Effect of ganglionated plexi ablation by high-density mapping on long-term suppression of paroxysmal atrial fibrillation – The first clinical survey on ablation of the dorsal right plexusus

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BACKGROUND Long-term outcomes of suppressing paroxysmal atrial fibrillation (PAF) with additive ganglionated plexus (GP) ablation (GPA) remains unknown.

OBJECTIVES The aim of the study is to assess potential role of additional GPA for PAF suppression.

METHODS This study consisted of 225 patients; 68 (group A: 58 male, aged 60 ± 11 years) underwent pulmonary vein isolation (PVI) alone and 157 (group B: 137 male, aged 61 ± 11 years) GPA followed by PVI. GPA was performed based on the high-density mapping with high-frequency stimulation (HFS) delivered to left atrial (LA) major GP. The latter 85 group B patients (54%) underwent ablation to a posteromedial area within superior vena cava as a part of dorsal right atrial GP (SVC-Ao GP).

RESULTS In group B, HFS was applied to 126 ± 32 sites, with a median of 47 GP sites (40.0%) being ablated. In patients undergoing an SVC-Ao GPA, HFS and the SVC-Ao GPA were applied at a median of 15 and 4 sites (29.4%), respectively. The PVI with a GPA provided higher PAF suppression than a PVI alone during more than 4 years of follow-up (56.7% vs 38.2%, odds ratio: 0.42, 95% confidence interval: 0.23–0.76, $P < .05$), but the SVC-Ao GPA did not provide further suppressive effects. Multivariate analyses revealed that tachycardia-bradycardia syndrome and non-PV foci were independent predictors of PAF recurrence after PVI with a GPA ($P < .01$).

CONCLUSION GPA to LA major GP by high-density mapping provides long-term benefits for PAF suppression over 4 years of follow-up, but the effect of an empiric SVC-Ao GPA could not be appreciated, suggesting little effect on suppressing non-PV foci.

KEYWORDS Ablation; Atrial fibrillation; Ganglionated plexus; Long-term follow-up; Non–pulmonary vein foci; Superior vena cava

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Introduction

Generation of atrial fibrillation (AF) had been proposed to be influenced by the cardiac autonomic nervous system (CANS).[1] Several experimental and clinical studies have reported CANS's role in AF.[2–4] Most AF is known to be triggered by ectopic firing within pulmonary veins.[5] Ganglionated plexi (GP), a CANS regulatory network, are preferentially clustered around pulmonary vein (PV) antrum and posterior wall of the left atrium (LA).[6] GP contain both sympathetic and parasympathetic nerves, and the activation of both nerves synergistically plays an important role in the genesis of PV ectopic firing.[7] PV isolation (PVI) by radiofrequency ablation (RFA) has been established to suppress AF. RFA's isolation durability has been a major concern of AF suppression, since reconnections between the LA and PV are often seen in recurrent patients.[8] An additive effect of GP ablation (GPA), which could eliminate PV firing, would be the complementary effect on AF suppression along with PVI. However, the efforts and approaches to finding and ablating GP vary among the studies, leading to different consequences of GPA.[9–13] In addition, part of GP clustered areas has been previously introduced in anatomical studies,[14,15] but the effect of ablation on such GP remains unclear. Ablation of such disregarded GP as well as GPA to LA major GP with PVI could lead to better outcomes for AF suppression than PVI alone or combination of LA GPA with PVI. This study also assessed long-term outcomes of AF suppression

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KEY FINDINGS

- Effect of ganglionated plexi (GP) ablation by high-density mapping with high-frequency stimulation (HFS) technique combined with pulmonary vein isolation (PVI) for suppression of paroxysmal atrial fibrillation on long-term outcome remains unknown.
- GP ablation by high-density mapping with HFS confers greater suppressive effect than PVI alone during long-term follow-ups over 4 years.
- Additive suppressive effect of ablation to clinically disregarded dorsal right atrial GP could not be appreciated for the long-term outcome and elimination of non–pulmonary foci.

after single GPA sessions with PVI and the factors contributing to AF recurrences.

Methods

Study population

This study consisted of 225 total patients with paroxysmal AF (PAF) (174 male, aged 60.7 ± 11.1 years). Sixty-eight patients underwent PVI alone before incorporating PVI with following GPA (group A: 57 male, aged 60.0 ± 11.4 years) and the remaining 157 (group B: 117 male, aged 61.3 ± 10.7 years) GPA based on high-density GP mapping with high-frequency stimulation (HFS) followed by PVI. Further, group B patients were divided into the following 2 subgroups: group B1 (n = 85, 61 male, aged 61.8 ± 10.4 years), which underwent HFS and GPA to the posteromedial area of the superior vena cava (SVC), outside of which contains a part of dorsal right atrial GP (SVC-Ao GPA); and group B2 (n = 72, 56 male, aged 60.2 ± 11.6 years), which did not undergo SVC-Ao GPA. Group B1 patients were the latter ones in group B after incorporating LA GPA along with PVI into SVC-Ao GPA with the former 2 interventions to expect better outcome for AF suppression than LA GPA with PVI.

Electrophysiologic study and PV isolation

An electrophysiologic (EP) study was performed in the fasting and deeply sedated state with intravenous administration of dexmedetomidine (0.2–1.4 μg/kg/h) and propofol (5–10 mg/kg/h). All antiarrhythmic dugs were withheld during for at least 5 half-lives before the ablation. In all patients, a 6F, 16-pole deflectable catheter (Japan Lifeline, Tokyo, Japan) was placed in the coronary sinus for pacing and recording, with the most distal electrode pair located at the 2- to 3-o'clock position on the mitral annulus. A 7F 10-pole electrode catheter (2 mm interelectrode spacing; Japan Lifeline) was positioned in the right ventricular outflow tract or apex for pacing and recording with its proximal electrodes in the His bundle region. A 20-pole deflectable circular catheter (1-2-1 mm interelectrode spacing; Lasso; Biosense Webster, Diamond Bar, CA) was placed at each PV orifice. A mapping and ablation catheter (Navistar ThermoCool or SmartTouch; Biosense Webster) was introduced into the LA for recording, mapping, and stimulation. PVI was performed with an ipsilateral circumferential isolation procedure. RFA power settings for PVI were 30–35 W for the anterior side of dual-sided PV, 25 W for the posterior portion of left-sided PV, and 25–30 W for the posterior portion of the right-sided PV. The duration of RFA was limited to 30 seconds at each point. After PVI, isoproterenol (0.01 μg/kg/min) was infused and a 20 mg adenosine triphosphate bolus (20 mg bolus) was injected to evaluate the dormant conduction (DC) and provoke non-PV foci triggering AF. When DC was documented, RFA was repeated until it disappeared. Finally, RFA of the cavotricuspid isthmus was performed in all patients. This study was approved by the Ethical Committee of Tokai University Hachioji Hospital (20R-126).

High-density GP mapping with high-frequency stimulation and ablation

Prior to PVI, HFS was performed using a mapping/ablation catheter and delivered with a frequency of 20 Hz, output of 10 V, and pulse width of 10 ms for 3–5 seconds with a cardiac stimulator (BC1100; Fukuda Denshi, Tokyo, Japan) to determine GP sites. The high-density GP mapping in this study is defined as that with distance of ≤5mm between the adjoining HFS-delivered sites. When a parasympathetic response (PR) was elicited by HRS at a site, defined as a transient R-R interval prolongation of ≥50% and/or decrease in systolic blood pressure of ≥20 mmHg compared to that before the HFS,[2,6,16] a GP was judged to be present, and GPA was performed with assistance of an electroanatomical map (CARTO XP or CARTO3; Biosense Webster). In this study, GP areas were classified into the following 5 GP areas according to previous studies by Armour and colleagues[17] and Pauza and colleagues[14,15]: superior left atrial GP (SLGP) including Marshall GP as a part of left dorsal GP, posterolateral left atrial GP (PLGP), posteromedial left atrial GP (PMGP), superior right atrial GP (SRGP), and posterior right atrial GP (PRGP), because more than one-third of GP have been shown to be located in the posterior LA (Figure 1).[18,19] The spatial order of delivering HFS and GPA was as follows, to minimize the interaction with GP coming late in the order[20]: SLGP, PLGP, PMGP, SRGP, and PRGP. PMGP was defined as that located inferiorly below the connecting line between bottom of left and right inferior PV in this study. The energy settings and RFA duration during GPA were 30–35 W for 30 seconds for SLGP and SRGP, 25–30 W for 30 seconds for PLGP and PRGP, and 20–25 W for 15–20 seconds for PMGP. In addition to LA GPA, HFS was delivered to SVC-Ao GP located in the posteromedial area 1–2 cm cranial to the SVC–right atrial junction. In the space surrounded by this area and the aorta, a third fad pad containing GP exists.[21] After LA GPA, SVC-Ao GPA was performed with a power setting of 20 W for 20 seconds in the latter 85 group B1 patients (54.1%). After

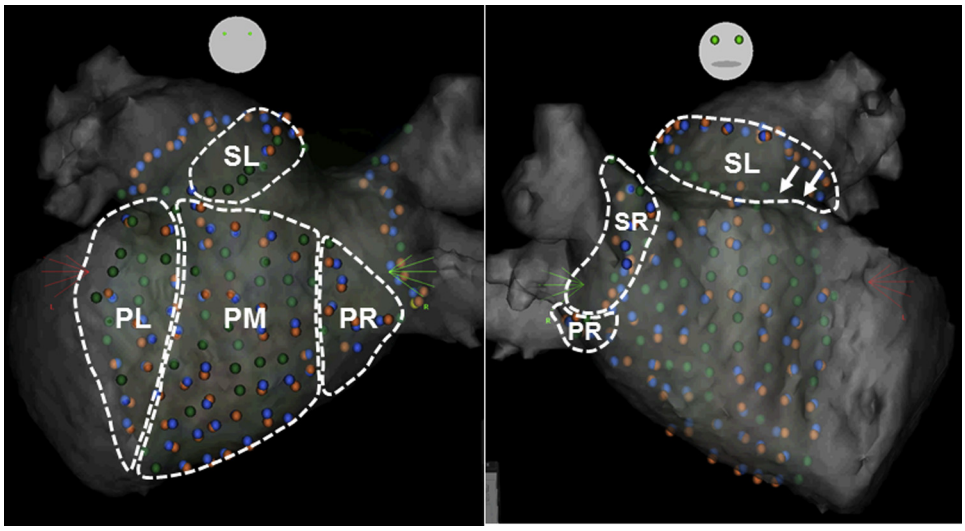

Figure 1 The spatial classification of ganglionated plexi (GP) in the left atrium (LA) from the posterior-anterior (left) and right anterior oblique (right) views in this study. The superior left GP contains the Marshall GP as a part of left dorsal GP, indicated by the arrows. Green and blue circles indicate the sites showing negative and positive parasympathetic reaction by high-frequency stimulation, respectively, and orange circles indicate GP ablation sites. PL = posterolateral left GP; PM = posteromedial left GP; PR = posterior right GP; SL = superior left GP; SR = superior right GP.

GPA to each point, HFS was applied to confirm disappearance of PR. When HFS still elicited PR, GPA was repeated until disappearance of PR by HFS. When the ablation catheter equipped with contact force was used, contact force was kept at ≥5 g during PVI and GPA.

Follow-up

The patients underwent ambulatory electrocardiogram (ECG) monitoring until discharge. The first hospital visit was 3–4 weeks after discharge and the second was scheduled at 6–8 weeks after the first visit, in which the patients underwent clinical interviews and ECG. The subsequent follow-ups containing ECG recordings were scheduled for every 3 months. The patients underwent 24-hour Holter ECG monitoring between 3 and 6 months after the procedure. If the patients complained of palpitations, the attending physicians performed arbitrary 24-hour Holter ECG. AF recurrence was defined as episodes with the same symptoms as their palpitations before RFA and/or documentation of any atrial tachycardia (AT) and/or AF lasting ≥30 seconds.

Statistical analysis

Data were expressed as the mean ± standard deviation (SD), if the variables were normally distributed; or as medians or first and third quartiles, if they were not. Differences in the metric variables between 2 groups were analyzed with unpaired *t* tests if the data were normally distributed, and with Wilcoxon signed rank or Mann-Whitney *U* tests otherwise. Categorical variables were compared with χ^2 or Fisher exact test. The PR rate among LA GP areas was compared using Kruskal-Wallis test. The survival curves were estimated by Kaplan-Meier method and assessed with a log-rank test. A multiple logistic regression analysis was applied to identify any independent predictors of AF recurrence. Variables that had a P value $< .05$ in the univariate analysis were included in the multiple regression model. All P values were 2-sided and a $P < .05$ was considered significant. All calculations were performed with SPSS statistical analysis software (Version 24; SPSS Inc, Chicago, IL).

Results

Patient characteristics

There was no difference in the patient characteristics except for valvular heart disease between groups A and B, as shown in Table 1. The comorbidity rate of valvular diseases, among which mitral regurgitation was most prominently documented in both groups, was significantly higher in group B than in group A, while LA dimension did not differ between groups. No patients underwent pacemaker (PM) implantations in group B, but 2 in group A underwent PM implantation before RFA. The rate of tachycardia-bradycardia syndrome (TBS) (defined as postconversion sinus pause for ≥3 seconds on AF termination) as a comorbidity was significantly higher in group B1 than in B2[22] (Supplemental Table A).

Positive rate of a PR in each GP area in group B

Of the 19,378 sites assessed by HFS (126 ± 32 sites per patient), PR was obtained at 7737 sites (39% ± 14%), all of which underwent GPA (median 47 [34–67] sites per patient) (Figure 2). In group B1, of total 1289 SVC-Ao GP sites (6.7%, median 15 [12–18.5] sites) assessed by HFS, PR was seen at 466 sites (29.4%, 4 [3–6] sites), where GPA was performed (Figure 3). A positive PR rate among each LA GP area did not differ (Figure 4), and the highest PR rate was documented at PMGP (50.0% [33%–75%]). Median PR rate among the remaining GP areas was almost similar, and that for SVC-Ao GP was 28.6% (17%–39%), which did not differ from the combined LA major GP area (nonsignificant [NS]).

Table 1 Comparison of patients' characteristics and electrophysiologic data between groups A and B

	Group A (N = 68)	Group B (N = 157)	Statistics
Male sex, n (%)	58 (85.5)	119 (75.8)	NS
Age (years)	60.0 ± 11.4	61.3 ± 10.7	NS
Height (m)	1.66 ± 0.08	1.66 ± 0.08	NS
Body weight (kg)	65.8 ± 10.7	65.7 ± 11.7	NS
BMI	23.7 ± 2.8	23.8 ± 3.3	NS
Hypertension, n (%)	31 (45.6)	65 (41.4)	NS
Diabetes mellitus, n (%)	4 (5.9)	18 (11.4)	NS
CHADS2 score	0.6 ± 0.7	0.6 ± 0.8	NS
Valvular disease, n (%)	25 (27.9)	90 (57.3)	$P < .01$
Structural heart disease (%)	2 (2.9)	13 (8.2)	NS
TBS, n (%)	7 (10.3)	22 (12.1)	NS
Echocardiographic data			
LVEF (%)	62.1 ± 9.1	61.6 ± 7.3	NS
LAD (mm)	40.8 ± 6.1	41.3 ± 6.3	NS
EP study data			
Documentation of ectopic foci other than PV, n (%)	17 (25.0)	38 (24.2)	NS
Ectopic foci from SVC, n (%)	10 (14.7)	23 (14.7)	NS
Evaluation for DC, n (%)	49 (72.1)	140 (89.2)	$P < .01$
Documentation of DC, n (%)	18 (36.7)	45 (32.1)	NS
Applied number of HFS	NA	126 ± 31	-
Median number of GPA (first, third quartile)	NA	47 (34, 65)	-
Median ratio of GPA to HFS (%) (first, third quartile)	NA	37 (30, 45)	-
AF termination during GPA, n (%)	NA	69 (43.9)	-
AFCL before GPA (ms)	NA	182 ± 30	-
AFCL after GPA (ms)	NA	199 ± 35[†]	-
Second session performed out of recurred patients, n (%)	28 (66.7)	49 (72.1)	NS
PV reconnection during second session performed, n (%)	27 (96.4)	45 (91.8)	NS

AF = atrial fibrillation; AFCL = local cycle length during atrial fibrillation; BMI = body mass index; DC = dormant conduction; EP = electrophysiologic; GPA = ganglionated plexi ablation; HFS = high-frequency stimulation; LAD = left atrial dimension; LVEF = left ventricular ejection fraction; NS = nonsignificant; PV = pulmonary vein; SVC = superior vena cava; TBS = tachycardia-bradycardia syndrome.
[†]$P < .001$ for comparison of AFCL between before and after GPA.

AF termination during the GPA and PVI

At the beginning of the session in group A, 45 patients (66%) presented with sinus rhythm (SR) and the remaining 23 had AF, out of whom AF could be converted to SR in 10 (43%) during PVI. Meanwhile, before the initial HFS, 126 patients (80%) presented in SR and the remaining 31 had AF in group B. HFS could induce AF in all patients presenting in SR. In SR patients, GPA was performed after AF sustainability was confirmed for at least 60 seconds. During GPA, SR could be restored in 69 patients (43.9%). SR restoration rate during GPA was significantly higher in patients presenting with SR than in those presenting with AF (48.4% vs 25.8%, $P < .001$). In 34 of the remaining 88 patients (39%) who remained in AF after GPA, SR could be restored during following PVI. The restoration rate during PVI was also significantly higher in the patients with SR than in those with AF (43.1% vs 26.1%, $P < .01$).

EP characteristics of both groups

Non-PV foci were documented after both isoproterenol and adenosine triphosphate injection in 17 (25.0%) and 38 (24.2%) group A and B patients, respectively (NS). The rate of SVC foci also did not differ between groups A and B or groups B1 and B2 (NS, Table 1 and Supplemental Table A). The rate of documenting DC did not differ between the groups, but the rate of evaluating DC was significantly higher in group B than in group A. The DC evaluation and documentation rates were significantly higher in group B1 than in group B2 (Supplemental Table A).

EP characteristics before and after GP ablation in group B

The AF cycle length (CL) before GPA had a mean value during 10 consecutive AF CLs recorded from distal coronary sinus of 182 ± 30 ms. It significantly prolonged to 199 ± 35 ms ($P < .01$) after GPA or immediately before AF terminated in the AF termination cases during GPA. However, CL after GPA did not differ between those with or without AF recurrences (Supplemental Table B).

Influence of the ablation on the heart rate and parameters for heart rate variability before and after the ablation

To evaluate an influence of PVI and GPA on CNS, the maximal, minimal, and mean heart rate (HR) and the

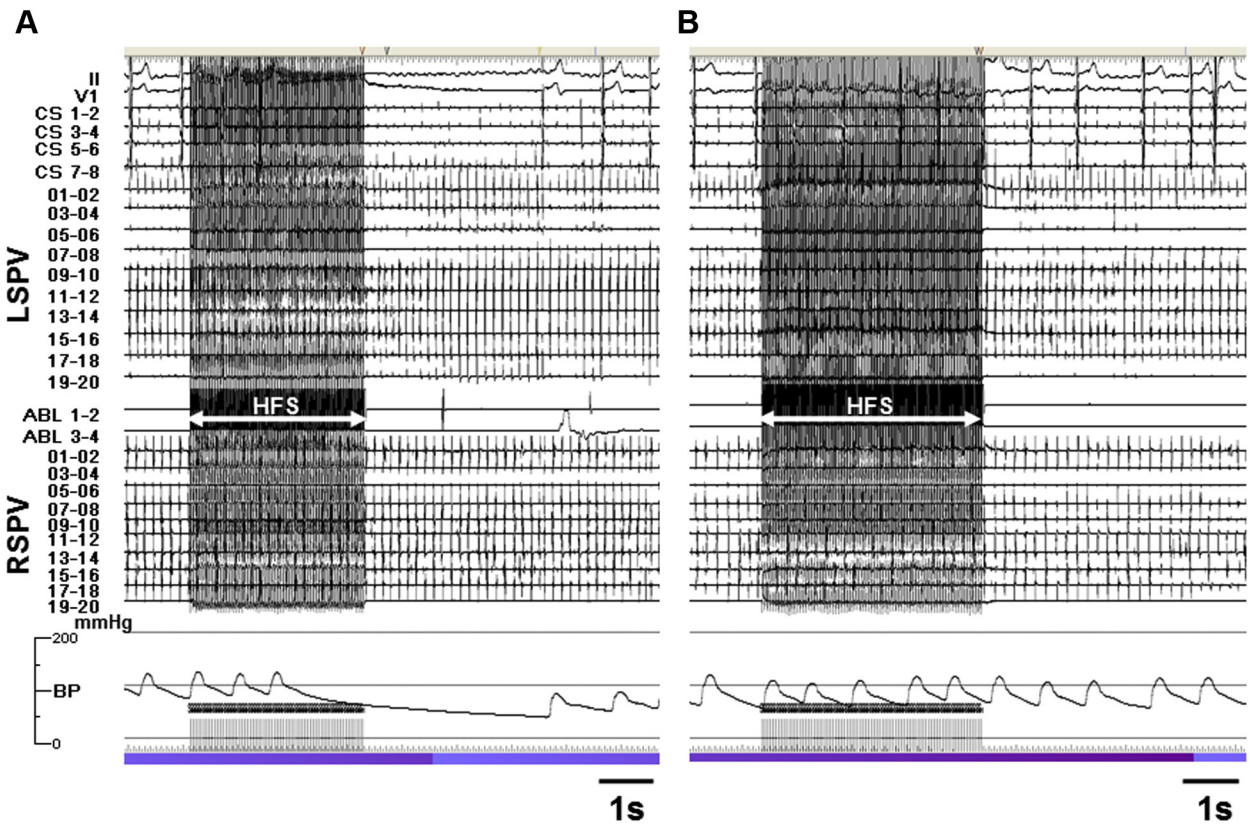

Figure 2 Representative recordings of positive parasympathetic reactions (PRs) elicited by high-frequency stimulation (HFS) indicated by double-headed arrows (**A**) and negative PRs (**B**). Shown from top to bottom are surface electrocardiogram lead II, lead V_1, and intracardiac bipolar signals from the most distal to proximal electrode pairs of the coronary sinus (CS) catheter, circular duodecapolar catheter located around the left superior pulmonary vein antrum (LSPV), distal and proximal pairs of the mapping catheter (ABL 1-2 and 3-4), and circular duodecapolar catheter located around the right superior pulmonary vein antrum (RSPV), and intra-arterial blood pressure (BP) measured from the left femoral artery. Note an obvious R-R prolongation and decreased blood pressure are elicited during and after the HFS in panel A. Refer to the text for details.

parameters reflecting parasympathetic activity, such as the standard deviation of all RR intervals (SDNN) and the mean of the standard deviations of all the RR intervals for each 5-minute segment of a 24-hour HR variability recording (SDNN), were compared between before and after the RFA based on the suitable data obtained from Holter monitoring for analysis. The data described above did not change in group A between before and after PVI. All these parameters except maximal HR were significantly changed after PVI and GPA (Supplemental Figure 1).

Follow-ups

The cumulative AF-free rate outside the initial 3-month blanking period during more than 4 years of follow-up was 38.2% and 56.7% for groups A and B, respectively (odds ratio: 0.42, 95% confidence interval [CI]: 0.23–0.76, $P < .05$). Kaplan-Meier analysis for freedom from any AT/AF in both groups is shown in Figure 5A. A log-rank test revealed that AT/AF-free rate in group B was significantly higher than in group A ($P < .01$). In a subgroup analysis of group B, that result did not differ between groups (61.2% vs 51.3% for group B1 and B2, respectively; odds ratio: 0.67, 95% CI: 0.36–1.27, NS). Kaplan-Meier analysis for freedom from any AT/AF in both subgroups is shown in Figure 5B. After RFA, 3 patients underwent PM implantations for symptomatic sinus node dysfunction (SND) (2 [28.6%] in group A and 1 [4.5%] in group B, NS).

PV-LA reconnection in recurrence patients

Among AF recurrence patients, 28 (66.7%) and 49 (72.1%) patients underwent the second session for groups A and B, respectively (NS). The PV-LA reconnection was documented in 27 (96.4%) and 45 patients (91.8%) for group A and B, respectively (NS) (Table 1). That also did not differ between groups B1 and B2 (Supplemental Table C).

Factors related to AF recurrences after PVI and GP ablation

The factors related to AF recurrences were compared between patients with and without recurrences (Supplemental Tables B and C). A univariate analysis revealed no difference in those factors in group A. Meanwhile, the rate of TBS documented before RFA and non-PV foci documented during the session were significantly higher in AF recurrence patients than those without in group B ($P < .01$). Non-PV foci were most frequently documented in SVC (n = 33 out of 61 total non-PV foci in 55 patents, 54%) in both groups. A multiple logistic regression analysis revealed that coexistent

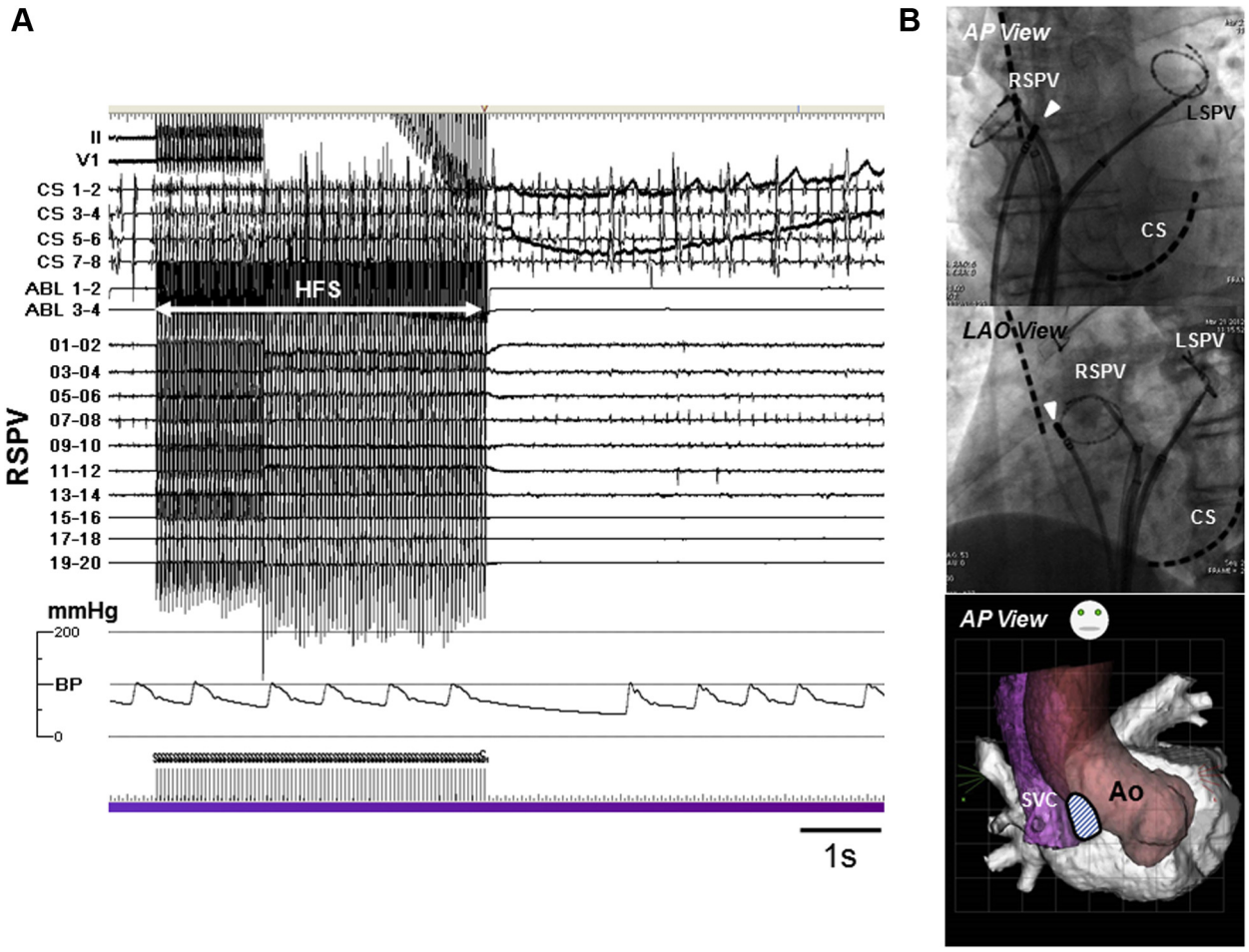

Figure 3 **A:** Representative recording of parasympathetic reactions elicited by high-frequency stimulation (HFS: *double embedded arrows*) of the SVC-Ao GP. **B:** Shown from top to bottom are the catheter positions for stimulating the SVC-Ao GP, indicated by the arrowheads on the cine-frame (top and middle panels); and schematic location of the SVC-Ao GP by the area indicated by oblique lines on the 3-dimenstional reconstructed image (bottom panel). Refer to the text for the details. Ao = aorta; GP = ganglionated plexus; SVC = superior vena cava. Other abbreviations are as in Figure 2.

TBS and documentation of non-PV foci were independent predictors of AF recurrences after GPA and PVI ($P < .01$, Table 2). Those factors also revealed significant differences between subgroup B1 patients with and without recurrences in the univariate analysis (Supplemental Table C) and independent predictors in group B1 (Supplemental Table D).

Discussion

The major findings in this study were as follows: first, GPA based on high-density mapping with HFS combined with PVI provided more suppressive effects on PAF than PVI alone during long-term follow-ups >4 years. Second, the first empiric RFA clinical survey on SVC-Ao GPA could not provide any additional benefit for PAF suppression. Lastly, coexisting TBS and non-PV foci were independent predictors of AF recurrences after GPA with PVI.

Suppressive effects of ablation to major LA GP and PVI

There have been studies assessing GPA's effect on suppressing PAF. GPA is inferior to PVI, but combined GPA and PVI provides better outcomes than GPA and/or PVI alone.[9–12] Those studies were mainly based on anatomical approaches, not functional approaches with HFS. Scherlag and colleagues[2] reported higher suppressing effects with functional GPA and PVI than PVI alone. When comparing anatomic and functional approaches, the former provided better outcomes than the latter. It could be possible that the better outcome of the former approach was attributed to more GPA applications than the latter.[13] PMGP in this study might include part of PLGP and PRGP on previous anatomical approach; thus total PLGP, PMGP, and PRGP area should be larger than PLGP and PRGP area in the previous classification,[6] implying greater effort than in the previous studies with high-density mapping. In addition, follow-up periods of previous studies were shorter- or mid-term, ranging from 12 to 24 months.[2,11,12] This study showed follow-up data of more than 4 years in PAF patients undergoing functional GPA and PVI.

Effect of SVC-Ao GPA on suppressing PAF

In 20% of AF patients, non-PV foci could be found.[23–25] In group B, SVC was the highest documented site (23 out

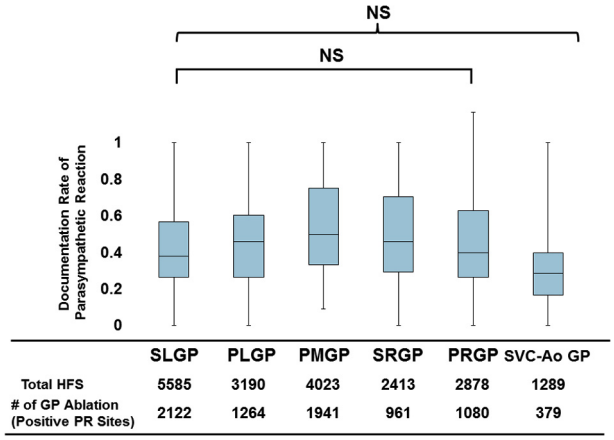

Figure 4 The comparison of the parasympathetic reaction (PR) rate elicited between the 5 left atrial (LA) ganglionated plexus (GP) areas and that of the overall LA GP and SVC-Ao GP areas. There was no difference in the PR rate among the LA GP areas (nonsignificant [NS]) or combined LA GP and SVC-Ao GP areas. Abbreviations are as in Figure 1.

of 44 foci [52.3%] in 38 patients), but other non-PV foci areas could not be determined because of inability to spatially determine non-PV foci with limited number of catheters. Chiou and colleagues[21] raised the importance of SVC-Ao GP within the third fad pad, since that GP is the head stage of intrinsic CANS, through which most efferent vagosympathetic fibers travel to the atrium. Lu and colleagues[26]

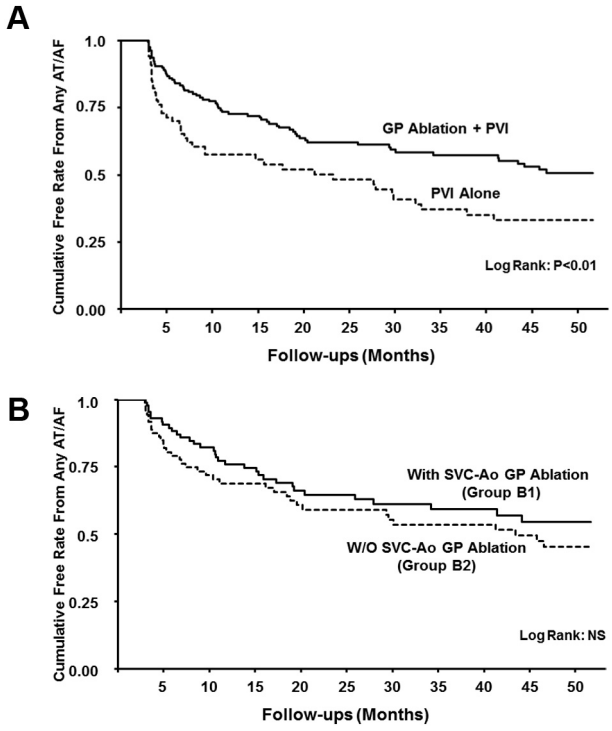

Figure 5 Kaplan-Meier curves of the cumulative atrial tachycardia (AT)-free and/or atrial fibrillation (AF)-free rate after single ablation procedures. **A:** The AT/AF-free rate in the patients undergoing a combined ganglionated plexus (GP) ablation and pulmonary vein isolation (PVI) was significantly higher than that for a PVI alone ($P < .05$). **B:** The rate in group B1 patients with additional SVC-Ao GP ablation did not differ from that in group B2 patients without (nonsignificant [NS]).

Table 2 Multiple logistic regression analysis for predictor of atrial fibrillation recurrence in group B

	Odds ratio	95% CI	Statistics
TBS (%)	3.97	1.40–11.3	$P < .01$
Documentation of ectopic foci other than PV (%)	4.50	1.46–13.9	$P < .01$
Ectopic foci from SVC (%)	0.99	0.25–3.90	NS

NS = nonsignificant; PV = pulmonary vein; SVC = superior vena cava; TBS = tachycardia-bradycardia syndrome.

demonstrated the causal relationship between SVC-Ao GP and SVC-initiated AF and SVC-Ao GPA's effect on suppressing AF. Half of group B patients underwent empiric SVC-Ao GPA irrespective of SVC firing. The AF-free rate, however, did not differ between those with and those without SVC-Ao GPA (Figure 5B). In group B1, the documented SVC foci as well as non-PV foci rate was significantly higher in recurrent patients than nonrecurrent patients (Supplemental Table C). Furthermore, among all group B patients with SVC foci (n = 23), 12 (52.1%) underwent SVC-Ao GPA. The AF recurrence rate did not differ between those with and without SVC-GPA (66.7% vs 72.7%, NS), suggesting that SVC-Ao GPA might have little benefit for AF suppression even in cases exhibiting SVC foci.

TBS and non-PV foci as factors for PAF recurrence after ablation

In previous studies that assessed RFA effects on suppressing PAF in SND patients, the AF-free rate ranged from 39% to 87% after the last session.[27–32] In our combined patients in both groups, the cumulative AF-free rate in TBS patients was 34.5%, which was lower than in those studies. Our lower suppression rate might be attributed to the results obtained from single sessions. The AF suppression rate in both patient groups without SND (TBS) was higher than that in those with SND, but not significantly (53.6%, odds ratio: 2.2, 95% CI: 0.42–4.96, $P < .1$). Two of 3 patients who needed PM implantation developed AF recurrences (1 in each group), which may indicate that progression of SND might be hampered by GPA and/or PVI, but AF suppression effect is limited in such patients.[28–30] AF can cause structural and electrophysiological remodeling in the sinoatrial node and its surrounding tissues. The structural remodeling caused by AF, which prevents the electric conduction, renders easier conducted wave break, thereby generating multiple wavefronts that signal AF initiation.[33,34] Such structural remodeling caused by AF, which normally occurs in sinoatrial node, suggests the potential mechanism for the development of SND.[35] There have been several known alterations of the ion channels involved in AF.[36] In the setting of fibrosis and reduced repolarization reserve caused by the ion channel, alteration caused by AF can promote early afterdepolarization and, in turn, atrial and ventricular arrhythmias.[37] Several reports have emphasized coexisting non-PV foci as recurrent factors.[23,27,38–40] The rationale for GPA is based on suppression of ectopic firings within PVs. Given that

PV-LA connections could recover, GPA may play a complementary role in subsequent AF suppression. The lesser AF recurrence rate in patients with combined GPA and PVI in this study might corroborate such a rationale, which was also ascertained by non-difference in the PV-LA reconnection rate during the second session between groups A and B. Furthermore, among those undergoing GPA, those with AF recurrence had more non-PV foci than those without, suggesting that GPA effect on suppressing firing from non-PV foci may be limited.

Limitations

Since this is a nonrandomized and single-center study, the results shown here drive the data from the retrospective observational study. AF recurrence could have been underestimated, since it was assessed only by ECG and patient symptoms during regular outpatient clinic visits and by 24-hour Holter monitoring at 3–6 months after RFA or arbitrarily. The results shown here should be verified using more frequent ECG monitoring with outpatient telemetry monitoring devices in future studies. Non-difference in the documented rate of non-PV foci between patients with and without recurrence in group A might be attributed to the significantly lower rate of the DC-provoking maneuver in group A than group B, which also might be related to greater recurrences of AF in group A, although PV-LA reconnection rate during the second session in the recurred patients did not differ between groups A and B. The nonrandomized nature in regard to the different therapies applied might influence the results obtained, since unknown confounders such as arbitrary attending physician requests and/or patients' visual aspects existed. Finally, SVC-Ao GP ablation might create new arrhythmogenicity, leading to recurring AF.[41]

Conclusion

The additive effects of GPA by high-density mapping with HFS combined with PVI confers >4-year PAF suppression benefit, more than PVI alone. The empiric SVC-Ao GPA added to LA GPA had no additional effect on suppressing PAF. The GPA's additive effect may have been attenuated in cases with TBS and/or non-PV foci, which could be independent predictors of AF recurrence after GPA with PVI.

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Disclosures

The authors have no conflicts to disclose.

Authorship

All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent

All participants gave written informed consent.

Ethics Statement

The research reported in this paper adhered to the guidelines set forth by the Helsinki Declaration.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.07.002.

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