± 0.4 mV; $P=0.3$), and this was also true for mean voltage of the HLRA (2.2 ± 0.6 vs 2.1 ± 0.7 vs 1.8 ± 0.7 mV; $P=0.25$) (Fig. 5). Figure 6 shows examples of electroanatomic maps in representative patients.

Regional Atrial Conduction Velocity

Before ablation, activation mapping was performed during sinus rhythm. Figure 7 shows the regional conduction velocities in the 3 groups. The conduction velocity in the HSRA was significantly different among the 3 groups ($P=0.005$). Although conduction velocities did not differ significantly in the HPRA and HLRA, group A had a lower conduction velocity than did group C in the HPRA (0.87 ± 0.13 vs 1.02 ± 0.21 mm/ms; $P=0.02$) and HLRA (0.89 ± 0.2 vs 1.1 ± 0.35 mm/ms; $P=0.04$). The conduction velocities were not significantly different in the LPRA ($P=0.12$), LLRA ($P=0.2$), or LSRA ($P=0.9$).

Complex Electrograms

Group C had significantly fewer points with double potentials and fractionated electrograms than did groups B and A ($5.8\% \pm 1.6\%$ vs $9.3\% \pm 1.6\%$ vs $11.4\% \pm 5.4\%$; $P <0.001$). Upon comparison, there was no statistical difference between groups A and B ($P=0.1$).

Follow-Up Results in the Study Cohort

In group A, 9 patients underwent a single ablation, 2 underwent a repeat procedure, and the remaining 2 had 3 ablations. After a mean follow-up duration of 24.1 ± 16.3 months after the last procedure, all patients in group A remained free from AF and PSP, and group C patients had no recurrence of SVT. Two patients in group B had recurrent atrial tachyarrhythmia, but they declined a repeat ablation. No sequelae were observed in any study patient during the perioperative period.

Discussion

The major findings in PAF patients with PSP in this study are as follows: 1) A lower amplitude and longer duration of the P_{II} wave suggest a loss of normal atrial
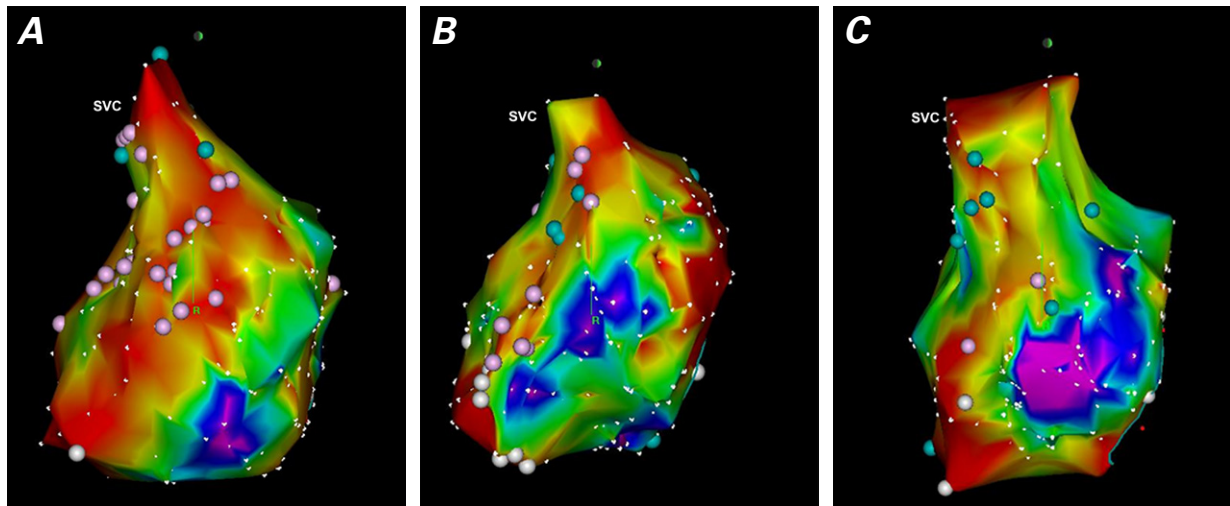
Fig. 6 *Electroanatomic bipolar voltage maps of the right atrium (right lateral projection) show complex signals from representative patients in each group.* **A**) *A patient with paroxysmal atrial fibrillation and prolonged sinus pause had more double potentials (blue dots) and fractionated signals (pink dots) than did* **B**) *a patient without prolonged sinus pause and* **C**) *a patient in the control group. Low-voltage areas (≤0.5 mV) are red, and high-voltage areas (≥5 mV) are purple.*
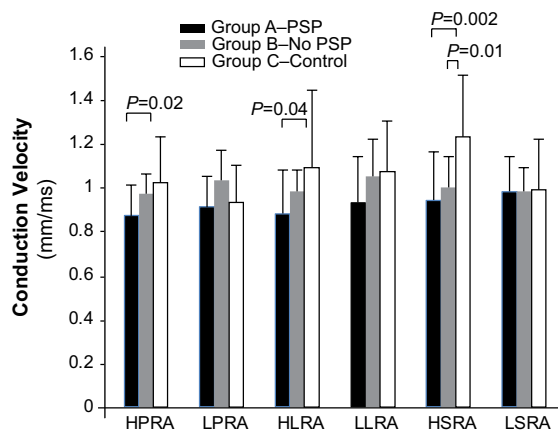
SVC = superior vena cava

Fig. 7 *Graph shows mean regional apparent conduction velocity in the 6 right atrial regions from the electroanatomic map.*

HLRA = high lateral right atrium; HPRA = high posterior right atrium; HSRA = high septal right atrium; LLRA = low lateral right atrium; LPRA = low posterior right atrium; LSRA = low septal right atrium; PSP = prolonged sinus pauses

P <0.05 was considered statistically significant.

myocardium; 2) sinus node function is impaired, as evidenced by the prolonged CSNRT during 400-ms pacing; 3) the negative response to ATP administration might help to exclude syncope mediated by vagal reflex, and it suggests indirectly that syncope was probably mediated by the termination of PAF with PSP; and 4) conduction abnormalities are characterized by a prolonged RA activation time, a slower conduction velocity, and an increased proportion of complex electrograms.

Effect of ATP Testing

The ATP test was introduced to help identify patients with unexplained syncope who had predominantly neurally mediated cardiac inhibition. In this study, we chose ATP instead of adenosine for testing. In addition, ATP can trigger a central vagal effect by activating P2X receptors on the vagal-nerve sensory terminals in the inferoposterior wall of the left ventricle.[13]

However, the ATP test, if positive, does not exclude the coexistence of other mechanisms potentially responsible for syncope. If the result is negative, syncope mediated by vagal reflex may be ruled out. Because the ATP test was negative in group A, we speculate that the syncope in other patients is chiefly correlated with PSP upon termination of AF.

Electroanatomic Remodeling in Patients with PAF and PSP

The association between sinus node dysfunction and atrial tachyarrhythmia is well recognized,[14,15] but the electrophysiologic mechanism has not been elucidated. We found that the electrophysiologic properties in group A, such as P_{II} duration and RA total activation time, were longer than those in groups B and C. In addition, electroanatomic mapping results showed that group A had the lowest global RA and HLRA voltage measurements.

Previous investigators found remodeling of both atria in lone-PAF patients, including structural abnormalities, lower conduction velocities, increased effective refractory periods, abnormal atrial histologic results, and inflammation.[8,16,17] In patients with sinus pauses >3 s or

unexplained sinus bradycardia (<40 beats/min), Sanders and colleagues[18] found an increased effective refractory period, longer conduction time, widespread and site-specific conduction abnormalities, lower RA voltage, and more complex electrograms than in their control group. However, PAF patients with PSP were excluded from their study.

Our study elucidated the remodeling of the RA substrate in PAF patients with PSP. In comparing group A with groups B and C, we found significantly longer RA total activation times and slower conduction velocities in the HPRA, HLRA, and HSRA. Although we found no significant differences in HLRA and global RA voltage among the 3 groups, there was a trend in substrate remodeling toward lower voltage from group C to B to A. In comparison with symptomatic sinus node disease, RA and HLRA substrate remodeling might be less diffuse—the main reason why PSP after PAF might be transient and reversible. Some investigators have shown positive results upon short- and long-term follow-up evaluation.[2,4,5] Inada and colleagues[5] determined that 8% of patients with sick sinus syndrome needed pacemaker implantation during 5-year follow-up. In our study, prolonged RA activation time, longer P_{II} duration, slower conduction velocity, lower HLRA voltage, and overall RA voltage might indicate the importance of substrate remodeling of the HLRA and RA—and the consequent necessity of intensive follow-up monitoring in these patients because of RA remodeling.

Sinus Node Remodeling in PAF Patients with PSP

Several mechanisms can explain the sinus node remodeling in PAF patients with PSP.[1,15] In our study, the CSNRT was longer in group A than in group C before ablation at different pacing CLs. The CSNRT was significantly longer in group A than in groups B and C at a CL of 400 ms after ablation. Our results show that sinus node function worsens significantly after the termination of AF.

We also found slower conduction velocities in the HLRA of group A patients, perhaps caused by the remodeling of the HLRA. The main reasons might be low voltage at the HLRA (implying impaired sinus node function) and more complex electrograms. Fewer depolarized myocardial cells and more interstitial fibrosis along linear ablation lesions decrease the local voltage, which leads to conduction block and low electrogram amplitude. Atrial fibrillation can alter patterns of connexins, causing interstitial fibrosis and apoptotic atrial myocyte death.[19] In pathologic studies of patients with sinus node disease, investigators have observed degeneration, fatty infiltration, and fibrosis of the sinus node region.[20] Aging of the atrium might partially explain impaired sinus node function; Roberts-Thomson and co-authors[9] observed that fractionated atrial electro-

grams increase in prevalence with age and occur predominantly along the HPRA and HSRA. In our study, patient age was similar among groups, suggesting that the findings cannot be explained by the aging process alone. Indeed, group A patients had a higher percentage of complex electrograms, higher RA volumes, and lower voltage in the HLRA and RA than did patients in groups B and C. Results of previous studies and our current study suggest that structural remodeling of the HLRA results in reduced sinus node function and conduction velocity.

Study Limitations

Our study had limitations. First, it included a small number of patients, because PAF with PSP is rare. Second, we did not evaluate sinus node function at follow-up; however, PAF patients with PSP had no recurrent presyncope or syncope during follow-up. These results imply that the sinus node functions normally after AF is eliminated. Third, the clinical outcome was evaluated in terms of the symptoms reported by patients, the results of electrocardiograms, and 24-hour ambulatory monitoring. Asymptomatic episodes of AF might have been missed. Fourth, ischemia, inflammation, and other factors might also play a role in the atrial remodeling in patients with PSP. Finally, we did not measure sinoatrial conduction time, another possibly useful variable for evaluating overall HLRA function.

We conclude that patients with PAF and PSP have RA electrophysiologic and substrate abnormalities that warrant intensive monitoring after successful ablation.

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