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Prognosis of high sinus heart rate after catheter ablation for atrial fibrillation

Hee Tae Yu, Tae-Hoon Kim, Jae-Sun Uhm, Jong-Youn Kim, Boyoung Joung, Moon-Hyoung Lee, and Hui-Nam Pak*

Yonsei University Health System, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Republic of Korea

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Aims Although atrial fibrillation (AF) catheter ablation increases sinus heart rate (HR), its mechanism and prognosis have not yet been clearly elucidated. We hypothesize that post-AF ablation high sinus HR (PA-HSR) is associated with a better clinical outcome of AF ablation without adverse cardiac effects.

Methods and results We studied 991 AF patients (75% male, 58 ± 11 years old, 70% paroxysmal AF) with HR variability (HRV) at 3 months and 1 year after catheter ablation, and pre- and post-1-year echocardiograms. Post-AF ablation high sinus HR was defined as an average HR greater than 2 SD (≥92 bpm) as measured by 24 h Holter. (1) Average HR increased significantly ($P < 0.001$), and PA-HSR was observed in 28 patients (2.8%) 3 months after AF ablation. At 1 year after catheter ablation, 21% were taking β-blockers and 36% maintained an average HR of ≥92 bpm. (2) Post-AF ablation high sinus HR was independently associated with pre-procedural high average HR (OR 1.097; 95% CI 1.029–1.169, $P = 0.005$), high left atrium (LA) electrogram voltage (OR 3.545; 95% CI 1.183–10.618, $P = 0.024$), and reduced root mean square of differences between successive NN intervals (rMSSD) at 3 months HRV (OR 0.959; 95% CI 0.919–0.999, $P = 0.047$). (3) At 1 year echocardiography, size reduction of LA ($P = 0.055$) or LV ($P = 0.372$) and the improvement in ejection fraction ($P = 0.529$) were not significantly different between patients with PA-HSR and those without. (4) Throughout 27 ± 17 months of follow-up, patients with PA-HSR showed significantly lower clinical recurrence than those without (log rank, $P = 0.020$).

Conclusion Post-AF ablation high sinus HR was observed in patients with smaller LA size and higher LA electrogram voltage and significant vagal modulation without adverse cardiac effects. Post-AF ablation high sinus HR was associated with a significantly lower clinical recurrence of AF after catheter ablation.

Keywords Atrial fibrillation • Catheter ablation • High sinus heart rate • Recurrence

Introduction

Several studies have demonstrated an increase in heart rate (HR) and a decrease in HR variability (HRV) after radiofrequency catheter ablation (RFCA) of supraventricular tachycardia or atrial fibrillation (AF).[1,2] Although the precise mechanism of this post-procedural phenomenon is uncertain, it has been suggested that autonomic dysfunction, caused by parasympathetic nervous withdrawal, may be a contributing factor.[3] Recently, RFCA became a standard therapy for rhythm control in symptomatic AF patients who are resistant to antiarrhythmic drugs or as a first-line rhythm control strategy. Intrinsic cardiac autonomic nervous activity plays a key role in the pathogenesis of AF,[4] and Pappone *et al.* have shown that autonomic modulation, especially vagal denervation, improves the clinical outcome of the RFCA of AF.[5] In contrast, high HR with reduced HRV is a poor prognostic factor in patients with heart failure.[6] Because catheter ablation for AF also changes cardiac autonomic nerve activity,[7] the role of post-AF ablation high sinus rate (PA-HSR) on prognosis remains unclear. In this study, we hypothesized that PA-HSR is not associated with the increase in clinical recurrence of AF or left ventricular (LV) dysfunction after catheter ablation for AF. We defined PA-HSR as an average HR greater than 2 SD (≥92 bpm) as measured by 24 h Holter monitor. The purposes of this study were (1) to evaluate PA-HSR-associated clinical factors and HRV

* Corresponding author. Tel: +82 2 2228 8460; fax: +82 2 393 2041. *E-mail address*: hnpak@yuhs.ac

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What's new?

- Here, we evaluated the prognosis of post-atrial fibrillation (AF) ablation high sinus rate (PA-HSR) in terms of rhythm control and cardiac remodelling based on long-term rhythm and heart rate variability (HRV) monitoring.
- Post-AF ablation high sinus HR was independently associated with pre-procedural high average heart rate, high left atrial electrogram voltage, and significant vagal modulation at 3 months post-ablation without adverse cardiac effects on follow-up echocardiogram 1 year post-ablation.
- Post-AF ablation high sinus HR was associated with significantly lower clinical recurrence rate of AF after catheter ablation.

and (2) to characterize the prognosis of PA-HSR in terms of rhythm control and cardiac remodelling.

Methods

Study population

The study protocol adhered to the Declaration of Helsinki and was approved by the Institutional Review Board of Yonsei University Health System. All patients provided written informed consent for inclusion in the Yonsei AF Ablation Cohort Database (Clinicaltrials.gov; NCT02138695). This study enrolled 991 patients (75.3% male, 57.6 $\pm$ 11.2 years old) who underwent RFCA for paroxysmal AF (PAF, $n = 695$) or persistent AF (PeAF, $n = 296$), and had 24 h Holter monitor records for HRV analysis pre-RFCA and 3 months and 1 year post-RFCA. The study population also underwent pre-RFCA and 1 year post-RFCA echocardiograms. Exclusion criteria were as follows: (1) permanent AF refractory to electrical cardioversion; (2) structural heart disease other than LV hypertrophy, such as significant valvular heart disease $\geq$ grade 2, hypertrophic, ischaemic, or dilated cardiomyopathies, and congenital heart diseases; (3) history of prior RFCA or cardiac surgery; and (4) lack of HRV data at pre-RFCA, 3 months, or 1 year post-RFCA. All antiarrhythmic drugs were discontinued for a minimum period of five half-lives before the procedure. Anticoagulation therapy was maintained before catheter ablation. Both transthoracic and transoesophageal echocardiography were performed before RFCA to determine whether patients had combined structural heart disease or left atrium (LA) thrombus. All patients were imaged with three-dimensional (3D) spiral computer tomography (CT) scans (64 Channel, Light Speed Volume CT, Philips, Brilliance 63, Amsterdam, the Netherlands) to visualize the anatomy of the LA and pulmonary veins (PVs).

Electroanatomical mapping and LA CT measurements

Intracardiac electrograms and haemodynamic measurements were recorded using the Prucka Cardio Lab^{TM} electrophysiology system (General Electric Medical Systems, Inc., Milwaukee, WI, USA). A 3D electroanatomical map (NavX; St. Jude Medical, Inc., Minnetonka, MN) was generated using a circular PV mapping catheter (Lasso; Biosense-Webster, Inc., Diamond Bar, CA). The NavX system-generated 3D geometry of the LA and PVs was merged with the corresponding 3D spiral CT images. Left atrium electrogram voltage maps were generated during high right atrial pacing at 500 ms to prevent rate-dependent activation changes, after maintaining sinus rhythm by circumferential PV isolation (CPVI) with or without cardioversion. If frequently recurring AF still persisted after three attempts of cardioversion, no further efforts were made to generate a LA voltage map. We obtained the peak-to-peak amplitude of contact bipolar electrograms from 350 to 500 points on the LA endocardium, and the mean LA electrogram voltage was calculated. The 3D spiral CT images of the LA were analysed on an image-processing workstation (Aquarius, Terarecon, Inc., USA). Each LA image was divided into portions according to embryological origin: the venous LA, anterior LA, and LA appendage.

Echocardiographic evaluation

All patients underwent transthoracic echocardiography (Sonos 5500, Philips Medical System, Andover, MA or Vivid 7; GE Vingmed Ultrasound, Horten, Norway) prior to the RFCA. On baseline echocardiographic analysis, 507 (51.2%) patients were in sinus rhythm and 484 (48.8%) patients were in AF. The chamber size, transmitral Doppler flow velocity, and ratio of the early diastolic peak mitral inflow velocity and early diastolic mitral annular velocity (E/Em) were acquired following the American Society of Echocardiography guidelines.[8] Transoesophageal echocardiography was performed to exclude any intracardiac thrombi. The emptying velocity of the LA appendage was measured in all patients.

Radiofrequency catheter ablation

An open-irrigated, 3.5 mm tip deflectable catheter (Celsius, Johnson & Johnson, Inc., Diamond Bar, CA; Coolflex, St. Jude Medical, Inc., Minnetonka, MN; 30–35 W; 47°C) was used for the RFCA. All patients initially underwent CPVI and cavo-tricuspid isthmus ablation. We conducted CPVI at the antral level of both PV and confirmed bidirectional block with circular mapping catheter. For the patients with PeAF (29.9%), a roof line, posterior inferior line, and anterior line were added as the standard lesion set,[9] which is also called as 'Dallas lesion' in mini-maze surgery. To generate the posterior box lesion, linear ablations of roof line and posterior inferior line were made by connecting both sides of the CPVI at the top and bottom levels, respectively. Anterior line was generated by ablation from the mitral annulus at the 12 O'clock direction towards the LA roof line.[9] The proportions of a mitral isthmus line, which means a line between the lower border of the left-side CPVI and posterolateral mitral annulus, complex fractionated atrial electrogram-guided ablation, and superior vena cava ablation were 6.0, 7.7, and 35.7%, respectively. The procedure ended when there was no immediate recurrence of AF within 10 min after cardioversion with an isoproterenol infusion (5–10 μg/min). Non-PV foci under isoproterenol infusion were also ablated.

Holter monitor records and heart rate variability analysis

Heart rate variability was analysed by 24 h Holter monitor recordings taken at pre- and post-ablation 3 months and 12 months periods for each patient with a GE Marquette MARS 8000 Holter analyzer (General Electric Medical System, Inc.). After identifying each QRS complex, the numerical series of RR intervals was calculated. Only high-quality recordings were considered for analysis. All recordings were digitized and reviewed by an experienced operator. Premature ventricular beats, premature atrial beats, and electrical artefacts were excluded from analysis. Heart rate variability parameters were used as indicators of autonomic activity according to previously published guidelines.[10] Mean HR and the following time-domain HRV parameters were analysed: mean RR interval (mean NN interval), standard deviation of NN intervals, standard deviation of 5 min means of NN intervals, and root mean

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square of differences between successive NN intervals (rMSSD). The following parameters were calculated: very-low-frequency components (VLF; <0.040 Hz), low-frequency components (LF; 0.040–0.150 Hz), high-frequency components (HF; 0.150–0.400 Hz), and LF/HF ratio. High-frequency components and rMSSD were indicators of parasympathetic nervous activity, and LF and LF/HF ratio reflected sympathetic nervous activity and sympathovagal balance, respectively.[10] In this study population, PA-HSR was defined as an average HR greater than 2 SDs (≥92 bpm) as measured by 24 h Holter monitor at 3 months after catheter ablation. All 991 patients had analysable HRV data pre-RFCA as well as 3 months and 1 year post-RFCA, after excluding those with sinus node dysfunction, a high number of AF (>1 h or >20 times per day), or other arrhythmia episodes. At 3-month HRV analysis, 920 (92.8%) patients were in sinus rhythm and 71 (7.2%) patients had PAF with analysable HRV.

Post-ablation follow-up

Patients were followed at the outpatient clinic at 1, 3, 6, and 12 months post-RFCA and every 6 months thereafter. Electrocardiogram (ECG) was performed at each visit, and 24 h Holter monitoring was evaluated pre-RFCA and at 3, 6, 12, 18, and 24 months post-RFCA following the 2012 HRS/EHRA/ECAS Expert Consensus Statement guidelines.[11] Holter monitor or event monitor recordings were obtained when patients reported symptoms of palpitation suggestive of arrhythmia recurrence. Atrial fibrillation recurrence was defined as any episode of AF or atrial tachycardia of at least 30 s in duration. Any ECG documentation of AF recurrence within a 3-month blanking period was diagnosed as an early recurrence, and AF recurrence more than 3 months after the procedure was diagnosed as a clinical recurrence.

Statistical analysis

Continuous variables are summarized as mean ± SD and compared by Student's *t*-tests and ANOVAs. Categorical variables are summarized as a percentage of the group total and compared by χ^2 tests or Fisher's exact tests. Multivariate logistic regression analysis was used to identify predictors of PA-HSR. The Kaplan–Meier analysis with log-rank test was used to calculate AF recurrence-free survival over time and to compare recurrence rates across groups. Propensity scores were used to

Table 1 Baseline characteristics of study population

	Overall (*n* = 991)	PA-HSR (*n* = 28)	Others (*n* = 963)	*P*-value
Age, years	57.6 ± 11.2	48.3 ± 16.0	57.9 ± 10.9	0.004*
Male, *n* (%)	746 (75.3)	16 (57.1)	730 (75.8)	0.042*
PAF, *n* (%)	695 (70.1)	27 (96.4)	668 (69.4)	0.001*
BMI, kg/m^2	24.8 ± 2.8	24.1 ± 3.7	24.8 ± 2.7	0.313
CHA_2DS_2-VASc score	1.5 ± 1.4	1.4 ± 1.4	1.6 ± 1.4	0.578
Heart failure, *n* (%)	63 (6.4)	4 (14.3)	59 (6.1)	0.096
Hypertension, *n* (%)	484 (48.8)	10 (35.7)	474 (49.2)	0.182
Age 65–74 years, *n* (%)	241 (24.3)	0 (0)	241 (25.0)	0.001*
Age ≥75 years, *n* (%)	53 (5.3)	4 (14.3)	49 (5.1)	0.057
Diabetes, *n* (%)	128 (12.9)	2 (7.1)	126 (13.1)	0.566
Stroke/TIA, *n* (%)	116 (11.7)	2 (7.1)	114 (11.8)	0.512
Vascular disease, *n* (%)	36 (3.6)	1 (3.6)	35 (3.6)	1.000
Echocardiographic parameters				
LA dimension, mm	41.5 ± 6.0	37.4 ± 5.7	41.6 ± 6.0	<0.001*
LA volume index, mL/m^2	34.4 ± 11.9	27.5 ± 11.6	34.6 ± 11.8	0.004*
LVEDD, mm	49.8 ± 4.2	49.0 ± 4.6	49.8 ± 4.2	0.300
LV ejection fraction, %	63.2 ± 8.2	63.2 ± 6.6	63.2 ± 8.3	0.975
E/E′	10.2 ± 4.3	9.7 ± 4.7	10.2 ± 4.3	0.535
NavX electroanatomical map				
Mean LA voltage, mV	1.2 ± 0.6	1.8 ± 0.6	1.2 ± 0.6	<0.001*
Mean LAA voltage, mV	2.4 ± 1.5	3.9 ± 1.5	2.3 ± 1.4	<0.001*
Medication				
β-Blocker, *n* (%)	277 (28.0)	6 (21.4)	271 (28.1)	0.664
AAD, *n* (%)	104 (10.5)	1 (3.6)	103 (10.7)	0.349
Ablation time, s	5056 ± 1583	4827 ± 1108	5063 ± 1595	0.438
Procedure time, min	190.6 ± 47.8	181.0 ± 33.3	190.9 ± 48.1	0.280
Additional linear ablation, *n* (%)	454 (45.8)	9 (32.1)	445 (46.2)	0.178
Early recurrence, *n* (%)	286 (28.9)	0 (0)	286 (29.7)	<0.001*
Clinical recurrence, *n* (%)	287 (29.0)	2 (7.1)	285 (29.6)	0.010*
Follow-up duration, months	26.6 ± 16.8	28.5 ± 17.5	26.5 ± 16.8	0.536

PAF, paroxysmal atrial fibrillation; BMI, body mass index; TIA, transient ischaemic attack; LA, left atrium; LVEDD, left ventricle end diastolic dimension; LV, left ventricle; E/E′, early mitral inflow velocity to early diastolic mitral annular velocity ratio; AAD, antiarrhythmic drug.
*$P < 0.05$.

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match the patients with PA-HSR to those without to reduce the potential confounding in this observational study. Propensity scores were estimated using a non-parsimonious multiple logistic regression model for PA-HSR and the other group. The following variables were entered: age, sex, and type of AF. Cases then were matched, without replacement, with controls based on the closest possible value of the propensity score (nearest neighbour matching). A matching calliper of 0.1 SD of the logit of the estimated propensity score was enforced to ensure that matches of poor fit were excluded. The matching procedure was performed using R packages (R Foundation for Statistical Computing, Vienna, Austria), including Matchit, RItools, and CEM. A *P*-value of <0.050 was considered to be statistically significant. Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows (version 20.0).

Results

Clinical characteristics of patients with post-atrial fibrillation ablation high sinus heart rate

Baseline clinical characteristics of the overall study population are shown in *Table 1*. At 3 months after AF ablation, average HR was significantly increased (68.8 ± 13.1 to 71.4 ± 10.7 bpm, $P < 0.001$), and PA-HSR [defined as an average HR greater than 2 SDs above the average HR for the entire study cohort ($\geq$92 bpm)] was observed in 28 patients (2.8%), among the total 991 study participants. None of PA-HSR group required hospital admission or specific intervention to slow down their HR, but 21% were taking β-blockers by primary care physician's decision. Thirty-six per cent of PA-HSR group maintained an average HR of $\geq$92 bpm at 1 year after RFCA. The patient group with PA-HSR was younger ($P = 0.004$), composed of more females ($P = 0.042$), and more likely to have PAF ($P = 0.001$), and a smaller LA dimension ($P < 0.001$) and LA volume index ($P = 0.004$). The mean voltage of LA and LAA electrogram was greater in patients with PA-HSR ($P < 0.001$ for both). No significant differences were seen in patients with or without PA-HSR for body mass index, CHA_2DS_2-VASc score, LV systolic and diastolic functions, procedure time, and medications (*Table 1*). In addition, the incidence of PA-HSR was not significantly different between CPVI only group (3.5%, 19/537) and additional linear ablation group (2.0%, 9/454, $P = 0.178$).

Heart rate variability parameters and reverse remodelling of the patients with post-atrial fibrillation ablation high sinus heart rate

Table 2 summarizes the pre-procedural and 3 months and 1 year post-ablation HRVs, comparing the PA-HSR group and others. There were no significant differences in pre-ablation rMSSD, LF, or HF between patients with and without PA-HSR. However, patients with PA-HSR showed a greater reduction in rMSSD ($P < 0.001$), LF ($P = 0.020$), and HF ($P = 0.015$) than those without at 3 months post-AF ablation, and this trends of rMSSD ($P < 0.001$) and HF ($P = 0.012$) were maintained at 1 year post-RFCA. When compared with pre-ablation values, reductions of HF ($P = 0.013$) and LF/HF ratio ($P = 0.005$) at 3 months after AF ablation were significantly greater in patients with PA-HSR than those without. In addition, the reduction in diameter of LA (ΔLA; -1.1 ± 3.7 vs. -3.0 ± 4.6 mm, $P = 0.055$) and LV (ΔLV end diastolic dimension; -0.7 ± 4.0 vs. 0 ± 3.5 mm, $P = 0.372$) and the improvement of ejection fraction (ΔEF; 0.7 ± 8.4 vs. 1.7 ± 7.7%, $P = 0.529$) were not significantly different between patients with and without PA-HSR on 1 year post-ablation echocardiogram (*Figure 1*).

Table 2 Comparisons of HRV parameters between patients with PA-HSR and those without

	PA-HSR ($n = 28$)	Others ($n = 963$)	*P*-value
HRV_{pre}			
Mean HR (bpm)	79.1 ± 11.4	68.5 ± 13.1	0.001*
rMSSD (ms)	24.7 ± 14.0	24.6 ± 19.9	0.973
LF (ms^2)	18.4 ± 11.9	15.5 ± 18.4	0.542
HF (ms^2)	11.1 ± 7.2	9.4 ± 9.0	0.462
LF/HF	1.7 ± 0.4	1.3 ± 0.8	0.001*
HRV_{3mo}			
Mean HR (bpm)	95.8 ± 3.8	70.5 ± 10.0	<0.001*
rMSSD (ms)	12.2 ± 9.3	21.5 ± 16.9	<0.001*
LF (ms^2)	4.6 ± 4.6	10.5 ± 13.4	0.020*
HF (ms^2)	4.6 ± 5.6	8.4 ± 8.1	0.015*
LF/HF	1.0 ± 0.6	1.2 ± 0.5	0.142
HRV change (3mo—pre)			
Δ Mean HR (bpm)	16.9 ± 10.0	2.2 ± 14.7	<0.001*
Δ rMSSD (ms)	-14.9 ± 14.6	-2.6 ± 24.7	0.058
Δ LF (ms^2)	-15.5 ± 11.7	-5.0 ± 20.6	0.051
Δ HF (ms^2)	-8.1 ± 7.2	-1.1 ± 10.6	0.013*
Δ LF/HF	-0.7 ± 0.6	-0.1 ± 0.9	0.005*
HRV_{1yr}			
Mean HR (bpm)	89.2 ± 8.7	71.6 ± 10.9	<0.001*
rMSSD (ms)	12.1 ± 5.5	20.7 ± 14.8	<0.001*
LF (ms^2)	8.8 ± 9.5	10.8 ± 13.2	0.475
HF (ms^2)	5.1 ± 5.0	8.0 ± 7.1	0.012*
LF/HF	1.7 ± 0.6	1.5 ± 3.9	0.751
HRV change (1yr—pre)			
Δ Mean HR (bpm)	10.9 ± 12.9	2.9 ± 15.1	0.036*
Δ rMSSD (ms)	-13.8 ± 14.5	-3.6 ± 22.0	0.087
Δ LF (ms^2)	-10.5 ± 16.6	-5.1 ± 18.2	0.273
Δ HF (ms^2)	-6.2 ± 9.2	-1.3 ± 9.4	0.060
Δ LF/HF	-0.5 ± 0.7	0.0 ± 0.8	0.859

HRV, heart rate variability; rMSSD, root mean square of differences between successive NN intervals; LF, low-frequency components; HF, high-frequency components.
*$P < 0.05$.

Post-atrial fibrillation ablation high sinus heart rate associated factors and clinical outcomes

We conducted uni- and multivariate regression analyses to determine echocardiographic and HRV parameters independently associated with PA-HSR (*Table 3*). In multivariate analysis, PA-HSR

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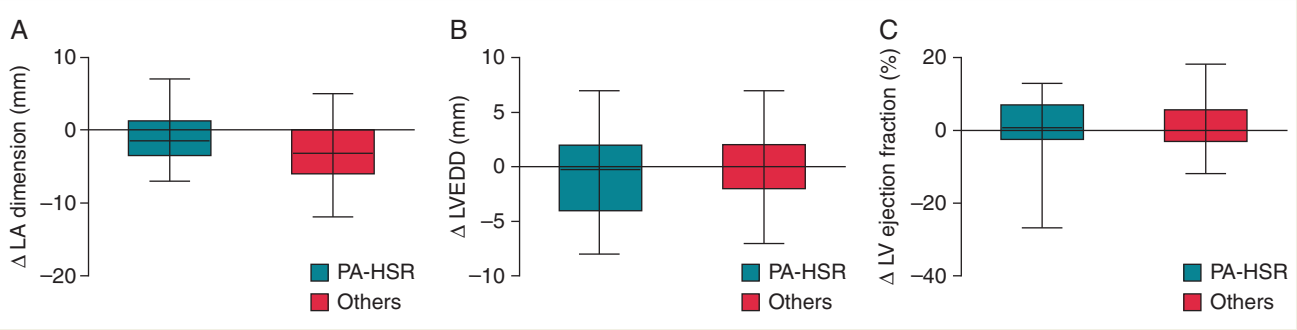

Figure 1 Changes on 1-year follow-up echocardiogram in patients with or without PA-HSR. Changes of LA dimension (*A*), LVEDD (*B*), and ejection fraction (*C*) in patients with and without PA-HSR at 1-year follow-up echocardiogram. PA-HSR, post-atrial fibrillation ablation high sinus rate; LVEDD, left ventricle end diastolic dimension.

Table 3 Independent predictors for PA-HSR

	Univariate		Multivariate	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
Age (years)	0.94 (0.91–0.96)	<0.001	0.95 (0.89–1.01)	0.119
Male	0.43 (0.20–0.91)	0.028	0.24 (0.05–1.18)	0.079
PAF	11.9 (1.61–88.16)	0.015	1.28 (0.08–20.81)	0.865
BMI (kg/m^2)	0.90 (0.78–1.04)	0.169		
LA dimension (mm)	0.88 (0.82–0.94)	<0.001	1.00 (0.88–1.14)	0.956
LV ejection fraction (%)	0.99 (0.96–1.05)	0.975		
Mean LA voltage (mV)	3.55 (1.96–6.42)	<0.001	3.55 (1.18–10.62)	0.024*
β-Blocker medication	0.73 (0.29–1.83)	0.499		
Mean HR_{pre} (bpm)	1.05 (1.02–1.08)	0.001	1.10 (1.03–1.17)	0.005*
Δ $rMSSD_{3mo}$ (ms)	0.98 (0.96–0.99)	0.043	0.96 (0.92–0.99)	0.047*
Δ LF_{3mo} (ms^2)	0.98 (0.96–1.00)	0.048		
Δ HF_{3mo} (ms^2)	0.95 (0.91–0.99)	0.010		
Δ LF/HF_{3mo}	0.38 (0.20–0.75)	0.005	0.66 (0.27–1.59)	0.355

PAF, paroxysmal atrial fibrillation; BMI, body mass index; LA, left atrium; LV, left ventricle; rMSSD, root mean square of differences between successive NN intervals; LF, low-frequency components; HF, high-frequency components.
*$P < 0.05$.

was independently associated with pre-procedural high average HR (OR 1.097; 95% CI 1.029–1.169, $P = 0.005$), high LA electrogram voltage (OR 3.545; 95% CI 1.183–10.618, $P = 0.024$), and reduced rMSSD on the 3-month post-procedural HRV (OR 0.959; 95% CI 0.919–0.999, $P = 0.047$). During 27 ± 17 months follow-up period, clinical recurrence rates of AF were significantly lower in patients with PA-HSR than those without (7.1 vs. 29.6%, $P = 0.010$; *Table 1*). The Kaplan–Meier analysis showed a significantly lower clinical recurrence rate in patients with PA-HSR compared with those without (log-rank test, $P = 0.020$, *Figure 2A*).

Comparison of post-atrial fibrillation ablation high sinus heart rate group with age-, sex-, and atrial fibrillation-type-matched control

We performed additional analysis for comparison of patients with PA-HSR to those without by using propensity score-matched population regarding age, gender, and type of AF (*Table 4*). The matched population showed consistent results compared with overall population without PA-HSR in terms of HRV parameter changes, reduction of LA diameter, and LV function. The Kaplan–Meier curves for the matched population according to PA-HSR also showed a significantly lower clinical recurrence rate in patients with PA-HSR compared with those without (log-rank test, $P = 0.030$, *Figure 2B*).

Discussion

In the current study, we investigated the clinical and prognostic implications of PA-HSR in patients who underwent RFCA for AF. We found that PA-HSR was independently associated with pre-procedural high average HR, high LA electrogram voltage, and reduced rMSSD of HRV at 3 months post-RFCA without adverse cardiac effects on follow-up echocardiogram 1 year post-RFCA.

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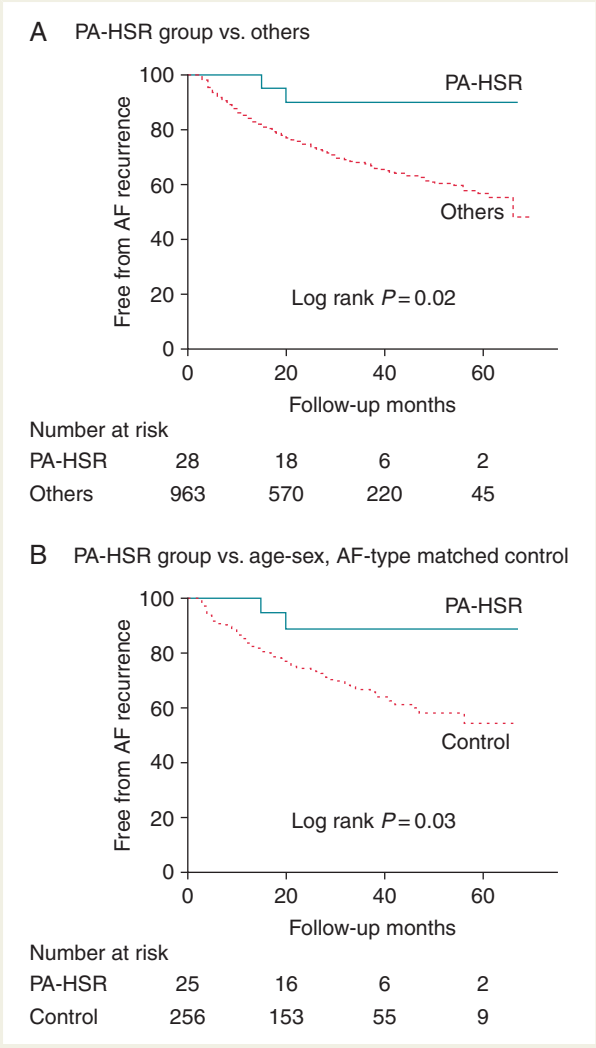

Figure 2 The Kaplan–Meier analysis for AF-free survival rates in patients with or without PA-HSR within total population and propensity score-matched population. Patients with PA-HSR showed a significantly lower clinical recurrence rate compared with those without in total population (*A*; log rank, $P = 0.020$) and propensity score-matched population (*B*; log rank, $P = 0.030$). PA-HSR, post-atrial fibrillation ablation high sinus rate.

Pre-procedural high HR is one of the most powerful predictors of PA-HSR in itself. The potential explanation can be that the patients with weak cardiac vagal effects at baseline were more susceptible to vagal denervation and PA-HSR after AF catheter ablation. In addition, patients with PA-HSR showed significantly lower clinical recurrence than those without.

High sinus heart rate in cardiovascular disease

As the depolarization of the sinoatrial node is mainly determined by autonomic nervous activity, there is little doubt that high sinus HR is directly related to the activity of the sympathetic nervous system or autonomic imbalance.[12] It is generally accepted that high sinus HR is an established risk factor for cardiovascular diseases and related poor clinical outcomes. In some disease states, such as hypertension or coronary artery disease, resting HR has been suggested to be a modifiable risk factor.[13,14] Appropriate HR reduction by β-blocker and ivabradine (I_f blocker) decreases mortality in patients with heart failure.[15] However, CPVI has been reported to increase HR, which positively correlates with the ablation success in a small population-based study.[16] This finding is consistent with those of the current study, and PA-HSR did not cause deterioration of ventricular function. Although the reason for this discrepancy is not clear, the pathophysiology of increased HR associated with primary underlying structural heart disease might be related to increased sympathetic nerve activity. In contrast, PA-HSR results mainly from parasympathetic modulation by RFCA.

Clinical implication of high sinus heart rate after atrial fibrillation ablation

Several studies have reported the relationship between AF and cardiac autonomic nerve activities. The projections of the parasympathetic nerve to the sinus node penetrate the epicardium in the origin of the PV complex.[17] Therefore, ablation of PVs could result in destruction of postganglionic parasympathetic fibres or specialized nerve terminals in PVs, which innervate the sinus node. Ablation from the superior vena cava to the right atrial septum after PV isolation also showed a vagal denervation effect, increased sinus HR, and better clinical outcomes.[7] Previously, Pappone *et al.* also described the relation between a higher HR with vagal denervation after AF ablation and a better outcome, however, changes in HRV parameters returned to pre-ablation levels at 6 months.[5] On the other hand, the reduction in HRV parameters in patients with PA-HSR lasts longer than 1 year post-RFCA in our study population. One of the possible explanation of these differences might be that open irrigation tip catheters we used increase transmural lesion formation and epicardial denervation more effectively than conventional catheters which is previously used.[18]

Heart rate variability parameters are useful marker of sympathovagal interaction,[19] and post-ablational attenuation of HRV parameters in our study populations, especially in PA-HSR group, yields effective parasympathetic denervation of the heart, which may predict better clinical outcomes after AF ablation. Furthermore, simultaneous reductions in LF and HF domains, which reflect sympathetic and parasympathetic nervous activity, respectively, were observed in the PA-HSR group, as well as a previous study.[5] Since intrinsic HR is predominantly suppressed by parasympathetic nerves, post-ablation HR increased after cardiac autonomic denervation. Even though cardiac sympathetic and parasympathetic nerves are frequently localized together, AF ablation mainly effects vagal denervation because the parasympathetic ganglia are located on the PV antrum.[20] Because parasympathetic hyperinnervation is one of important mechanisms of AF, PA-HSR, which is caused by vagal denervation, did not deteriorate in ventricular function or result in deleterious clinical outcomes. However, aggressive AF catheter ablation can induce vagus nerve damage with gastric hypomotility as collateral damage,[21] and a longer period of follow-up is warranted in these patients group.

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Table 4. Comparison of PA-HSR group with propensity score (age, sex, and AF type)-matched population

	PA-HSR (n = 25)	Others (n = 256)	P-value
Age, years	51.1 ± 14.4	53.8 ± 11.9	0.293
Male, n (%)	15 (60.0)	169 (66.0)	0.660
PAF, n (%)	24 (96.0)	238 (93.0)	1.000
BMI, kg/m^2	24.6 ± 3.6	24.7 ± 2.8	0.810
CHA_2DS_2-VASc score	1.5 ± 1.5	1.3 ± 1.2	0.436
Echocardiographic parameters			
LA dimension, mm	38.1 ± 5.5	40.1 ± 5.7	0.092
LA volume index, mL/m^2	28.2 ± 12.0	32.0 ± 11.7	0.148
LVEDD, mm	49.8 ± 4.3	49.5 ± 4.5	0.811
LV ejection fraction, %	62.7 ± 6.5	63.9 ± 6.9	0.390
E/E'	9.7 ± 5.0	10.3 ± 5.3	0.625
Δ LA dimension, mm	−1.0 ± 3.8	−2.6 ± 4.2	0.106
Δ LVEDD, mm	−0.8 ± 4.2	−0.1 ± 3.8	0.414
Δ LV ejection fraction, %	1.1 ± 8.6	1.0 ± 7.6	0.933
NavX electroanatomical map			
Mean LA voltage, mV	1.9 ± 0.6	1.3 ± 0.6	<0.001*
Mean LAA voltage, mV	4.1 ± 1.5	2.4 ± 1.5	<0.001*
Medication			
β-Blocker, n (%)	6 (24.0)	76 (29.7)	0.650
AAD, n (%)	1 (4.0)	25 (9.8)	0.488
HRV change			
Δ Mean HR_{3mo}	17.0 ± 10.5	3.1 ± 14.1	<0.001*
Δ $rMSSD_{3mo}$	−14.3 ± 15.6	−2.8 ± 24.5	0.101
Δ LF_{3mo}	−14.8 ± 12.5	−6.0 ± 21.9	0.160
Δ HF_{3mo}	−8.0 ± 7.8	−1.7 ± 11.2	0.049*
Δ LF/HF_{3mo}	−0.6 ± 0.6	−0.1 ± 0.8	0.029*
Δ Mean HR_{1yr}	10.6 ± 13.5	4.1 ± 13.4	0.084
Δ $rMSSD_{1yr}$	−13.8 ± 15.7	−3.6 ± 21.9	0.121
Δ LF_{1yr}	−13.5 ± 13.0	−6.6 ± 22.2	0.300
Δ HF_{1yr}	−7.7 ± 7.6	−1.6 ± 10.1	0.044*
Δ LF/HF_{1yr}	−0.1 ± 0.8	−0.1 ± 0.7	0.834
Ablation time, s	4934 ± 1099	4716 ± 1433	0.461
Procedure time, min	183.4 ± 34.2	184.5 ± 47.2	0.912
Early recurrence, n (%)	0 (0)	70 (27.3)	0.001*
Clinical recurrence, n (%)	2 (8.0)	78 (30.5)	0.019*
Follow-up duration, months	29.3 ± 18.1	26.3 ± 16.5	0.393

PAF, paroxysmal atrial fibrillation; BMI, body mass index; LA, left atrium; LVEDD, left ventricle end diastolic dimension; LV, left ventricle; E/E', early mitral inflow velocity to early diastolic mitral annular velocity ratio; AAD, antiarrhythmic drug; HRV, heart rate variability; rMSSD, root mean square of differences between successive NN intervals; LF, low-frequency components; HF, high-frequency components.
*$P < 0.05$.

Study limitations

This is an observational study from a single-centre prospective cohort registry that included a select group of patients referred for AF catheter ablation. Also, the relatively small population in the PA-HSR group limits the statistical power of predicting clinical outcome. A validation study in a separate group will help to determine the clinical significance of PA-HSR after AF ablation. Although the mean follow-up duration was 27 months, we evaluated cardiac function 1 year after RFCA. We expect our cohort database will provide data regarding the long-term effects of PA-HSR.

Conclusion

Post-AF ablation high sinus HR is observed in AF patients with smaller LA size and higher LA electrogram voltage and significant vagal modulation, without adverse cardiac effects demonstrated by 1-year follow-up echocardiogram. Post-AF ablation high sinus HR was associated with a significantly lower clinical recurrence rate of AF after catheter ablation.

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