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Impact of atrial fibrillation ablation on cardiac sympathetic nervous system in patients with and without heart failure

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ABSTRACT

Background/objectives: Catheter ablation of atrial fibrillation (AF) might influence the cardiac autonomic nervous system. To investigate the impact of catheter ablation on the sympathetic nervous function in AF patients with and without heart failure (HF) using cardiac iodine-123-metaiodobenzylguanidine (^{123}I-mIBG) scintigraphy, and the association of this effect with AF recurrence.

Methods: Forty consecutive patients (median age, 65 (54–69) years; male, 29) with paroxysmal ($n = 22$) and persistent ($n = 18$) AF who were scheduled for ablation were enrolled. Twelve (30%) of these patients also exhibited either stable HF, defined as an ejection fraction <40%, or a history of symptomatic HF. ^{123}I-mIBG scintigraphy was performed at baseline and 3 months post-ablation. The heart-to-mediastinum ratio of ^{123}I-mIBG uptake at 15 min ($H/M_{15\ min}$) and 240 min ($H/M_{240\ min}$), as well as the washout rate (WR) were measured.

Results: During an 11 ± 4-month follow-up, AF recurrence was observed in 8 (20%) patients receiving no antiarrhythmic drugs. Patients with HF had a tendency toward a lower baseline $H/M_{15\ min}$ (1.91 ± 0.06 vs. 2.05 ± 0.04, $p = 0.07$), significantly lower $H/M_{240\ min}$ (1.88 ± 0.22 vs. 2.14 ± 0.28, $p = 0.008$), and higher WR (40.3 ± 9.0 vs. 32.3 ± 7.4, $p = 0.007$). Post-ablation, WR decreased in patients with HF (40.2 ± 8.5 to 29.0 ± 8.9, $p = 0.02$) but slightly increased in those without (32.0 ± 7.4 to 34.6 ± 10.3, $p = 0.04$). WR post-ablation independently predicted AF recurrence (adjusted hazard ratio = 1.14 for 1 percentage point increase in the WR, 95% coincidence interval = 1.02–1.34, $p = 0.02$).

Conclusions: AF ablation restores sympathetic nervous system status via attenuation of excessive adrenergic tone in HF patients. Elevated sympathetic nervous tone 3 months post-ablation was a reliable predictor of AF recurrence.

1. Background/objectives

Atrial fibrillation (AF) is the most common arrhythmia and often coincides with heart failure. Disorders of the automatic nervous system are thought to be a common underlying pathophysiology of these diseases. A reduced cardiac performance due to the loss of the atrial contraction and an inappropriate ventricular rate among AF patients could increase the sympathetic tone, particularly in patients with heart failure in whom atrial contraction and an optimal ventricular rate are relatively important.

Catheter ablation of AF might influence the cardiac autonomic nervous system due to decreased AF burden, or coincidental modification of ganglionated plexi during left atrial ablation. Scintigraphy with cardiac iodine-123-metaiodobenzylguanidine (^{123}I-mIBG) enables the reliable visualization of abnormal behavior of norepinephrine at sympathetic nerve endings and has been used in several studies to assess sympathetic nervous dysfunction such as AF and heart failure [1–3]. Here, we investigated the impact of AF ablation on the cardiac sympathetic nervous system using ^{123}I-mIBG scintigraphy in AF patients with and without heart failure.

2. Methods

2.1. Patients

From December 2012 to December 2013, consecutive patients that underwent an initial ablation for symptomatic AF at our hospital were enrolled. Patients with a history of heart failure were only included if their heart failure had been stable for at least the previous 3 months under medical treatment. Exclusion criteria were as follows: age <20 years old, decompensated heart failure, prior cardiac surgery, pacemaker implantation, or severe mitral valve disease. Patients with a left ventricular ejection fraction <40% or a history of related symptoms were diagnosed with heart failure. No changes to medication for AF or heart failure were permitted for 1 month pre-ablation and 3 months post-ablation. Informed consent was obtained from each patient and the study protocol conforms to the

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ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Cardiac ^{123}I-mIBG scintigraphy

Cardiac ^{123}I-mIBG scintigraphy was performed 1 month pre-ablation and 3 months post-ablation. No patients were taking any tricyclic antidepressant drugs or sympathomimetic agents during the month prior to scintigraphy.

A 111-MBq dose of ^{123}I-mIBG (FUJIFILM RI Pharma, Tokyo, Japan) was intravenously injected at rest following fasting overnight. All images were acquired using a gamma camera with a large field of view and a low-energy, high-resolution collimator (BrightView; Philips, Amsterdam, Netherlands). Early and delayed image acquisitions were carried out in the anterior chest view 15 and 240 min post-isotope injection.

An independent observer who was unaware of the clinical status of the patients assessed cardiac ^{123}I-mIBG uptake. Planner ^{123}I-mIBG images were analyzed by a region-of-interest technique to obtain the semi-quantitative parameters for tracer distribution. The region-of-interest was manually drawn over the whole heart, and a rectangular region-of-interest over the mediastinum was obtained as a reference. The ^{123}I-mIBG count densities of the heart (H) and mediastinum (M) were then determined, and the heart-to-mediastinum ratio of the ^{123}I-mIBG uptake values at 15 min ($H/M_{15\ min}$) and 240 min ($H/M_{240\ min}$) were calculated. Washout rate (WR) was calculated as (H at 15 min − H at 240 min) × 100/H at 15 min (%).

2.3. Catheter ablation

An electrophysiological study and catheter ablation were performed under intravenous sedation using dexmedetomidine. After a transseptal puncture at the fossa ovalis, a 20-pole circular catheter was placed at each pulmonary vein. Mapping and ablation were then performed under guidance from an electroanatomical mapping system (CARTO3, Biosense Webster, Diamond Bar, CA, USA). Circumferential ablation around both ipsilateral pulmonary veins was performed using an irrigated ablation catheter with a 3.5-mm tip (Navi-Star ThermoCool, Biosense Webster). Radiofrequency energy was applied for 15 to 30 s at each site using a maximum temperature of 42 °C, maximum power of 35 W and flow rate of 17 ml/min. When atrial flutter was observed spontaneously or induced by atrial burst stimuli, additional ablation was performed. Electrical cardioversion was performed when AF continued at the end of the ablation procedure.

2.4. Follow up for AF recurrence

Patients were followed up every 2 to 4 weeks at the dedicated arrhythmia clinic of our institution. Routine ECGs were obtained at each outpatient visit, and 24-h ambulatory Holter monitoring was performed every 3 months post-ablation. When patients experienced symptoms suggestive of arrhythmia, a surface ECG, ambulatory ECG, and/or cardiac event recording were also obtained. Any of the following events after the initial 3 months from ablation were considered to indicate AF recurrence: [1] AF (or any other atrial tachyarrhythmia) recorded on a routine or symptom-triggered ECG during the outpatient visit, or [2] AF of at least 30 sec duration on the ambulatory ECG monitoring. Early AF recurrence was defined as recurrence during an initial blanking period of 3 months post-ablation and was treated by pharmacological or electrical cardioversion as soon as possible. No antiarrhythmic drugs were prescribed 3 months post-ablation unless AF recurrence was observed.

2.5. Statistical analysis

Continuous data are expressed as mean ± standard deviation (SD) or median (interquartile range). Categorical data are presented as absolute values and percentages. Tests for significance were conducted using the unpaired t-tests or nonparametric test (Mann–Whiney U test) for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. A Pearson's correlation coefficient was calculated to assess correlations between continuous variables. Univariate and multivariate Cox proportional hazards models were used to determine the clinical factors associated with AF recurrence. Variables with a p value ≤0.05 in the univariate analysis were included in the multivariate analysis. Survival rates free from AF recurrence were calculated using the Kaplan–Meier method. A log-rank test was used to compare the event-free survival curves between groups. All analyses were performed using SPSS version 15.0.

3. Results

3.1. Patient characteristics

During the study period, 40 eligible patients were enrolled and followed up for a mean period of 11 ± 4 months. Of these patients, 12 (30%) had concomitant heart failure and non-ischemic etiology. Further, 6 (50%) of these 12 patients had a reduced left ventricular ejection fraction of <50%, and 6 (50%) had diastolic heart failure with a preserved ejection fraction. As shown in Table 1, patients with heart failure were less likely to have concomitant hypertension, had a higher CHADS2 score, lower systolic blood pressure, and a lower left ventricular ejection fraction than those without. Pulmonary vein isolation was successfully completed in all patients. Although persistent AF was observed more frequently in patients with heart failure, additional ablation other than pulmonary vein isolation were performed in the same proportion of patients in both groups. No differences were noted in the incidence of early AF recurrence within 3 months post-ablation, and all early recurrent AF episodes were converted to sinus rhythm as soon as possible by pharmacological and/or electrical cardioversion. All patients therefore remained in sinus rhythm for the majority of the initial 3 months post-ablation prior to follow-up examination.

Table 1
Patient characteristics.

Variable	Heart failure		p
	With (n = 12)	Without (n = 28)	
Age, years	66 (54–71)	65 (54–69)	0.72
Male, n (%)	9 (75)	20 (71)	0.99
Body mass index, kg/m^2	23.8 ± 2.3	23.7 ± 2.7	0.91
Persistent atrial fibrillation, n (%)	10 (83)	8 (29)	0.002
Period of atrial fibrillation, months	13 (6–81)	36 (9–69)	0.76
Hypertension, n (%)	3 (25)	18 (64)	0.04
Diabetes mellitus, n (%)	1 (8)	7 (25)	0.40
CHADS2 score	2 (1–3)	1 (0–2)	0.01
Heart rate, bpm	69 ± 10	71 ± 11	0.51
Systolic blood pressure, mm Hg	115 ± 14	127 ± 13	0.02
Pre-procedural medications			
Antiarrhythmic drugs class I, n (%)	3 (25)	12 (43)	0.48
Antiarrhythmic drugs class III, n (%)	1 (8)	5 (18)	0.65
Beta-blockers, n (%)	9 (75)	11 (39)	0.08
Angiotensin converting enzyme inhibitor, n (%)	7 (58)	14 (50)	0.74
Echocardiography			
Left atrial volume index, cm^3/m^2	47 ± 26	35 ± 11	0.09
Left ventricular EF, %	51 ± 13	65 ± 7	<0.0001
E/e′	8.7 ± 2.0	8.6 ± 3.0	0.90
Mitral regurgitation (mild or moderate), n (%)	9 (75)	10 (36)	0.07
Plasma brain natriuretic peptides, pg/ml	118 (58–149)	102 (31–165)	0.72
Procedural characteristics			
Cavotricuspid isthmus linear ablation	1 (8)	2 (7)	0.99
Left atrial roof linear ablation	0	2 (7)	
Mitral isthmus linear ablation	1 (8)	0	
Total radiofrequency application time, min	28.1 ± 6.7	30.4 ± 8.6	0.43
Early recurrence within 3 months	4 (33)	16 (57)	0.30

EF, ejection fraction; E/e′, diastolic early transmitral flow velocity/mitral annular velocity.

3.2. Baseline sympathetic nervous function

In total, the mean $H/M_{15\ min}$ was 2.01 ± 0.22, and $H/M_{240\ min}$ was 2.06 ± 0.29. All patients had a lower $H/M_{15\ min}$ and $H/M_{240\ min}$ than the standard respective ranges of 2.67 to 3.14 and 2.69 to 3.73, which were previously calculated as the mean ± 2SD among healthy subjects in our hospital. Patients with heart failure tended to have a lower $H/M_{15\ min}$ and significantly lower $H/M_{240\ min}$, as depicted in Fig. 1A and B. Baseline ^{123}I-mIBG scintigraphic data in association with various clinical parameters are shown in Table 2. Relatively low $H/M_{15\ min}$ and $H/M_{240\ min}$ were observed in the patients with persistent AF, along with a left atrial volume index greater than or equal to a median of 37 cm^3/m^2.

The mean WR among total study patients was 34% ± 9%. The standard value of the WR at our institute ranged from 13.1% to 41.5%, and 8 (20%) patients had a WR exceeding the standard range in the present study. Fig. 1C shows a higher WR in patients with heart failure than in those without. A higher WR was also observed in the patients treated with beta blockers (Table 2).