Original Article

I Impact of Atrial Fibrillation on the Vagal Response to Ganglionated Plexi Stimulation: Comparison Between Patients with and without Atrial Fibrillation

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Background: Pacing induced atrial fibrillation (AF) has been shown to induce significant increases in sympathetic and parasympathetic neurons in dogs, and the efficacy of cardiac autonomic denervation by ganglionated plexi (GP) has been shown to increase the freedom from recurrence of AF. We compared the GP response to high-frequency stimulation (HFS) in patients with and without AF.

Methods: The responses to HFS (20 Hz, 25 mA, 10 ms) at 5 left atrial GP sites were evaluated in 24 patients with AF (paroxysmal: 11, persistent AF: 5) and 16 patients with left side accessory pathways.

Results: Vagal responses (> 50% increase in RR interval) to HFS were more frequently observed in patients with AF (Table).

Conclusions: AF increases left atrial cardiac autonomic nervous system activity, which may contribute to the adjunct role of GP ablation following pulmonary vein isolation.

Table

	Marshall GP	LSGP	LIGP	RAGP	RIGP
Control group	9/16 (56%)	7/16 (44%)	7/16 (44%)	8/16 (50%)	7/16 (42%)
AF Group	23/32 (72%)	20/32 (63%)	31/32 (97%) [†]	28/32 (88%)*	26/32 (81%) [§]

GP: ganglionated plexi, SR: sinus rhythm, AF: atrial fibrillation, LSGP: left superior GP,

LIGP: left inferior GP, RAGP: right anterior GP, RIGP: right inferior GP,

[†]: $P < 0.0001$ vs. control group, *: $P = 0.0108$ vs. control group, [§]: $P = 0.00185$ vs. control group

Key words: left atrial ganglionated plexi, autonomic nervous system, atrial fibrillation

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Introduction

The autonomic nervous system is intricately associated with the atrial fibrillation (AF) substrate as well as its initiation and persistence^{1–3)}. Changes in the sympatho-vagal balance have been recorded during the onset of AF in both human and animal studies^{4, 5)}. The mechanisms by which an autonomic change can promote and sustain AF are highly complex and involve enhanced automaticity, early/delayed after-depolarizations, and a spatial heterogeneous abbreviation of refractoriness^{2, 6)}. A recent randomized trial and meta-analysis showed a superior outcome when a GP ablation was performed in conjunction with a pulmonary vein isolation (PVI) for paroxysmal and persistent AF, and also the presence of a GP response after

an extensive PVI was significantly associated with an AF recurrence^{7–10)}. High-frequency stimulation from the left atrial endocardium has been used for the localization of left atrial ganglionated plexi¹¹⁾. However, the degree and area of a vagal response to high-frequency stimulation to the left atrial GP sites have not been compared between patients with and without AF. The purpose of this study was to elucidate the effect of AF on the vagal response to high-frequency stimulation.

Methods

Study patients

This study consisted of 32 AF patients (26 men, 6 women; age 55.9 ± 7.0 years) who underwent an extensive encircling PVI (EEPVI) by RFA for paroxysmal AF

(PAF, AF lasting ≤ 7 days; $n = 12$) or persistent AF (PerAF, AF lasting > 7 days; $n = 20$), and 16 control patients who underwent a left sided atrio-ventricular accessory pathway ablation at Nihon University Itabashi Hospital between September 2013 and April 2016. None had undergone a previous ablation procedure or had any significant valvular heart disease, left ventricular (LV) contraction abnormality, marked LV hypertrophy, or thyroid disease. In the AF patients, all had been on adequate oral anticoagulant therapy for at least 1 month before the ablation, and all antiarrhythmic drugs had been discontinued for at least 5 half-lives before the ablation. Upon admission, transesophageal and transthoracic echocardiograms were obtained. The study was approved by the Nihon University Hospital Institutional Review Board (May 25, 2016; RK-160614-10). All patients provided written informed consent for the electrophysiologic study and ablation.

Electrophysiologic study

An electrophysiologic study was performed with patients under conscious sedation achieved with dexmedetomidine, propofol, and fentanyl. After vascular access was obtained, a single transseptal puncture was performed, and intravenous heparin was administered for maintenance of an activated clotting time of > 300 seconds.

Left atrial GP stimulation

High-frequency stimulation of the LA GPs was performed before the PVI in the AF patients, and after an atrio-ventricular accessory pathway ablation in the control patients. The LA GP stimulation was performed as previously described¹². In brief, a THERMOCOOL SMART-TOUCH ablation catheter (Biosence-Webster, Diamond

Bar, CA, USA) or EPstar Snake decapolar catheter (Japan Lifeline Co, Tokyo, Japan) was placed at each of the presumed anatomic areas of the 5 major GPs in the LA, i.e., the superior left GP (LSGP), inferior left GP (LIGP), Marshall tract GP, anterior right GP (RAGP), and inferior right GP (RIGP) (Fig. 1)¹³. High-frequency stimulation (20 Hz, 10 ms, 25 mA) was applied for 5 seconds at 3 different endocardial sites within each of the areas, and the GP response was assessed. A positive GP response was defined as a vagal response identified as an increase of 50% or more in the RR interval (Fig. 1)¹³. The GP response was calculated as the total number of positive GP responses (three times per each GP location; $3 \times 5 = 15$ GP stimuli).

Pulmonary vein isolation

Two decapolar Lasso catheters (Biosence-Webster, Diamond Bar, CA, USA) and a THERMOCOOL SMART-TOUCH catheter (Biosence-Webster) were placed in the left atrium. The 3-dimensional (3D) geometry of the left atrium and 4 PVs was reconstructed with a CARTO 3 mapping system (Biosence-Webster) from data obtained from a decapolar Lasso catheter. The EEPVI was performed by the double-lasso technique, with delivery of the RF energy at a target contact force of 10–20 g and power setting of 30 W for 30 seconds along the anterior wall and 25 W for 30 seconds along the posterior wall, as previously described^{14,15}.

Induction of atrial fibrillation after ablation

After the pulmonary vein isolation or ablation of the left atrial accessory pathway, rapid atrial pacing at a cycle length of 100–150 ms at 10 mA and 2 msec for 5 sec

Fig. 1 Location of the 5 major left atrial (LA) ganglionated plexi (GP) areas (upper panel) and sinus arrest by LSGP high-frequency stimulation (HFS) (lower panel).

RAGP: right anterior GP, LSGP: left superior GP, LIGP: left inferior GP, RIGP: right inferior GP, AP: antero-posterior, PA: postero-anterior.

was performed three times to induce AF, and induced AF lasted more than 5 minutes was defined as sustained AF.

Statistical analysis

Continuous variables are expressed as the mean $\pm$ SD or median and interquartile ranges. The differences between the AF group and Control group were analyzed by a Mann-Whitney U test. Categorical variables are expressed as percentages, and the differences were analyzed by a chi-square test. All statistical analyses were performed with the JMP software program (version 11; SAS Institute, Inc., Cary, NC, USA), and a $p < 0.05$ was considered significant.

Results

Patient clinical and echocardiographic characteristics

The clinical and echocardiographic characteristics of the study group are shown per group in Table 1. The AF group was significantly older than the control group ($P = 0.0484$) and had a larger left atrial diameter than the control patients ($P < 0.0001$). Hypertension was marginally more prevalent in the control patients ($p = 0.0597$). The

duration of AF in the PAF patients was 12 [6–57] months, and 14 [5–96] months in the PerAF patients.

GP responses in the AF and control groups

The total number of positive GP response sites is shown in Fig. 2. The AF group had a significantly higher prevalence of positive GP response sites (8.1 ± 3.3 vs. 4.3 ± 3.2 sites per patient, $P = 0.0007$). At each GP site, the LI, RA, and RI GPs exhibited a significantly greater GP response in the AF group, but the Marshall tract and LS GP did not exhibit any significant difference between the AF and control groups (Fig. 3). In the control group, in the 4 patients in whom sustained AF was induced, the prevalence of a positive GP response was significantly greater than that in the 12 patients without any sustained AF induction (7.3 ± 2.5 versus 3.1 ± 2.7 sites, $P = 0.0209$, Fig. 4).

Table 1 Comparison of the clinical characteristics between the AF and control groups.

	AF group (n = 32)	Control group (n = 16)	P value
Age (y)	55.9 ± 7.0	50.8 ± 10.1	0.0484
Sex, male, n (%)	26 (81)	10 (63)	0.1776
Paroxysmal/Persistent AF	12/20	0	
Hypertension, n (%)	16 (50)	3 (19)	0.0597
Body mass index (kg/m ²)	24.2 ± 2.9	23.4 ± 3.0	0.3614
LAD (mm)	40.1 ± 5.5	32.3 ± 4.7	< 0.0001
LVEF (%)	65.9 ± 7.8	70.00 ± 5.6	0.0822

AF: atrial fibrillation, LAD: left atrial diameter, LVEF: left ventricular ejection fraction.

Fig. 2 Incidence of a positive vagal response by high-frequency stimulation between the atrial fibrillation (AF) and control groups.

Fig. 3 Distribution of a positive vagal response among the 5 ganglionated plexi sites

Fig. 4 Comparison of the incidence of a positive vagal response between induced atrial fibrillation (AF) lasting ≥ 5 minutes and AF lasting < 5 minutes in the control group.

Discussion

In the present study, we demonstrated that there was a higher incidence of a positive LA GP response with high-frequency stimulation in patients with AF, and a higher incidence of a positive LA GP response in control patients in whom sustained AF was induced by rapid atrial stimulation.

Epicardial adipose tissue (EAT) contains abundant ganglionated plexi^{16, 17)}. Inflammation of the left atrial adipose tissue demonstrated by the EAT density calculated by computed tomography and 18-fluorodeoxyglucose uptake by positron emission tomography was shown to be associated with AF^{18, 19)}. Cellular inflammation, mainly consisting of functional cytotoxic T lymphocytes, was observed in human atria²⁰⁾. Therefore, inflammation of the epicardial adipose tissue might contribute to the higher sensitivity of the LA GPs to high-frequency stimulation.

Autonomic neural remodeling (higher average density and heterogeneity of both tyrosine hydroxylase and choline acetyltransferase) was shown to exist in the PV-LA junction and GPs after prolonged atrial pacing in a canine model^{21, 22)}. An LA GP ablation alone (before the PV antrum isolation) was shown to decrease the occurrence of PV firing and to decrease the inducibility of sustained AF²³⁾. Extensively ablating the LA covering the GP areas identified as fat pads around the LA surface along with the PVA isolation enhanced the denervation of the autonomic nervous system and improved the procedural outcome in patients with AF^{23, 24)}.

Therefore, the results of the present study that AF patients had greater hyperactive GPs than the control patients, may be due to inflammation of the EAT leading

to activation of the cytotoxic T lymphocytes and secretion of adipokines and/or autonomic neural remodeling by AF.

Limitations

The limitation of the present study was the difference in the age between the AF and control patients. The AF patients were older than the control group, and the prevalence of AF has been shown to increase with age. Therefore, the age itself may have contributed to the difference in the GP response. Therefore, influence of age on the GP response should have been compared within the control and AF group. Secondly, 63% of the AF group had PerAF because of the small number in each group. If the PAF and PerAF patients were analyzed separately, the influence of the AF duration and extent of the structural remodeling of the LA on the GP response might have been clarified. AF recurrence after PVI and incidence of GP response before PVI and disappearance of GP response by PVI and AF recurrence were not evaluated in the present study. Finally, atrioventricular reentrant tachycardia patients via left-sided accessory pathway were selected as control patients. The incidence of AF has been shown to be higher in patients with atrioventricular accessory pathway, however left atrial approach without history of AF was only available only in patients with left-sided atrioventricular accessory pathway ablation.

Conclusion

AF increases the left atrial cardiac autonomic nervous system activity, which may in part contribute to the adjunctive role of the GP ablation following pulmonary vein isolation.

Conflict of Interest

The authors have no conflicts of interest related to this study.

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