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Left atrial low-voltage areas predict atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation

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ABSTRACT

Background: Association between the presence of left atrial low-voltage areas and atrial fibrillation (AF) recurrence after pulmonary vein isolation (PVI) has been shown mainly in persistent AF patients. We sought to compare the AF recurrence rate in paroxysmal AF patients with and without left atrial low-voltage areas.
Methods: This prospective observational study included 147 consecutive patients undergoing initial ablation for paroxysmal AF. Voltage mapping was performed after PVI during sinus rhythm, and low-voltage areas were defined as regions where bipolar peak-to-peak voltage was <0.50 mV.
Results: Left atrial low-voltage areas after PVI were observed in 22 (15%) patients. Patients with low-voltage areas were significantly older (72 ± 6 vs. 66 ± 10, $p < 0.0001$), more likely to be female (68% vs. 32%, $p = 0.002$), and had higher CHA_2DS_2-VASc score (2.5 ± 1.5 vs. 1.8 ± 1.3, $p = 0.028$). During a mean follow-up of 22 (18, 26) months, AF recurrence was observed in 24 (16%) and 16 (11%) patients after the single and multiple ablation procedures, respectively. AF recurrence rate after multiple ablations was higher in patients with low-voltage areas than without (36% vs. 6%, $p < 0.001$). Low-voltage areas were independently associated with AF recurrence even after adjustment for the other related factors (Hazard ratio, 5.89; 95% confidence interval, 2.16 to 16.0, $p = 0.001$).
Conclusion: The presence of left atrial low-voltage areas after PVI predicts AF recurrence in patients with paroxysmal AF as well as in patients with persistent AF.

1. Introduction

Left atrial bipolar voltage during sinus rhythm (SR) decreases in parallel with the progression of atrial fibrillation (AF) [1]. Recently, the presence of left atrial low-voltage areas after pulmonary vein isolation (PVI) has been shown to be a powerful predictor of AF recurrence, and patients with low-voltage area ablation following PVI demonstrated better long-term outcomes than historical controls receiving PVI alone [2–7]. Because a majority of these study patients had persistent AF, low-voltage ablation has become an important option for the treatment of persistent AF. Some paroxysmal AF patients also have these low-voltage areas. However, the impact of low-voltage areas on rhythm outcomes after PVI in paroxysmal AF patients has not sufficiently been studied.

Here, we sought to compare the AF recurrence rates in paroxysmal AF patients with and without left atrial low-voltage areas.

2. Methods

2.1. Patients

This prospective observational study enrolled 147 consecutive patients who underwent initial ablation of paroxysmal AF at Kansai Rosai Hospital from December 2014 to March 2016. Paroxysmal AF was defined as episodes of AF that terminated spontaneously in <7 days. Exclusion criteria were age <20 years, prior cardiac surgery, and prior catheter ablation. This study complied with the Declaration of Helsinki. Written informed consent for the ablation and participation in the study was obtained from all patients, and the protocol was approved by our institutional review board.

2.2. Radiofrequency catheter ablation procedure

Electrophysiological studies and catheter ablation were performed by two experienced operators (MM and TK) with the patient under intravenous sedation with dexmedetomidine. A 6-Fr decapolar electrode was inserted into the coronary sinus while a second 6-Fr decapolar electrode was placed in the right atrium. Following a transseptal puncture at the fossa ovalis, two long sheaths were introduced into the left atrium. A 20-pole circular catheter was placed in a pulmonary vein via the sheath. During sinus rhythm, isoproterenol was infused at 5, 10, and 20 μg/min at 2-minute intervals and discontinued to provoke ectopies and AF. Subsequently, the operators performed mapping

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and ablation guided by an electroanatomical mapping system (Carto3®; Biosense Webster, Diamond Bar CA, USA).

A dragging technique was employed to perform circumferential ablation around both ipsilateral pulmonary veins using an open-irrigated ablation catheter with a 3.5-mm tip (Thermocool SmartTouch®; Biosense Webster) via an Agilis® or SL0® sheath (St. Jude Medical, St. Paul MN, USA). Radiofrequency energy was applied for 30 s (15 s at the posterior left atrial wall near the esophagus) at each site using a maximum temperature of 42 °C and maximum power of 35 W. The irrigation rate was 17 ml/min. Operators attempted to maintain an appropriate contact force between the catheter and endocardium of between 5 and 20 g. PVI was considered complete when both entrance and exit blocks were created. If atrial flutter was observed spontaneously or induced by atrial burst stimuli, additional ablation was performed. After a >20-min waiting period following the last ablation lesion, 20 mg of adenosine was rapidly administered intravenously to provoke possible dormant conduction. Further ablation was performed until every dormant conduction provoked by repeat adenosine injection was eliminated.

2.3. Voltage mapping

Following the PVI, detailed voltage mapping using a bipolar 3.5-mm tip catheter (Thermocool SmartTouch®) was performed during sinus rhythm in accordance with a previous study (Fig. S1) [2]. Mapping points were acquired evenly throughout the entire left atrium to fill all color gaps on the voltage map using the electroanatomical mapping system with an interpolation threshold of 15 mm for the fill threshold and 23 mm for the color threshold. In addition, high-density mapping was performed at sites where low-voltage areas had been detected to delineate exactly the extent of each low-voltage area. We confirmed adequate endocardial contact by stable electrograms, the distance to the geometry surface, and contact force ≥5 g. The band pass filter was set at 30 to 500 Hz. Bipolar peak-to-peak voltage at each acquired point was measured. We defined low-voltage areas as sites of ≥3 adjacent low-voltage (< 0.5 mV) points which were <5 mm apart.

2.4. Follow-up

Patients were followed up every 4–8 weeks at the dedicated arrhythmia clinic of our institution for a minimum of 1 year. Routine ECGs were obtained at each outpatient visit, and 24-h ambulatory Holter monitoring was performed 6 and 12 months post-ablation. When patients experienced symptoms suggestive of an arrhythmia, a surface ECG, ambulatory ECG, and/or cardiac event recording were also obtained. Either of the following events after the initial 3 months from the ablation (blanking period) was considered to indicate atrial tachyarrhythmia (AF and regular atrial tachycardia) recurrence: [1] atrial tachyarrhythmia recorded on a routine or symptom-triggered ECG during an outpatient visit, or [2] atrial tachyarrhythmia of at least a 30 s duration on ambulatory ECG monitoring. No antiarrhythmic drugs were prescribed after the ablation procedure unless recurrent atrial tachyarrhythmia was observed. Patients with recurrent atrial tachyarrhythmia were recommended to undergo a repeat ablation procedure including re-isolation of reconnected PVs, ablation of AF triggers from any non-PV foci, and ablation for induced atrial tachycardia.

2.5. Statistical analysis

Continuous data are expressed as the mean ± standard deviation or median (interquartile range). Categorical data are presented as absolute values and percentages. Tests for significance were conducted using the unpaired *t*-test, or nonparametric test (Mann–Whiney *U* test) for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables. Univariate and multivariate Cox proportional hazard models were used to determine the clinical factors that were associated with atrial-tachyarrhythmia recurrence. Variables with a p value ≤0.10 in the univariate models were included in the multivariate analysis. Atrial tachyarrhythmia-free survival rates were calculated using the Kaplan–Meier method. Comparison of survival curves between the groups was performed with a 2-sided Mantel–Haenszel (log-rank) test. All analyses were performed using commercial software (SPSS version 22.0®, SPSS, Inc., Chicago IL, USA).

3. Results

3.1. Patient characteristics

Left atrial low-voltage areas after PV isolation were observed in 22 (15%) patients. Comparisons of baseline and procedural characteristics are shown in Table 1. Patients with low-voltage areas were significantly older, more likely to be female, had higher CHA_2DS_2-VASc score, higher DR-FLASH score [8], and higher early transmitral flow velocity/early mitral annular velocity (E/e′) than those without. In addition, there were tendencies toward higher brain natriuretic peptide levels and lower creatinine clearance in patients with low-voltage areas than in those without.

PVI was achieved in all patients. The rates of other ablations for clinical and induced ectopies or tachyarrhythmias were equal between the two groups. No severe complication associated with the ablation procedures developed.

3.2. Voltage mapping

After the PVI, a voltage map was created during sinus rhythm in all patients. The number of mapping points was 142 (101, 170). LVAs existed in 22 (15%) patients with an area of 16 ± 13 cm^2, occupying 17% ± 13% of the left atrial surface area. LVAs were predominantly observed in the septal (14 [10%] patients), anterior (11 [7%]), roof (9 [6%]), and posterior (9 [6%]) regions, and rarely observed in the inferior (3 [2%]) and posterolateral (1 [1%]) regions.

3.3. AF recurrence after the initial ablation

During a mean follow-up period of 22 (18, 26) months, AF recurrence developed in 24 (16%) patients after the initial ablation. AF recurrence rate after the initial ablation procedure was higher in patients with low-voltage areas than in those without (9 [41%] vs. 15[12%], $p = 0.001$). On the other hand, patients with low-voltage areas demonstrated a significantly higher AF recurrence rate after multiple procedures than those without (8 [36%] vs. 8 [6%], $p < 0.0001$). The Kaplan–Meier curves of AF recurrence-free rates are shown in Fig. 1.

3.4. Repeated ablation procedures

Among the 24 patients with AF recurrence after the initial ablation, 16 (67%) patients underwent repeated ablations. The other eight patients did not receive a repeated ablation due to (1) retreat from

Table 1
Baseline and procedural characteristics.

	Low-voltage area		*p*
	With	Without	
	n = 22	n = 125	
Age, years	72 ± 6	66 ± 10	<0.0001
Female, n (%)	15 (68)	40 (32)	0.002
Body mass index, kg/m^2	23.1 ± 4.8	23.5 ± 3.5	0.61
Atrial fibrillation duration, months	6 (3, 12)	6 (4, 20)	0.53
Hypertension, n (%)	12 (55)	67 (54)	1.0
Diabetes mellitus, n (%)	3 (14)	14 (11)	0.72
Heart failure, n (%)	2 (9)	5 (14)	0.28
Coronary artery disease, n (%)	2 (9)	5 (4)	0.28
CHA_2DS_2-VASc score	2.5 ± 1.5	1.8 ± 1.3	0.028
Brain natriuretic peptide, pg/ml	79 (38, 227)	38 (18, 73)	0.057
Creatinine clearance, ml/min	67 ± 21	79 ± 29	0.059
Echocardiography findings			
Left atrial diameter, mm	38 ± 7	36 ± 6	0.34
Left ventricular ejection fraction, %	61 ± 10	60 ± 11	0.77
E/A	1.15 ± 0.59	1.02 ± 0.40	0.25
E/e′	13.3 ± 5.1	10.1 ± 3.3	0.019
Mitral regurgitation, n (%)	5 (23)	18 (14)	0.34
Maintenance dialysis, n (%)	2 (9)	3 (2)	0.16
DR-FLASH score[a]	2.6 ± 0.9	1.8 ± 1.1	0.001
Antiarrhythmic drug usage, n (%)	15 (68)	63 (50)	0.17
Ablation procedure			
Pulmonary vein isolation, n (%)	22 (100)	125 (100)	
Cavo-tricuspid isthmus ablation, n (%)	2 (9)	12 (10)	0.99
Other ablations[b], n (%)	1 (5)	3 (2)	0.99
Radiofrequency time, s	1574 ± 471	1560 ± 570	0.94

E and A indicates diastolic early and late transmitral flow velocities; e′, diastolic early mitral annular velocity.

[a] DR-FLASH is a score to estimate the presence of low-voltage area by assigning 1 point for each quality: diabetes mellitus, renal dysfunction, persistent form of atrial fibrillation, left atrial diameter >45 mm, age >65 years, female sex, and hypertension.

[b] Other ablation procedures included a superior vena cava isolation for atrial fibrillation trigger ectopy (2 patients) and a mitral isthmus linear ablation for an induced perimitral flutter (2 patients).