Relation Between Autonomic Nervous Activity after Pulmonary Vein Isolation and Recurrence in Paroxysmal Atrial Fibrillation Patients

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Objective: Pulmonary vein isolation (PVI) has been widely used for the treatments of paroxysmal atrial fibrillation (PAF); however, AF recurrence remains a significant challenge. We evaluated relation between autonomic nervous activity and AF recurrence using heart rate variability (HRV) and deceleration and acceleration capacity (DC/AC) analyses.
Methods: High-resolution Holter electrocardiogram was performed in 56 PAF patients pre- and 3 and 6 months post-PVI by cryoballoon. HRV and DC/AC analysis data were compared between the non-recurrence and recurrence groups.
Results: AF recurrence occurred in 10 cases. Total heart beats and maximum heart rate significantly decreased and minimum heart rate increased only in the non-recurrence group post-PVI. In HRV analysis, root mean square successive difference (RMSSD), low-frequency components (LF), high frequency components (HF) and LF/HF significantly decreased only in the non-recurrence group at both 3 and 6 months post-PVI; in contrast, significant decreases in RMSSD, LF and HF were observed in the recurrence group only at 6 months. In DC/AC analysis, DC significantly decreased in both groups post-PVI; in contrast, AC increased only in the non-recurrence group, resulting in significantly greater [AC]/DC ratio in the recurrence group at 3 months post-PVI.
Conclusions: To prevent AF recurrence after PVI, it is important not only to reduce vagosympathetic overall activity but also to minimize imbalance between vagosympathetic reflex responses.

Key words: paroxysmal atrial fibrillation, pulmonary vein isolation, recurrence, cryoballoon ablation, autonomic nervous activity

INTRODUCTION

The Japanese Circulation Society has been performing an epidemiological research for atrial fibrillation (AF). In approximately 630,000 people aged 40 and over that received medical checkup in 2003, the incidence of AF increased with age, for instance the incidences of AF are 3.44% and 1.12% in men and women in their 70s, and 4.43% and 2.19% in men and women in their 80s, respectively. Currently it is expected that there are approximately 800,000 patients with paroxysmal atrial fibrillation (PAF) as well as 1,700,000 AF patients in total in Japan.

Arrhythmia substrate of AF is attributed to abnormal automaticity in the pulmonary vein-left atrial junction as primary pathogenesis; therefore, pulmonary vein isolation (PVI) with percutaneous radiofrequency catheter ablation (RFCA) has been applied as standard therapy. Cryoballoon as an alternative ablation has been also recently developed. It has been reported that sinus rhythm had been maintained in 47% and 67 to 94% of the patients for 1 to 3 years after a single PVI and two or more PVIs, respectively [1]. After a single PVI, rates of preservation of sinus rhythm were 40%, 37%, and 29% at 1, 2, and 5 years post-PVI, respectively, showing gradual decrease; however, most of AF recurrence occurred within the first 6-months post-PVI [2]; therefore, pulmonary vein isolation (PVI) has been applied as standard therapy. Percutaneous radiofrequency catheter ablation (RFCA) had been widely used for PVI; however, cryoballoon had been also recently developed as an alternative ablation and it has been becoming more popular.

Onset and persistence of AF are attributed to sympathetic/parasympathetic enhancement or imbalance [3, 4]; therefore, in addition to PVI against arrhythmia substrate, therapies modulating autonomic nervous activity have been applied as effective treatment. Standard medications for the treatment of AF include β-blockers and sodium channel blockers with antimuscarinic effect (class Ia antiarrhythmic agents). In addition to PVI, another ablation targeting the ganglionated plexi (GP) localized close to the atrium, ie, GP ablation, has been also used for the treatment of PAF [5–7].

It has been reported that a decrease in low/high frequency component ratio (LF/HF) in heart rate variability (HRV) analysis was independently associated

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with post-PVI AF recurrence as a risk factor [8]. Bauer *et al.* [9] proposed deceleration capacity (DC) and acceleration capacity (AC) of instantaneous heart rate to selectively quantify vagal and sympathetic activities as an alternative of autonomic nervous activity indices separately from HRV analysis [9]. Their study demonstrated that mortality in patients with decreased DC (<4.5 msec) after myocardial infarction was significantly higher indicating DC as a powerful prognostic predictor. We evaluated relation between autonomic nervous activity and AF recurrence.in the patients that received cryoballoon PVI, using 2 independent analyses, i.e. heart rate variability (HRV) and deceleration and acceleration capacity (DC/AC) analyses.

PATIENTS AND METHODS

Study Subjects

We examined 83 consecutive patients that received cryoballoon PVI for the treatment of PAF at Tokai University Hospital during the period from April 2017 through March 2018 as candidates of study subjects. High-resolution Holter electrocardiogram (ECG) was performed in all of them before and after PVI. After excluding patients with persistent atrial fibrillation, bundle branch block, pacemaker rhythm, or extrasystole (>1000/24 hours) preventing detailed analysis, 56 patients were enrolled to the study. The study conformed with the principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board of the facility, and all study subjects provided written informed consent.

Patients' baseline characteristics including age, sex, history of smoking, body mass index (BMI), CHADS2 Score (congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, history of stroke/transient ischemic attack [TIA]), and presence or absence of renal dysfunction or dyslipidemia were obtained from all of the study subjects. In addition, blood test (hemoglobin, creatinine clearance, and brain natriuretic peptide), echocardiography (left ventricular ejection fraction [%], left atrial diameter [mm], early diastolic filling velocity [E] to the atrial filling velocity [A], early diastolic transmitral flow velocity [E] to the mitral annular velocity [e']) as well as questionnaire about medication were performed prior to PVI. Furthermore, total procedure time of PVI, fluoroscopy time, cryoablation time, and complications (including cardiac tamponade, cerebral infarction, esophageal ulceration, vascular accident, pulmonary vein stenosis, phrenic nerve palsy, and perioperative death) were also evaluated.

The study subjects were classified into two groups, AF non-recurrence group and recurrence group, to determine prognostic factors for AF recurrence. AF recurrence was defined when paroxysmal atrial arrhythmias; such as atrial tachycardia, atrial flutter and AF lasting at least 30 seconds were determined with high-resolution Holter, 12-lead, or event ECG at outpatient visit.

Cryoballoon Pulmonary vein isolation (PVI)

Anticoagulants had been applied since at least 4 weeks prior to PVI and continued during the perioperative period. Treatment with β-blockers, non-dihydropyridine calcium channel blockers, or antiarrhythmics was discontinued 3 days prior to PVI. After PVI, antiarrhythmic (Bepridil, 50 mg b.i.d., for 1 month), anticoagulant (for 3 months) and β-blocker (Bisoprolol fumarate 1.25mg for 6 months) were applied. Administration of anticoagulant was continued in recurrence cases. Dexmedetomidine and/or sevoflurane was used as a sedative during the operation. As a catheter approach, the sheaths were inserted from right internal jugular vein, left and right femoral veins, and left femoral artery, and electrode catheters were placed in the coronary sinus to great cardiac vein. A transseptal puncture was performed with Brockenbrough method using a radiofrequency transseptal needle (Japan Lifeline Co., Ltd., Tokyo, Japan) for left atrial access with echocardiographically identifying the fossa ovalis. Intravenous anticoagulant of heparin sodium was applied at 7000 unit at the initial time, followed by additional intravenous administrations at 1000 to 2000 unit to maintain an activated clotting time (ACT) of ≥ 350 seconds.

In the PVI using cryoballoon ablation, 2 sheaths (FlexCath Advance™ Steerable Sheath: 15-French, Medtronic, Minneapolis, MN, USA and SL0: 8-French, St. Jude Medical Inc., Little Canada, MN) were inserted through the left atrium, and a ring catheter with 8 evenly spaced electrodes (20 mm in diameter, Achieve™ Mapping Catheter, Medtronic) was inserted into each of the pulmonary veins, using a balloon catheter (Arctic Front Advance™ Cardiac Cryoablation Catheter, Medtronic). The balloon was inflated with vaporized nitrous oxide at the vestibular entrance to obstruct the pulmonary vein and cooled down to -40 to -60°C to lead to cryocoagulation and degeneration in the adherent tissues. The time of balloon inflation was up to 180 seconds at time for each of the pulmonary veins; the balloon inflation was terminated in the left pulmonary vein when esophageal temperature dropped to ≤ 16°C, and in the right pulmonary vein when phrenic nervous stimuli was decreased, or compound motor action potential reached 70% of baseline level. When pulmonary vein potential persisted indicating insufficient isolation after cryocoagulation, radiofrequency ablation was added with deflectable irrigated catheter (Tip electrode: 4 mm, 8-French, FlexAbility-Ablation Catheter, St. Jude Medical, Inc. St. Paul, MN, USA).

The success endpoint was predetermined as a bidirectional block of conduction between the left atrium and pulmonary vein. No GP ablation was added in any cases.

High-resolution Holter electrocardiogram

A 24-hour high-resolution Holter ECG recording (FM-180S, Fukuda Denshi Co., Ltd., Tokyo, Japan) was performed with CC5, NASA and CB2 leads for all study subject's pre and 3 and 6 months post-PVI. The first recordings were performed within 1 month before PVI enforcement (averaged 9.7 days, median 8.9 days). Obtained data were analyzed with analytical software (SCM-8000, Fukuda Denshi Co., Ltd.), followed by manual confirmation by 2 independent cardiologists. For the analysis of HRV, RMSSD was calculated as a time domain analysis, and LF, HF, and LF/HF as frequency-domain analysis. For the DC/AC analysis, following the method reported by Bauer *et al.* [9], RR

interval was analyzed, and the RR intervals longer and shorter than the preceding interval were identified as the anchors for DC and AC, respectively. Segments of RR interval data (60 beats before and after each anchor) were extracted, and all segments were aligned at the anchors as zero of x-axis, then the average of RR interval data were calculated by each heart beat before and after the anchor.

Statistical Analysis

For clinical background factors and PVI related factors, data in continuous variables are shown as mean ± standard deviation, and data in nominal scale as number (%) (Tables 1 and 2). Comparisons in variables between non-recurrence and recurrence groups were performed with Student's t-test or chi-squared test using a statistical analysis software (SPSS® Statistics V22.0, IBM). In time series analysis at pre, 3 and 6 months post-PVI, repeated-measures ANOVA tests were performed (Supplement Tables 1 and 2), followed by a post hoc test in comparison between pre (baseline) and post-PVI values on the index with significant difference observed with ANOVA (Fig. 1–3). Statistical significance was defined as $p < 0.05$.

RESULTS

Baseline Characteristics of the Study Subjects

There were 56 study subjects enrolled in the study, including 46 non-recurrent cases (82%) and 10 recurrent cases (18%) determined post-PVI (follow-up observation period: 301 ± 33.4 days ranged from 243 to 379 days) (Table 1). Duration from PVI to recurrence was 121.3 days (median 73 days). There were no statistically significant differences in any factors of patients' baseline between non-recurrence and recurrence groups. There were no statistically significant differences in any time factors related to PVI procedures (Table 2). No postoperative complications were observed in any subjects irrespective of presence or absence of AF recurrence.

High-resolution Holter electrocardiography

According to repeated-measures ANOVA, there were significant differences in all parameters except [AC]/DC between pre- and post-PVI in the non-recurrence group (Supplement Table 1). In contrast, there were significant differences only in limited parameters including RMSSD, LF, HF, DC, and [AC]/DC in the recurrence group (Supplement Table 2). In the post hoc test, total heart beats and maximum heart rate significantly decreased and minimum heart rate increased only in the non-recurrence group post-PVI. Supraventricular premature contraction (SVC) significantly decreased in the non-recurrence group at 3 months post-PVI compared to the baseline; however, such statistically significant decrease was no longer observed at 6 months post-PVI (Fig. 1). There were no statistically significant differences in total heart beats, maximum heart rate, minimum heart rate or frequency of SVC between non-recurrence and recurrence groups at any time points.

The results of HRV analysis are shown in Fig. 2. RMSSD, LF and HF values were significantly greater in the recurrence group compared to the non-recurrence group at baseline. At 3 months post-PVI, RMSSD, LF, and HF values significantly decreased compared to baseline values only in the non-recurrence group but not in the recurrence group, maintaining the statistically significant difference between 2 groups at 3 months. At 6 months post-PVI, however, RMSSD, LF, and HF values decreased both recurrence and non-recurrence groups, resulting in no statistically significant difference between 2 groups at 6 months. LF/HF values significantly decreased only in the non-recurrence group post-PVI compared to the baseline, but there was no statistically significant difference in LF/HF between 2 groups either pre- or post-PVI.

DC significantly decreased in both groups post-PVI compared to baseline, with no statistically significant difference between 2 groups at either pre- or post-PVI time point (Fig. 3). AC had no statistically significant difference between 2 groups at baseline, however significantly increased only in the non-recurrence group post-PVI, resulting in statistically significant difference between 2 groups at both 3 and 6 months. The time-course of the change in DC and AC demonstrated a similar pattern to the results of HRV only in the non-recurrence group, but not in the recurrence group. [AC]/DC ratio was significantly greater in the recurrence group compared to the non-recurrence group at 3 months post-PVI.

DISCUSSION

We evaluated relation between autonomic nervous activity and AF recurrence.in the patients that received PVI, using 2 independent analyses, i.e. HRV and DC/AC analyses, and obtained the following 3 critical points: First, total heart beats and maximum heart rates significantly decreased and minimum heart rate increased only in the non-recurrence group post-PVI. Second, HRV parameters significantly decreased only in the non-recurrence group at both 3 and 6 months post-PVI. Lastly, in DC/AC analysis, DC significantly decreased in both groups post-PVI; in contrast, AC increased only in the non-recurrence group post-PVI, resulting in significantly greater [AC]/DC ratio in the recurrence group than the non-recurrence group at 3 months post-PVI.

Relation between AF and autonomic nervous activity

AF development is attributed to abnormal impulse formation and cardiac conduction [10]. The former includes abnormal automaticity and triggered activity, and the latter includes re-entry circuit attributed to delayed or inhomogeneous conduction. In addition to these critical factors, variations of the autonomic nerve are important modifiers. The autonomic nerve consists of the sympathetic and parasympathetic nerves. Noradrenaline released from the sympathetic-nerve terminals has positive chronotropic response while acetylcholine (Ach) released from the parasympathetic-nerve terminals has negative chronotropic response. Coumel *et al.* [3, 11] reported that vagal AF tended to occur nocturnally in patients with no underlying heart disease; in contrast, AF often develops in patient with underlying heart disease under enhanced sympathetic nervous activity due to exercise and mental excitement. HRV analysis using Holter ECG revealed that a primary increase in adrenergic sympathetic tone followed by a marked modulation toward vagal predominance

Table 1 Comparison of Baseline Characteristics

	Non-recurrence (N = 46)	Recurrence (N = 10)	*P* value
Age (years)	63 ± 8.5	65 ± 7.4	0.24
Men	32 (70%)	9 (90%)	0.35
Current smoker	18 (39%)	4 (40%)	0.99
Body mass index (kg/m^2)	23.5 ± 3.8	23.9 ± 2.2	0.37
Congestive heart failure	6 (13%)	1 (10%)	0.99
Hypertension	29 (63%)	6 (60%)	0.86
Age ≥ 75 y/o	3 (7%)	0	-
Diabetes mellitus	8 (17%)	3 (30%)	0.39
Stroke/Transient ischemic attack	0	1 (10%)	-
Chronic kidney disease	9 (20%)	2 (20%)	0.99
Hyperlipidemia	19 (41%)	4 (40%)	0.99
CHADS2 score			
0	16 (35%)	5 (50%)	0.59
1	20 (44%)	2 (20%)	0.29
2	10 (22%)	3 (30%)	0.68
3	0	0	-
Laboratory exam			
Hemoglobin (g/dL)	14 ± 1.8	15 ± 1.8	0.10
Creatinine clearance (mL/min)	70.3 ± 22.1	70.1 ± 21.4	0.44
Brain natriuretic peptide (pg/mL)	55 ± 66.1	53 ± 45.6	0.36
Ultrasound cartdiogarphy			
Left ventricular ejection fraction (%)	71 ± 8.4	72 ± 7.5	0.33
Left atrial diameter (mm)	36 ± 6.2	38 ± 6.9	0.26
E-wave deceleration time (msec)	207 ± 42.4	206 ± 53.0	0.37
E/A	1.1 ± 0.4	1.2 ± 0.4	0.11
E/e'	11.0 ± 4.4	9.3 ± 2.6	0.14
Medications before procedure			
Anti-coagulant	*46 (100%)*	*10 (100%)*	-
Beta-blocker	*38 (83%)*	*9 (90%)*	0.92
Antiarrhythmic drugs	*30 (65%)*	*8 (80%)*	0.59
Statin	*11 (24%)*	*1 (10%)*	0.43
ACE inhibitor/ARB	*13 (28%)*	*1 (10%)*	0.42
Calcium-blocker	*4 (9%)*	*1 (10%)*	0.99

Data are presented as mean ± standard deviation or as number (%). E/A, early diastolic filling velocity (E) to the atrial filling velocity (A); E/e', early diastolic transmitral flow velocity (E) to the mitral annular velocity (e'); ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Table 2 Procedure success and prognosis

	Non-recurrence (N = 46)	Recurrence (N = 10)	*P* value
Procedure success	50 (100%)	11 (100%)	-
Total procedure time (min)	206 ± 49.5	220 ± 35.0	0.20
Fluoroscopy time (min)	58 ± 16.1	66 ± 16.3	0.10
Cryoablation time (min)	15 ± 4.9	14 ± 4.5	0.39
Complications during procedure			
Cardiac tamponade	0	0	-
Cerebral infarction	0	0	-
Esophageal ulceration	0	0	-
Vascular accident	0	0	-
Pulmonary vein stenosis	0	0	-
Phrenic nerve palsy	0	0	-
Perioperative death	0	0	-

Data are presented as mean ± standard deviation or as number (%). PVI, pulmonary vein isolation.

can cause PAF [4, 12]. The cardiac nerve receives dual innervation by sympathetic and vagal nerves, which balances under normal condition. Dynamic vagosympathetic variations, however, are composed by complex factors including humoral factor, body temperature, enzyme, and blood pressure; therefore, it is difficult to measure the balance in an integrated fashion.

It has been reported that LF and HF significantly decreased up to 6 months after PVI with RFCA as changes in HRV parameters in 120 PAF patients in Japan; they were independent relative factors in the non-recurrence group, and independent of PVI procedure (either segmental or circumferential PVI) [13]. A study in 144 AF patients that received PVI using irrigation tip catheter also reported that a reduction in LF/HF (Δ LF/HF) of ≥ 0.26 at 3 months post-PVI was an independent relative factor in the non-recurrence group as a PVI efficacy [8]. HRV analysis in the 40 patients that underwent cryoballoon PVI revealed significant decreases in both standard deviation of the

Supplement Table 1 Longitudinal changes of Holter parameters in the non-recurrence group (n = 46)

	Baseline	3 month	6 month	*P* value (ANOVA)
Total heart beats (count)	110911 ± 26357.5	9915 ± 16329.9	9969 ± 12768.5	< 0.01*
Maximum heart rate (bpm)	114 ± 29.1	99 ± 17.1	102 ± 13.5	< 0.01*
Minimum heart rate (bpm)	51 ± 7.2	55 ± 7.0	56 ± 12.6	< 0.01*
Supraventricular contraction (count)	1439 ± 3086.1	392 ± 811.8	825 ± 2307.0	0.03*
RMSSD	54 ± 52.0	32 ± 37.0	30 ± 42.3	< 0.01*
Low-frequency components (LF)	854 ± 1309.6	288 ± 836.9	245 ± 443.3	< 0.01*
High-frequency components (HF)	1277 ± 3149.9	439 ± 1527.2	431 ± 1637.9	0.04*
LF/HF	2.6 ± 2.2	1.3 ± 1.0	1.7 ± 1.3	< 0.01*
Deceleration capacity (DC)	6.0 ± 2.5	3.8 ± 1.7	3.8 ± 1.6	< 0.01*
Acceleration capacity (AC)	-7.4 ± 2.8	-4.7 ± 3.0	-4.9 ± 2.5	< 0.01*
[AC]/DC	1.4 ± 1.1	1.3 ± 1.2	1.6 ± 2.2	0.34

Data are presented as mean ± standard deviation. RMSSD, root mean square successive difference.

Supplement Table 2 Longitudinal changes of Holter parameters in the recurrence group (n = 10)

	Baseline	3 month	6 month	*P* value (ANOVA)
Total heart beats (count)	103352 ± 13615.2	97427 ± 9131.3	9907 ± 11205.3	0.23
Maximum heart rate (bpm)	109 ± 24.7	106 ± 28.7	108 ± 20.6	0.49
Minimum heart rate (bpm)	49 ± 6.4	54 ± 6.5	53 ± 5.6	0.07
Supraventricular contraction (count)	128 ± 206.1	309 ± 678.7	1146 ± 2427.5	0.14
RMSSD	119 ± 111.6	66 ± 73.6	37 ± 32.2	< 0.01*
Low-frequency components (LF)	3106 ± 3963.2	1506 ± 2523.0	363 ± 413.4	0.03*
High-frequency components (HF)	3419 ± 5052.6	1855 ± 3181.6	565 ± 887.9	0.03*
LF/HF	1.6 ± 1.4	1.1 ± 0.7	1.5 ± 1.8	0.27
Deceleration capacity (DC)	7.6 ± 2.2	3.9 ± 2.1	3.7 ± 1.1	< 0.01*
Acceleration capacity (AC)	-8.2 ± 2.2	-6.9 ± 3.5	-6.7 ± 6.3	0.30
[AC]/DC	1.1 ± 0.2	2.5 ± 2.6	2.0 ± 2.6	0.04*

Data are presented as mean ± standard deviation. RMSSD, root mean square successive difference.

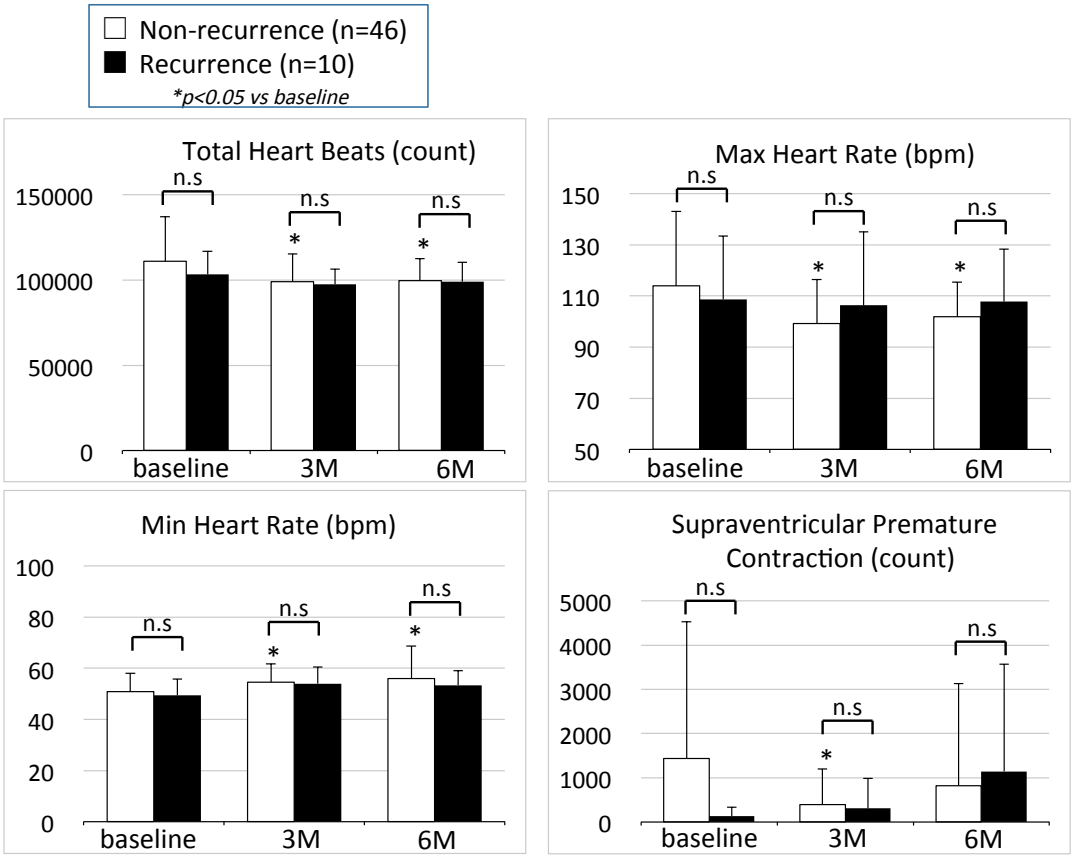

Fig. 1 Heart rate parameters and frequency of supraventricular contraction
Total heart rate (A), maximum heart rate (B), minimum heart rate (C) and frequency of supraventricular contraction (D) were compared between the non-recurrence group (white bar) and recurrence group (black bar) at each time point (statistical results described either p value or n.s. [no statistically significant difference]), and between baseline (pre-PVI) and 3 and 6 months post-PVI (*p < 0.05 vs baseline for each group).

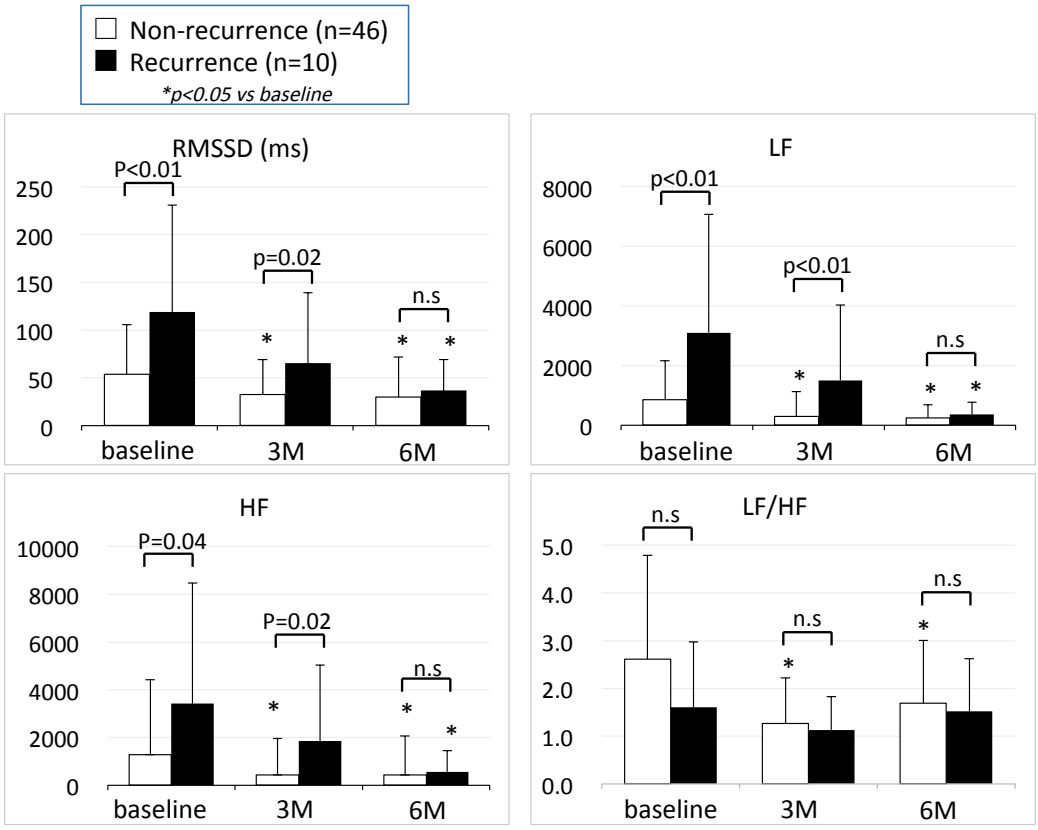

Fig. 2 Heart rate variability analysis
RMSSD (A), LF (B), HF (C) and LF/HF (D) were compared between the non-recurrence group (white bar) and recurrence group (black bar) (statistical results described either p value or n.s. [no statistically significant difference]), and between baseline (pre-PVI) and 3 and 6 months post-PVI (*p < 0.05 vs baseline for each group).

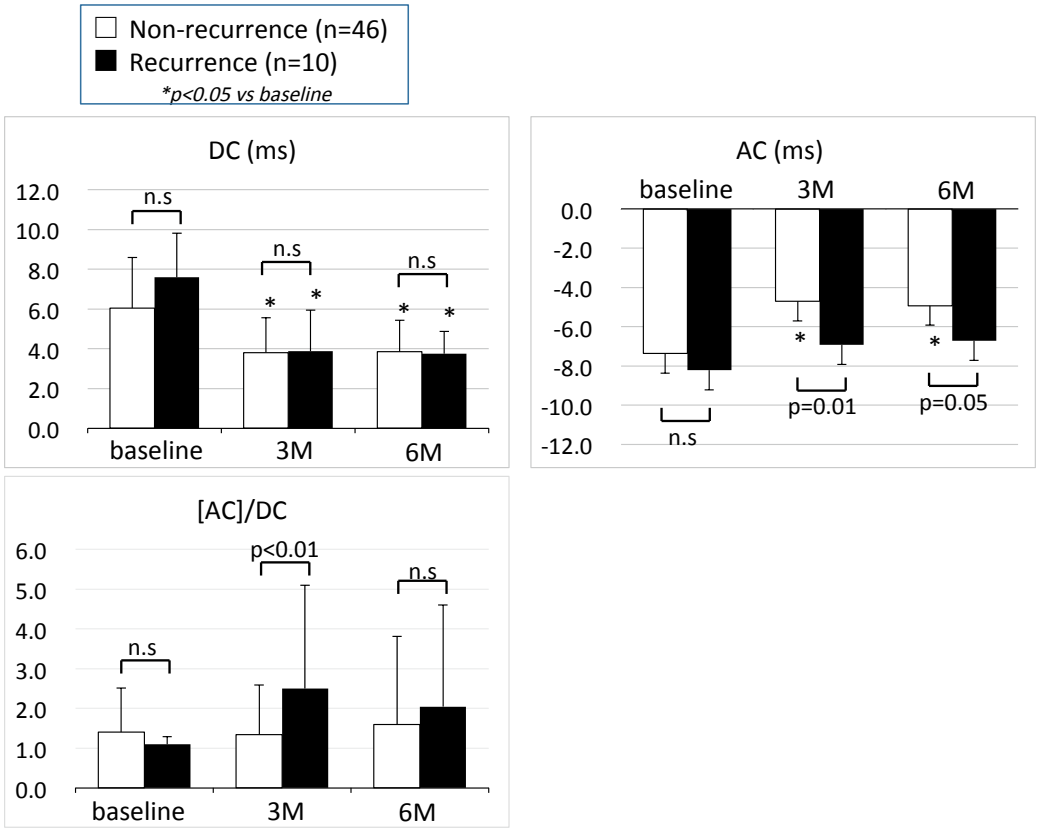

Fig. 3 Deceleration and Acceleration Capacity Analyses
DC (A), AC (B), and [AC]/DC (C) were compared between the non-recurrence group (white bar) and recurrence group (black bar) (statistical result described either p value or n.s. [no statistically significant difference]), and between baseline (pre-PVI) and 3 and 6 months post-PVI (*p < 0.05 vs baseline for each group).

NN interval (SDNN) and triangular index throughout one month after the procedure; thereafter, these changes were gradually normalized within 3 months [14]. However, subanalysis using 5 patients with AF recurrence and 9 patients without AF recurrence did not show any differences in post-PVI HRV modulations between the 2 populations. A recent study demonstrated that HRV parameters decreased to the same extent after PVI irrespective of ablation methods in 235 patients (119 patients with irrigated-tip, 51 with contact-force sensing-guided, and 65 with second-generation cryoballoon ablation). HF at 12 months post-PVI was significantly higher in the recurrence group than in the non-recurrence group as an independent predictor of AF recurrence [15].

In our study as well, HRV parameters significantly decreased in the non-recurrence group at both 3 and 6 months post-PVI. Decreased RMSSD and HF indicate diminished vagal tone, while decreased LF/HF diminished relative sympathetic nervous tone. In contrast, in the recurrence group, only parasympathetic parameters significantly decreased at 6 months, but LF/HF failed to decrease. Control of AF requires reduction of both HF and LF/HF, indicating denervation of both the vagus and sympathetic nerves as a critical factor for the prevention of AF recurrence.

PVI and Autonomic Nerve Ablation

Pappone *et al.* [16] reported lower incidence of AF recurrence in PAF patients with ablation-induced bradycardia occurring during the line ablation around the pulmonary vein, and expected the lower incidence was attributed to ablation effects not only the substrates but also autonomic ganglion. Thus, the concept of GP ablation intended for autonomic denervation has been established, and to identify the target site, the radiofrequency ablation with high-frequency stimulation in 4 positions superior to the left upper pulmonary vein, anterior to the right upper pulmonary vein, inferior to the right and left inferior pulmonary veins has been applied [17]. However, there is no consensus in terms of procedure to determine the target of GP ablation and adequate number of ablation, and clinical outcomes of GP ablation were not consistent. Some studies demonstrated superiority of GP ablation over conventional PVI [6], but some other studies inferiority [5, 7]. Although our study did not apply GP ablation in parallel, significant changes in autonomic nervous tonus were observed with PVI alone, suggesting broad target of PVI may be overlapped with the GP region around the pulmonary vein.

No studies using DC/AC analysis in PVI or GP ablation have been reported. However, Sun *et al.* [18] investigated the effect of left atrium GP ablation on cardiac autonomic modulation using DC analysis in patients with refractory vasovagal syncrope. The vagal tone was suppressed in the non-recurrence group (n = 30) at least throughout 12 months after ablation compared to the recurrence group (n = 5). They speculated that denervation of the GPs was capable of breaking both the efferent and afferent pathways of the abnormal Bezold-Jarisch reflex.

This time, we performed HRV analysis as well as DC/AC analysis to separately observe overall autonomic activities projected to the sinus node and direct reflex response. DC decreased in both groups post-PVI, while AC changed only in the non-recurrence group. As a result, [AC]/DC ratio was significantly greater in the recurrence group than the non-recurrence group at 3 months post-PVI, suggesting excessive sympathetic nervous response relative to reflex vagal response. These findings were not completely corresponded to the results from heart rate and HRV analyses although they showed similar tendency. In the observational study for long period of time, we sometimes experience a small discrepancy across various autonomic parameters. DC analysis is a quantitative evaluation for beat by beat via sinus nodule, which is different from conventional HRV, but reflection routes associated with DC have not yet been elucidated. [AC]/DC obtained from DC analysis may enable us to evaluate potential heterogeneous nerve sprouting in the reinnervation process after denervation. Our results indicate that it is important not only to reduce vagosympathetic overall activity but also to minimize imbalance between vagosympathetic reflex responses to prevent AF recurrence after PVI.

CONCLUSION

To prevent AF recurrence after PVI, it is important not only to reduce overall activity of vagosympathetic nerves, but also minimize imbalance in vagosympathetic nervous reflex responses. Adequate denervation achieved by cryoballoon PVI may be the critical factor to prevent AF recurrence.

LIMITATION

Since only patients with PAF requiring PVI were strictly enrolled to the study, the number of study subjects is limited. Although no acute vital events such as remarkable bradycardia (< 40bpm) and hypotension (< 80mmHg) were observed during the ablation, baroreflex function was not monitored; therefore, autonomic nervous responses were not thoroughly confirmed. No long-term clinical time-course exceeding a 6-month follow-up period was evaluated; for instance, potential development of sympathetic hypersensitivity secondary to autonomic inhibition remains unknown. Further follow-up assessment for time-course in larger population is warranted.

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DISCLOSURE

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