

Heart and Vessels (2024) 39:240–251
https://doi.org/10.1007/s00380-023-02329-7

ORIGINAL ARTICLE



Treatment with catheter ablation for patients with arrhythmia-induced cardiomyopathy caused by atrial fibrillation promises a good prognosis

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Received: 7 June 2023 / Accepted: 4 October 2023 / Published online: 23 October 2023
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Abstract

Clinical outcomes after catheter ablation in patients with reduced left ventricular (LV) ejection fraction (EF) and atrial fibrillation (AF) remain unclear. This study aimed to explore the clinical outcomes of patients with arrhythmia-induced cardiomyopathy (AIC) and the influence of pharmacological treatment on clinical outcomes in patients with AIC after the procedure. Ninety-six patients with AF with a reduced LVEF (LVEF < 50%, 66.7 ± 10.9 years; 72 males) underwent AF ablation. AIC was defined as patients whose LVEF recovered ≥ 50% after catheter ablation ($n=67$) and patients whose LVEF remained reduced were defined as non-AIC ($n=29$). During a median follow-up of 25 (13–40) months, Kaplan–Meier analysis demonstrated that patients with AIC were associated with less frequent cardiovascular death ($p=0.025$) and hospitalization for worsening heart failure ($p<0.001$) than those without AIC. Freedom from AF recurrence was similar between the two groups ($p=0.47$). In multivariate analysis, the LV end-diastolic diameter ($p=0.0002$) and the CHA₂DS₂-VASc scores ($p=0.0062$) were independent predictors of AIC. Among the 67 patients with AIC, no significant differences in baseline characteristics, except for LV chamber size and cryoballoon use, were observed between patients with AIC with ($n=31$) and without renin–angiotensin system (RAS) inhibitors ($n=36$). In the Kaplan–Meier analysis, cardiovascular death, hospitalization for worsening heart failure, and AF recurrence after catheter ablation did not differ between patients treated with and without RAS inhibitors (all $p>0.05$). Catheter ablation in patients with AIC due to AF is associated with a good post-procedural prognosis.

IRB information The study was approved by the Research Ethics Committee of the University of Fukui (No. 20220151) and clinical trial registration (UMIN000050391).

Keywords Catheter ablation · Atrial fibrillation · Arrhythmia-induced cardiomyopathy · Heart failure with recovered ejection fraction

Introduction

Atrial fibrillation (AF) worsens patient prognosis by increasing the risk of heart failure. Moreover, in patients with heart failure, AF is associated with high odds of death [1]. Catheter ablation for AF reduces death from any cause and hospitalization for worsening heart failure among patients with AF with reduced left ventricular (LV) ejection fraction (EF) [2]. Therefore, some guidelines recommend that AF ablation for patients with heart failure should be considered for the prevention or treatment of AF regardless of appropriate medical therapy [3, 4].

LVEF is widely used as an essential indicator for classification and prognosis in patients with heart failure and is

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defined as the reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF), using the value of LVEF [5]. Patients with heart failure with recovered ejection fraction are novel clinical entities and have significantly better outcomes than those with HFrEF and HFpEF [6]. Patients with heart failure with recovered ejection fraction by maintaining sinus rhythm after catheter ablation were defined as those with arrhythmia-induced cardiomyopathy (AIC). In contrast, the other patients whose LVEF did not recover (<50%) after the procedure were defined as with non-AIC. Although the prognosis of patients with recovered LVEF after catheter ablation is expected to be better than that of those without recovered LVEF, very few clinical studies have been conducted to evaluate or compare the prognoses of these two groups of patients. Furthermore, although it is generally accepted that pharmacological treatments for heart failure [e.g., heart renin–angiotensin system (RAS) inhibitors and beta-blockers] reduce morbidity and mortality in patients with HFrEF [5, 7, 8], it remains to be clarified whether patients with AIC can be treated with or without pharmacological treatments for heart failure after catheter ablation.

This study aimed to explore the clinical outcomes after catheter ablation in patients with and without AIC. Moreover, we evaluated the influence of treatment with or without RAS inhibitors and that with or without beta-blockers on patients with AIC after the procedure.

Methods

Study population

This was a multicenter retrospective cohort analysis (University of Fukui, Fukui, Japan; Hikone Municipal Hospital, Shiga, Japan; Sugita Genpaku Memorial Obama Municipal Hospital, Fukui, Japan). In total, 129 consecutive patients with AF and reduced LVEF (<50%) underwent initial AF ablation at our hospital from November 2014 to December 2021. Patients with an old myocardial infarction in ≥2 vessels and left ventricular hypertrophy, defined as a maximum LV wall thickness ≥13 mm on echocardiography, were excluded. [9, 10]. AIC was defined as patients whose LVEF post-procedurally recovered to the normal range (≥50%; “LVEF recovery”) and/or increased >20% from baseline by maintaining sinus rhythm after catheter ablation [11]. Post-procedural LVEF was evaluated under maintained sinus rhythm between 3 and 12 months after initial catheter ablation. If patients experienced AF before follow-up echocardiographic measurements, echocardiographic parameters were evaluated while maintaining sinus rhythm from 3 to 12 months after the repeat procedure. The exclusion criteria were: missing echocardiographic parameter data from 3 to

12 months after the procedure ($n=19$), follow-up period of <12 months ($n=9$), and receiving dialysis ($n=3$). Finally, 96 patients were included. The study complied with the principles of the Declaration of Helsinki. Written informed consent was obtained from all the patients. The study protocol was approved by the Institutional Review Board of our hospital (Clinical Trial Registration: UMIN000050391).

Medical treatment and laboratory data

All patients with AF underwent medical therapy for heart failure, and treatment was decided by each attending physician, according to the guidelines, which included diuretics, RAS inhibitors (angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers), beta-blockers, aldosterone antagonists, and anti-arrhythmic drugs (types I and III), as appropriate. Medication use was assessed at the last outpatient visit. Moreover, patients with AIC were divided into 2 groups: those with or without RAS inhibitors, and those with or without beta-blockers. Patients without RAS inhibitors were defined as those who did not receive RAS inhibitors throughout the study period and patients with RAS inhibitors were defined as patients who had been taking RAS inhibitors since the study began or who started post-procedurally. Additionally, we collected data on plasma levels of B-type natriuretic peptide, creatinine, blood urea nitrogen, C-reactive protein, hemoglobin, and echocardiographic parameters before catheter ablation.

AF ablation protocol and follow-up

Direct oral anticoagulants and warfarin were not discontinued during the peri-procedural period. Furthermore, the intra-procedural activated clotting time was maintained at 300–350 s. After trans-septal puncture, pulmonary vein isolation was performed using either a contact force-sensing irrigated-tip radiofrequency catheter (SmartTouch Surround Flow; Biosense Webster, Diamond Bar, CA, USA) guided by a three-dimensional mapping system (CARTO3; Biosense Webster) or a 28-mm fourth-generation cryoballoon (Arctic Front Advance; Medtronic, Minneapolis, MN, USA). Additional substrate modifications were performed at the discretion of the operator. The procedural endpoint was a bidirectional conduction block between the pulmonary veins and left atrium.

In-hospital electrocardiogram monitoring was performed 3–5 days after the procedure. The regular follow-up period comprised outpatient clinic visits 1 and 3 months after the procedure. Subsequent follow-up visits involved clinical interview, 12-lead electrocardiogram, and/or 24-h Holter electrocardiogram recordings performed at 3-month intervals. Anticoagulation therapy was continued for at least 3 months. Based on the latest guidelines, recurrence was

defined as atrial arrhythmia lasting > 30 s after a 3-month blanking period [4]. Moreover, we recorded cases of cardiovascular death, hospitalization for worsening heart failure, and AF recurrence from electronic medical records. The composite endpoint was defined as cardiovascular death or hospitalization owing to heart failure.

Statistical analysis

Continuous data were expressed as mean \pm standard deviation and median (25th, 75th percentiles) for normally and non-normally distributed variables and were compared using a Student's *t*-test or Mann–Whitney *U*-test, respectively. Categorical variables were compared using the chi-square test. We built a multivariate stepwise logistic regression model to identify independent pre-procedural clinical parameters associated with AIC. The model entry criterion was significance ($p < 0.05$) in univariate analysis. Kaplan–Meier analysis was used to evaluate the clinical outcomes and AF recurrence between patients with and without AIC, and the log-rank test was used to compare the groups. Moreover, the analysis assessed clinical outcomes and AF recurrence in patients with AIC with or without RAS inhibitors and in those with or without beta-blockers. Echocardiographic parameters were analyzed using repeated measures analysis of variance (ANOVA) in patients with AIC with or without RAS inhibitors use and in those with or without beta-blockers. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using JMP, version 12.0 (SAS Institute, Cary, NC, USA).

Results

Characteristics and clinical outcomes of patients with or without AIC

All patients underwent successful pulmonary vein isolation without any procedural complications, except for transient gastric hypo-motility in 2 patients and cerebral infarction in 1 patient. Ninety-six patients (66.7 ± 10.9 years; 72 males, LVEF $39.3 \pm 7.7\%$) were included in our study and divided into the AIC group [$n = 67$ (69.8%)] and non-AIC group [$n = 29$ (30.2%)]. The patients with AIC were younger, had a higher body weight, and were more likely to have a history of symptomatic chronic heart failure than those without AIC. In addition, patients with AIC had lower CHADS₂ and CHA₂DS₂-VASc scores, faster heart rates, and smaller LV chamber sizes (Table 1). However, there were no significant differences in the procedure methods or post-procedural medications (Table 1). In the multivariate logistic regression analysis with a stepwise selection, the LV end-diastolic diameter [odds ratio (OR) = 1.18; 95% confidence interval

(CI) = 1.08–1.31, $p = 0.0002$] and the CHA₂DS₂-VASc scores (OR = 1.62; 95% CI 1.14–2.37, $p = 0.0062$) were independent predictors of AIC after AF ablation (Table 2). During a median follow-up of 25 (13–40) months after the procedure, a total of 9 (9.4%) patients, including 1 (1.5%) and 8 (27.6%) patients ($p < 0.0001$) in the AIC and non-AIC groups, respectively, experienced composite endpoints (Table 1). Notably, no hospitalizations for worsening heart failure were observed in patients with AIC, although 7 (24.1%) in the non-AIC group were hospitalized due to heart failure ($p < 0.0001$; Table 1).

Kaplan–Meier analysis demonstrated that patients with AIC had less frequent composite endpoints ($p < 0.0001$), cardiovascular death ($p = 0.025$), and hospitalization due to heart failure ($p < 0.001$) than those without AIC (Fig. 1). A total of 23 patients, including 17 (25.4%) in AIC and 6 (20.7%) in the non-AIC groups ($p = 0.62$), experienced AF recurrence. According to Kaplan–Meier analysis, whether AF recurred after initial AF ablation was comparable in the 2 groups, regardless of whether anti-arrhythmic drugs were administered ($p = 0.47$; Fig. 1).

Comparison with and without RAS inhibitors or beta-blockers in patients with AIC

Subsequently, of the 67 patients, 29 patients were on RAS inhibitors at the time of ablation, 6 patients added RAS inhibitors postoperatively, and 6 patients terminated RAS inhibitors. Finally, 29 patients were taking a RAS inhibitor at the time of their last follow-up. Patients with AIC were divided into two groups: those who had been taking RAS inhibitors since the study began or who started post-procedurally, and those who did not receive RAS inhibitors throughout the study period (with RAS inhibitors, $n = 35$; without RAS inhibitors, $n = 32$). No significant differences, except for LV chamber size and use of cryoballoons for pulmonary vein isolation, were observed between the 2 groups (Table 3). Only 1 patient died due to acute myocardial infarction in the RAS inhibitor group, and the patient was included in the beta-blocker group. In the Kaplan–Meier analysis, between patients with and without RAS inhibitors, composite endpoints ($p = 0.34$), cardiovascular death ($p = 0.34$), hospitalization for worsening heart failure ($p = 1.0$), and AF recurrence after catheter ablation ($p = 0.86$) did not differ. On comparing those with and without using beta-blockers (with beta-blockers; $n = 42$, without beta-blockers; $n = 25$), there were significant differences in LV chamber size, medical history (symptomatic chronic heart failure), additional substrate modification (cavotricuspid isthmus ablation and mitral isthmus line ablation), and medications after the procedure (aldosterone antagonist and anti-arrhythmic drug type I) (Table 4). In the Kaplan–Meier analysis, between patients with and without beta-blockers, composite

Table 1 Clinical characteristics of the patients included in the study

	Overall (n=96)	AIC group (n=67)	Non-AIC group (n=29)	p value
Age, years	66.7±10.9	64.7±10.7	71.3±9.8	0.0057
Men, n (%)	72 (75.0)	51 (76.2)	21 (72.4)	0.70
Height, cm	164.5±10.1	165.6±9.4	162.0±11.2	0.11
Weight, kg	64.8±13.8	66.6±11.1	60.8±18.2	0.049
Body mass index, kg/m ²	23.8±3.7	24.2±3.2	22.9±4.5	0.091
CHADS ₂ score	2.0±1.1	1.8±1.1	2.5±1.1	0.0050
CHA ₂ DS ₂ -VASc score	3.1±1.6	2.7±1.6	3.9±1.4	0.0011
Chronic heart failure, n (%)	86 (89.6)	57 (85.1)	29 (100.0)	0.0056
Hypertension, n (%)	49 (51.0)	30 (44.8)	19 (65.5)	0.060
Diabetes mellitus, n (%)	22 (22.9)	13 (19.4)	9 (31.0)	0.22
Vascular disease, n (%)	17 (17.7)	9 (13.4)	8 (27.6)	0.11
Stroke, n (%)	7 (7.3)	4 (6.0)	3 (10.3)	0.46
Non-paroxysmal AF, n (%)	70 (72.9)	51 (76.1)	19 (65.5)	0.29
Ablation methods				0.56
Radiofrequency ablation, n (%)	54 (56.3)	39 (58.2)	15 (51.7)	
Cryoballoon, n (%)	42 (43.8)	28 (41.8)	14 (48.3)	
Details of ablation procedures				
Pulmonary vein isolation, n (%)	96 (100.0)	67 (100.0)	29 (100.0)	–
Cavotricuspid isthmus ablation, n (%)	82 (85.4)	57 (85.1)	25 (86.2)	0.88
Superior vena cava isolation, n (%)	10 (10.4)	5 (7.5)	5 (17.2)	0.17
Mitral isthmus line ablation, n (%)	20 (20.8)	15 (22.4)	5 (17.2)	0.56
Roof line ablation, n (%)	34 (35.4)	24 (35.8)	10 (34.5)	0.90
Bottom line ablation, n (%)	8 (8.3)	7 (10.4)	1 (3.4)	0.22
CFAEs ablation, n (%)	7 (7.3)	5 (7.5)	2 (6.9)	0.92
Ablation of non-pulmonary vein foci, n (%)	3 (3.1)	3 (4.5)	0 (0.0)	0.14
Physiological function test				
Heart rate, bpm	92.3±24.2	96.1±24.8	83.4±20.7	0.018
LV ejection fraction, %	39.3±7.7	40.2±7.2	37.2±8.6	0.084
LV end-diastolic diameter, mm	52.6±6.4	51.2±5.7	55.6±6.9	0.0017
LV end-systolic diameter, mm	42.3±7.0	40.9±6.1	45.6±8.0	0.0018
Left atrial diameter, mm	42.4±5.0	42.3±5.0	42.7±5.1	0.70
Laboratory test				
Brain natriuretic peptide, pg/mL	148.7 (74.1–251.9)	122.7 (60.3–240.0)	179.1 (100.8–312.2)	0.15
Creatinine, mg/dL	1.03±0.26	1.04±0.28	1.00±0.22	0.50
Blood urea nitrogen, mg/dL	19.1±6.5	19.0±6.5	19.5±6.6	0.74
C-reactive protein, mg/dL	0.08 (0.04–0.24)	0.08 (0.04–0.22)	0.12 (0.06–0.35)	0.11
Hemoglobin, g/dL	14.2±1.8	14.4±1.7	13.7±1.9	0.058
Medications at the time of the procedure				
Diuretics, n (%)	45 (46.9)	30 (44.8)	15 (51.7)	0.48
RAS inhibitor	41 (42.7)	29 (43.3)	12 (41.4)	0.87
ACEI, n (%)	14 (14.6)	8 (11.9)	2 (6.9)	0.56
ARB, n (%)	31 (32.3)	21 (31.3)	10 (34.5)	0.59
Beta-blocker, n (%)	54 (56.3)	37 (55.2)	17 (58.6)	0.94
Aldosterone antagonist, n (%)	19 (19.8)	12 (17.9)	7 (24.1)	0.64
Anti-arrhythmic drug type I, n (%)	7 (7.3)	4 (6.0)	3 (10.3)	0.36
Anti-arrhythmic drug type III, n (%)	21 (21.9)	13 (19.4)	8 (27.6)	0.32
Medications after the procedure				
Diuretics, n (%)	42 (43.8)	25 (37.3)	17 (58.6)	0.054
RAS inhibitor	45 (46.9)	29 (43.3)	16 (55.2)	0.28
ACEI, n (%)	15 (15.6)	9 (13.4)	6 (20.7)	0.49

Table 1 (continued)

	Overall (n=96)	AIC group (n=67)	Non-AIC group (n=29)	p value
ARB, n (%)	30 (31.3)	20 (29.9)	10 (34.5)	0.76
Beta-blocker, n (%)	59 (61.5)	42 (62.7)	17 (58.6)	0.71
Aldosterone antagonist, n (%)	22 (22.9)	13 (19.4)	9 (31.0)	0.22
Anti-arrhythmic drug type I, n (%)	1 (3.1)	1 (1.5)	0 (0.0)	0.39
Anti-arrhythmic drug type III, n (%)	29 (30.2)	17 (25.4)	12 (41.4)	0.12
Clinical outcome				
Follow-up duration, month	25 (13–40)	23 (12–41)	25 (17–36)	0.33
Composite endpoint, n (%)	9 (9.4)	1 (1.5)	8 (27.6)	<0.0001
Cardiovascular death, n (%)	5 (5.2)	1 (1.5)	4 (13.8)	0.013
Hospitalization for heart failure, n (%)	7 (7.3)	0 (0.0)	7 (24.1)	<0.0001
Recurrence of AF, n (%)	23 (24.0)	17 (25.4)	6 (20.7)	0.62

Values are reported as the mean \pm standard deviation or number of patients (%), unless otherwise noted. Levels of brain natriuretic peptide, C-reactive protein, and TnI are non-normally distributed, and the values are reported as medians (25th and 75th percentiles)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; AF, atrial fibrillation; CFAEs, complex fractionated atrial electrogram; LV, left ventricular; TnI, troponin I; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2

Table 2 Predictors of AIC in the multivariate stepwise logistic regression analysis

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% confidence interval	p value	Odds ratio	95% confidence interval	p value
Age, years	1.07	1.022–1.139	0.003			
Weight, kg	0.96	0.924–0.999	0.044	0.97	0.925–1.009	0.13
CHA ₂ DS ₂ -VASc score	1.59	1.194–2.184	0.001	1.62	1.144–2.369	0.0062
Heart rate, bpm	0.98	0.956–0.996	0.016			
LVDd, mm	1.12	1.042–1.224	0.002	1.18	1.075–1.311	0.0002

Values are reported as confidence intervals and odds ratios

AIC, arrhythmia-induced cardiomyopathy; LVDd, left ventricular end-diastolic diameter

endpoints ($p=0.44$), cardiovascular death ($p=0.44$), hospitalization for worsening heart failure ($p=1.0$), and AF recurrence after catheter ablation ($p=0.55$) did not differ.

Serial changes in echocardiographic parameters with or without pharmacological treatment in patients with AIC

A significant post-procedural improvement in LVEF in patients with RAS inhibitors ($p<0.0001$) and without RAS inhibitors ($p<0.0001$) was observed using the paired *t*-test. Furthermore, there was a significant decrease in the LV end-systolic diameter and left atrial diameter after the procedure, compared to baseline levels in patients with and without RAS inhibitors. Though the LV end-diastolic and end-systolic diameters were larger in patients with RAS inhibitors than in those without RAS inhibitors, when analyzed using a two-way repeated measured ANOVA, there were no statistically significant differences in the time \times group interaction with the LVEF ($F_{(1,65)}=1.42$, $p=0.23$), LV end-diastolic

diameters ($F_{(1,65)}=2.37$, $p=0.13$), and left atrial diameters ($F_{(1,65)}=0.26$, $p=0.61$), except for LV end-diastolic diameters ($F_{(1,65)}=4.32$, $p=0.042$), between patients with and without RAS inhibitors (Fig. 2). Furthermore, between patients with and without beta-blockers, time \times group interaction with the LVEF ($F_{(1,65)}=0.09$, $p=0.76$), LV end-diastolic diameters ($F_{(1,65)}=3.62$, $p=0.062$), LV end-diastolic diameters ($F_{(1,65)}=2.85$, $p=0.096$), and left atrial diameters ($F_{(1,65)}=1.99$, $p=0.16$) did not differ significantly by the analysis (Fig. 3).

Discussion

We found that (1) AIC was associated with freedom from the composite endpoint, cardiovascular death, and hospitalization for worsening heart failure after AF ablation; (2) LV end-diastolic diameter and CHA₂DS₂-VASc scores were independent predictors of AIC; (3) between patients with AIC with and without RAS inhibitors use, clinical outcomes,

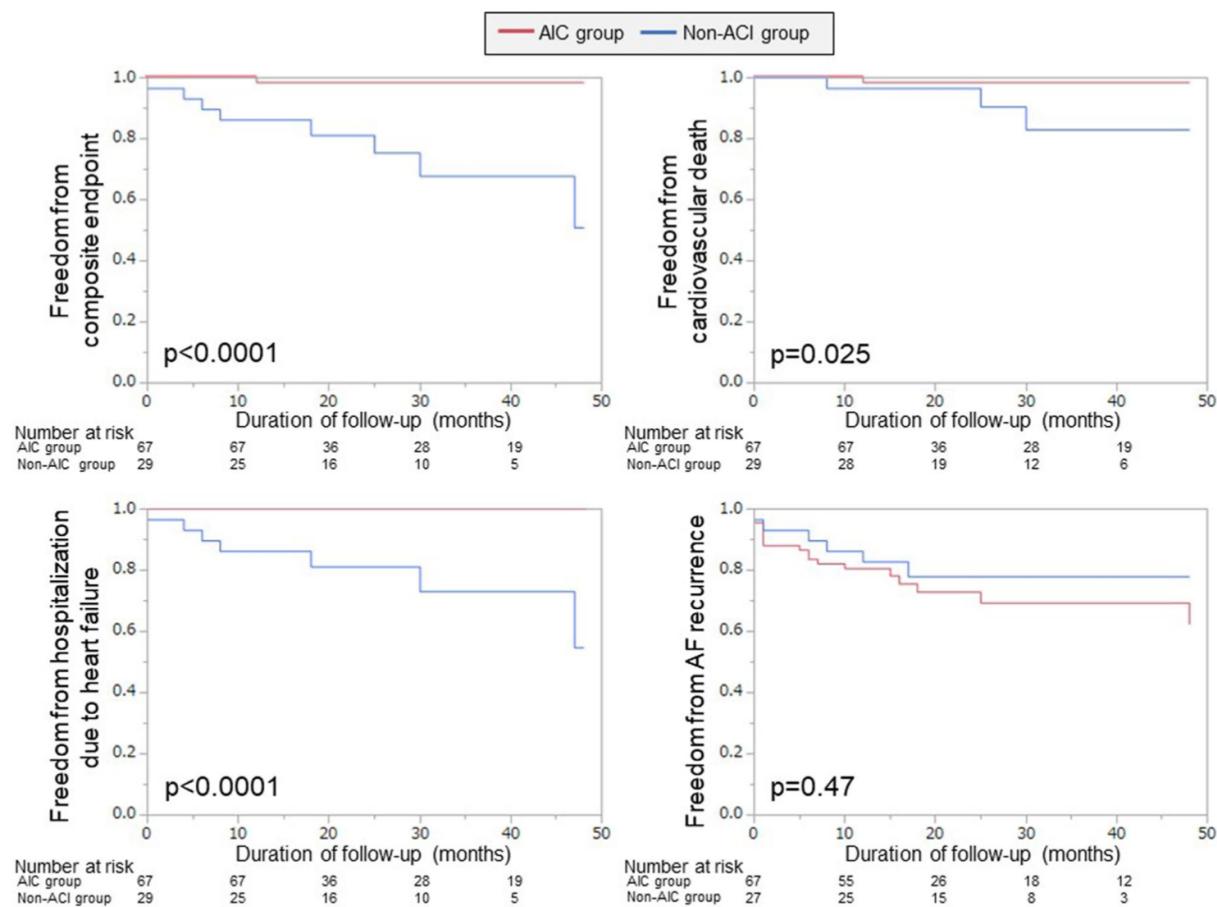


Fig. 1 Clinical outcomes after catheter ablation. In the Kaplan–Meier analysis, AIC is significantly associated with the lower composite endpoint, cardiovascular mortality, and hospitalization for worsening heart failure after catheter ablation. However, no significant differences in AF recurrence after the procedure between patients with AIC and other cardiomyopathy are observed. AF, atrial fibrillation; AIC, arrhythmia-induced cardiomyopathy

ences in AF recurrence after the procedure between patients with AIC and other cardiomyopathy are observed. AF, atrial fibrillation; AIC, arrhythmia-induced cardiomyopathy

including cardiovascular death, hospitalization for worsening heart failure, and AF recurrence, did not differ after the procedure; (4) though there were differences in baseline characteristics between patients with AIC with and without beta-blockers, no significant differences in clinical outcomes were observed between two groups; (5) serial change of pre- and post-procedural echocardiographic parameters, except for LV end-diastolic diameters, did not differ between those with and without RAS inhibitors or with and without beta-blocker usage.

Prognosis of AIC after catheter ablation

The prognosis of AIC after AF ablation is expected to be better than that of other cardiomyopathies, including dilated cardiomyopathy (DCM) and ischemic heart disease, because heart failure caused by AIC recovers completely after arrhythmia treatment. A prior study classified

patients with reduced LVEF as “pure” AIC or “impure” AIC. The pure AIC occurs in patients with an uncontrolled arrhythmia, which is the sole pathogenic factor to a normal myocardium. In contrast, the impure AIC occurs in patients with structural heart diseases and the cardiac dysfunction only recovers incompletely after the termination of the arrhythmia. Between the pure AIC and the impure AIC groups, there were no statistically significant differences in the survival rate after catheter ablation [12]. Furthermore, it was revealed that LVEF $\leq 42\%$ and worsening renal function after AF ablation contributed significantly to mortality and heart failure events [13]. However, the novelty of our study is that after restoring and maintaining sinus rhythm by catheter ablation for AF, the composite endpoints, the cardiovascular mortality rates, and the hospitalization due to heart failure in the AIC group were significantly lower than those in the non-AIC group. Notably,

Table 3 Arrhythmia-induced cardiomyopathy patients treated with or without RAS inhibitors

	Overall (n=67)	With RASI (n=35)	Without RASI (n=32)	p value
Age, years	64.7±10.7	65.6±9.9	63.7±11.6	0.46
Men, n (%)	51 (76.1)	28 (80.0)	23 (71.9)	0.44
Height, cm	165.6±9.4	165.9±8.6	165.3±10.4	0.79
Weight, kg	66.6±11.1	66.9±9.5	66.2±12.8	0.78
Body mass index, kg/m ²	24.2±3.2	24.3±3.1	24.1±3.3	0.77
CHADS ₂ score	1.8±1.1	1.9±0.9	1.7±1.3	0.60
CHA ₂ DS ₂ -VASc score	2.7±1.6	2.8±1.4	2.7±1.8	0.89
Chronic heart failure, n (%)	57 (85.1)	31 (88.6)	26 (81.3)	0.40
Hypertension, n (%)	30 (44.8)	18 (51.4)	12 (37.5)	0.25
Diabetes mellitus, n (%)	13 (19.4)	5 (14.3)	8 (25.0)	0.27
Vascular disease, n (%)	9 (13.4)	5 (14.3)	4 (12.5)	0.83
Stroke, n (%)	4 (6.0)	2 (5.7)	2 (6.3)	0.93
Non-paroxysmal AF, n (%)	51 (76.1)	24 (68.6)	27 (84.4)	0.13
Ablation methods				0.007
Radiofrequency ablation, n (%)	39 (58.2)	15 (42.9)	24 (75.0)	
Cryoballoon, n (%)	28 (41.8)	20 (57.1)	8 (25.0)	
Details of ablation procedures				
Pulmonary vein isolation, n (%)	67 (100.0)	35 (100.0)	32 (100.0)	–
Cavotricuspid isthmus ablation, n (%)	57 (85.1)	31 (88.6)	26 (81.3)	0.40
Superior vena cava isolation, n (%)	5 (7.5)	1 (2.9)	4 (12.5)	0.12
Mitral isthmus line ablation, n (%)	15 (22.4)	7 (20.0)	8 (25.0)	0.62
Roof line ablation, n (%)	24 (35.8)	13 (37.1)	11 (34.3)	0.81
Bottom line ablation, n (%)	7 (10.4)	4 (11.4)	3 (9.4)	0.78
CFAEs ablation, n (%)	5 (7.5)	1 (2.9)	4 (12.5)	0.12
Ablation of non-pulmonary vein foci, n (%)	3 (4.5)	1 (2.9)	2 (6.3)	0.50
Physiological function test				
Heart rate, bpm	96.1±24.8	92.2±26.1	100.0±23.0	0.18
LV ejection fraction, %	40.2±7.2	39.5±7.8	40.9±6.6	0.43
LV end-diastolic diameter, mm	51.2±5.7	53.2±5.5	49.1±5.3	0.0028
LV end-systolic diameter, mm	40.9±6.1	43.3±5.9	38.2±5.2	0.0004
Left atrial diameter, mm	42.3±5.0	42.1±5.0	42.5±5.0	0.75
Laboratory test				
B-type natriuretic peptide, pg/mL	122.7 (60.3–240.0)	109.7 (57.3–193.5)	171.5 (74.1–313.0)	0.080
Creatinine, mg/dL	1.04±0.28	1.04±0.18	1.04±0.36	0.90
Blood urea nitrogen, mg/dL	19.0±6.5	20.2±7.0	17.7±5.8	0.12
C-reactive protein, mg/dL	0.08 (0.04–0.22)	0.08 (0.05–0.30)	0.05 (0.03–0.15)	0.14
Hemoglobin, g/dL	14.4±1.7	14.3±1.8	14.5±1.6	0.76
Medications after the procedure				
Diuretics, n (%)	25 (37.3)	15 (42.9)	10 (31.3)	0.33
Beta-blocker, n (%)	42 (62.7)	23 (65.7)	21 (65.6)	0.99
Aldosterone antagonist, n (%)	13 (19.4)	9 (25.7)	4 (12.5)	0.17
Anti-arrhythmic drug type I, n (%)	1 (1.5)	1 (2.9)	0 (0.0)	0.25
Anti-arrhythmic drug type III, n (%)	17 (25.4)	12 (34.3)	5 (14.3)	0.076
Clinical outcome				
Follow-up duration, month	23 (12–41)	24 (13–49)	22 (12–39)	0.63
Composite endpoint, n (%)	1 (1.5)	1 (2.9)	0 (0.0)	0.25
Cardiovascular death, n (%)	1 (1.5)	1 (2.9)	0 (0.0)	0.25
Hospitalization for heart failure, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Recurrence of AF, n (%)	17 (25.4)	9 (25.7)	8 (25.0)	0.74

Values are reported as the mean±standard deviation or number of patients (%), unless otherwise noted. Levels of brain natriuretic peptide, C-reactive protein, and TnI are non-normally distributed, and the values are reported as medians (25th and 75th percentiles)

AF, atrial fibrillation; CFAEs, complex fractionated atrial electrogram; LV, left ventricle; TnI, troponin I; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter 2

Table 4 Arrhythmia-induced cardiomyopathy patients treated with or without beta-blockers

	Overall (n=67)	With B blocker (n=42)	Without B blocker (n=25)	p value
Age, years	64.7±10.7	65.3±11.6	63.6±9.3	0.53
Men, n (%)	51 (76.1)	29 (69.0)	22 (88.0)	0.068
Height, cm	165.6±9.4	164.4±10.0	167.5±8.2	0.19
Weight, kg	66.6±11.1	66.7±12.0	66.4±9.7	0.90
Body mass index, kg/m ²	24.2±3.2	24.6±3.5	23.6±2.7	0.21
CHADS ₂ score	1.8±1.1	2.0±1.0	1.5±1.1	0.11
CHA ₂ DS ₂ -VASc score	2.7±1.6	3.0±1.5	2.3±1.6	0.088
Chronic heart failure, n (%)	57 (85.1)	40 (95.2)	17 (68.0)	0.0026
Hypertension, n (%)	30 (44.8)	18 (42.9)	12 (48.0)	0.68
Diabetes mellitus, n (%)	13 (19.4)	10 (23.8)	3 (12.0)	0.22
Vascular disease, n (%)	9 (13.4)	7 (16.7)	2 (8.0)	0.30
Stroke, n (%)	4 (6.0)	2 (4.8)	2 (8.0)	0.59
Non-paroxysmal AF, n (%)	51 (76.1)	33 (78.6)	18 (72.0)	0.54
Ablation methods				0.074
Radiofrequency ablation, n (%)	39 (58.2)	21 (50.0)	18 (72.0)	
Cryoballoon, n (%)	28 (41.8)	21 (50.0)	7 (28.0)	
Details of ablation procedures				
Pulmonary vein isolation, n (%)	67 (100.0)	42 (100.0)	25 (100.0)	–
Cavotricuspid isthmus ablation, n (%)	57 (85.1)	39 (92.9)	18 (72.0)	0.023
Superior vena cava isolation, n (%)	5 (7.5)	2 (4.8)	3 (12.0)	0.29
Mitral isthmus line ablation, n (%)	15 (22.4)	13 (31.0)	2 (8.0)	0.021
Roof line ablation, n (%)	24 (35.8)	17 (40.5)	7 (28.0)	0.29
Bottom line ablation, n (%)	7 (10.4)	4 (9.5)	3 (12.0)	0.75
CFAEs ablation, n (%)	5 (7.5)	5 (11.9)	0 (0.0)	0.027
Ablation of non-pulmonary vein foci, n (%)	3 (4.5)	2 (4.8)	1 (4.0)	0.88
Physiological function test				
Heart rate, bpm	96.1±24.8	92.8±23.9	101.7±25.8	0.16
LV ejection fraction, %	40.2±7.2	39.0±6.6	42.2±7.8	0.075
LV end-diastolic diameter, mm	51.2±5.7	52.5±5.7	49.2±5.3	0.018
LV end-systolic diameter, mm	40.9±6.1	42.3±6.0	38.4±5.6	0.0088
Left atrial diameter, mm	42.3±5.0	42.6±4.9	41.8±5.2	0.56
Laboratory test				
B-type natriuretic peptide, pg/mL	122.7 (60.3–240.0)	164.5 (70.7–285.3)	101.2 (46.1–143.6)	0.072
Creatinine, mg/dL	1.04±0.28	1.08±0.32	0.98±0.20	0.16
Blood urea nitrogen, mg/dL	19.0±6.5	19.9±7.2	17.6±5.0	0.16
C-reactive protein, mg/dL	0.08 (0.04–0.22)	0.09 (0.04–0.29)	0.05 (0.03–0.09)	0.14
Hemoglobin, g/dL	14.4±1.7	14.3±1.6	14.5±1.8	0.64
Medications after the procedure				
Diuretics, n (%)	25 (37.3)	18 (42.9)	7 (28.0)	0.27
RAS inhibitor	31 (46.3)	19 (45.2)	10 (40.0)	0.68
ACEI, n (%)	10 (14.9)	8 (19.0)	9 (36.0)	0.20
ARB, n (%)	21 (31.3)	12 (28.6)	2 (8.0)	0.53
Aldosterone antagonist, n (%)	13 (19.4)	12 (28.6)	1 (4.0)	0.0070
Anti-arrhythmic drug type I, n (%)	1 (1.5)	0 (0.0)	1 (4.0)	0.16
Anti-arrhythmic drug type III, n (%)	17 (25.4)	12 (28.6)	5 (20.0)	0.43
Clinical outcome				
Follow-up duration, month	23 (12–41)	29 (13–41)	15 (12–36)	0.21
Composite endpoint, n (%)	1 (1.5)	1 (2.4)	0 (0.0)	0.33
Cardiovascular death, n (%)	1 (1.5)	1 (2.4)	0 (0.0)	0.33
Hospitalization for heart failure, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Recurrence of AF, n (%)	17 (25.4)	10 (23.8)	7 (28.0)	0.70

Values are reported as the mean±standard deviation or number of patients (%), unless otherwise noted. Levels of brain natriuretic peptide, C-reactive protein, and TnI are non-normally distributed, and the values are reported as medians (25th and 75th percentiles)

Table 4 (continued)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin 2 receptor blocker; AF, atrial fibrillation; CFAEs, complex fractionated atrial electrogram; LV, left ventricular; TnI, troponin I; RAS, renin-angiotensin system; SGLT2, sodium–glucose cotransporter 2

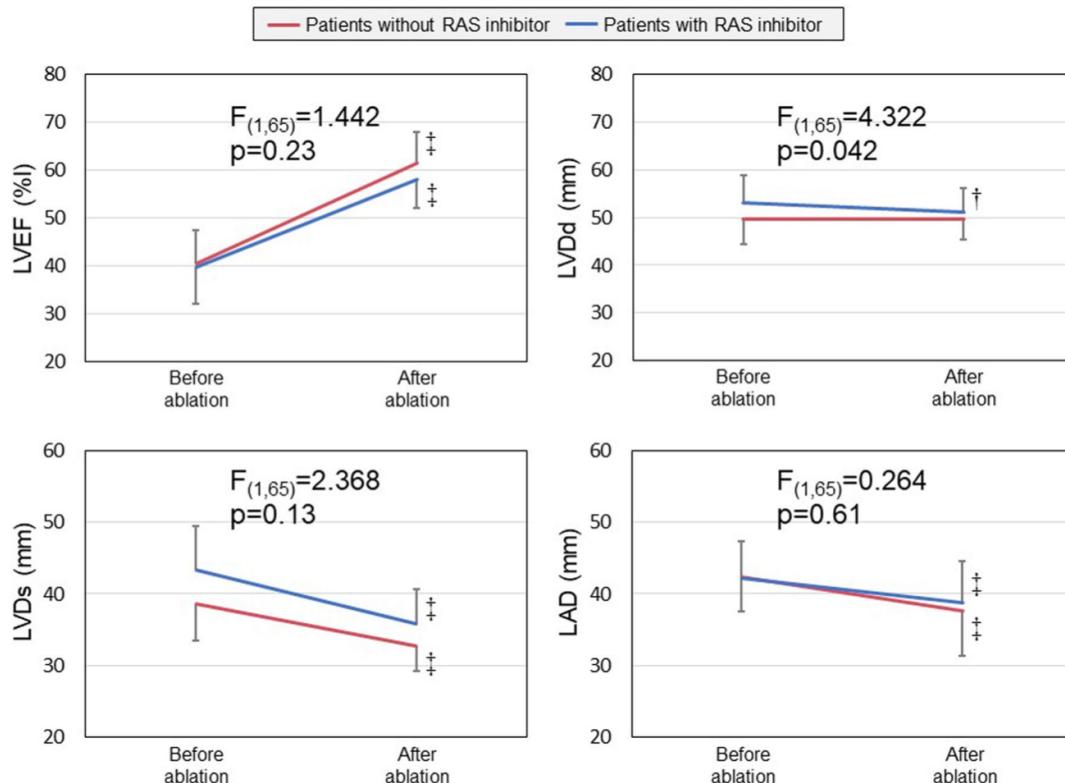


Fig. 2 Serial changes in the echocardiographic parameters before and after the procedure in patients treated with or without RAS inhibitors. Serial changes in the LVEF, LV end-diastolic diameter, LV end-systolic diameter, and left atrial diameter before and after catheter ablation are analyzed using repeated measures ANOVA. The blue and red lines indicate the patients with RAS inhibitors and those without

RAS inhibitors, respectively. $\dagger p$ value <0.05 versus pre-procedure analyzed by a paired t -test. $\ddagger p$ value <0.001 versus pre-procedure analyzed by a paired t -test. LAD, left atrial diameter; LVDd, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; RAS, renin-angiotensin system

none of the patients in the AIC group were hospitalized for worsening heart failure during follow-up.

Pre-procedural predictors of LVEF recovery after the procedure

Our study revealed that patients with AIC have an excellent clinical course after catheter ablation. Therefore, it is important to identify the pre-procedural factors that can predict the AIC. Our study showed that the pre-procedural LV end-diastolic diameter could be an indicator predicting the recovery of the LVEF, which might aid in discriminating between patients with and without AIC. This result is similar to that of a previous study [14]. Moreover, in our study, the CHA₂DS₂-VASc score was an indicator of LVEF recovery.

Furthermore, several studies reported that the absence of late gadolinium enhancement on cardiac magnetic resonance imaging and low serum troponin levels can predict AIC [15, 16]. Evaluating these parameters before the procedure to predict prognosis may be useful.

Whether to use pharmacological treatment for heart failure post-procedurally

The mechanism of AIC has not been clarified, although AF may cause AIC through rapid rates, ventricular irregularities, and autonomic effects of the loss of atrial contraction [17]. Moreover, some individuals with heart failure, including those with AIC and peripartum cardiomyopathy, may recover completely after eliminating the causative factor

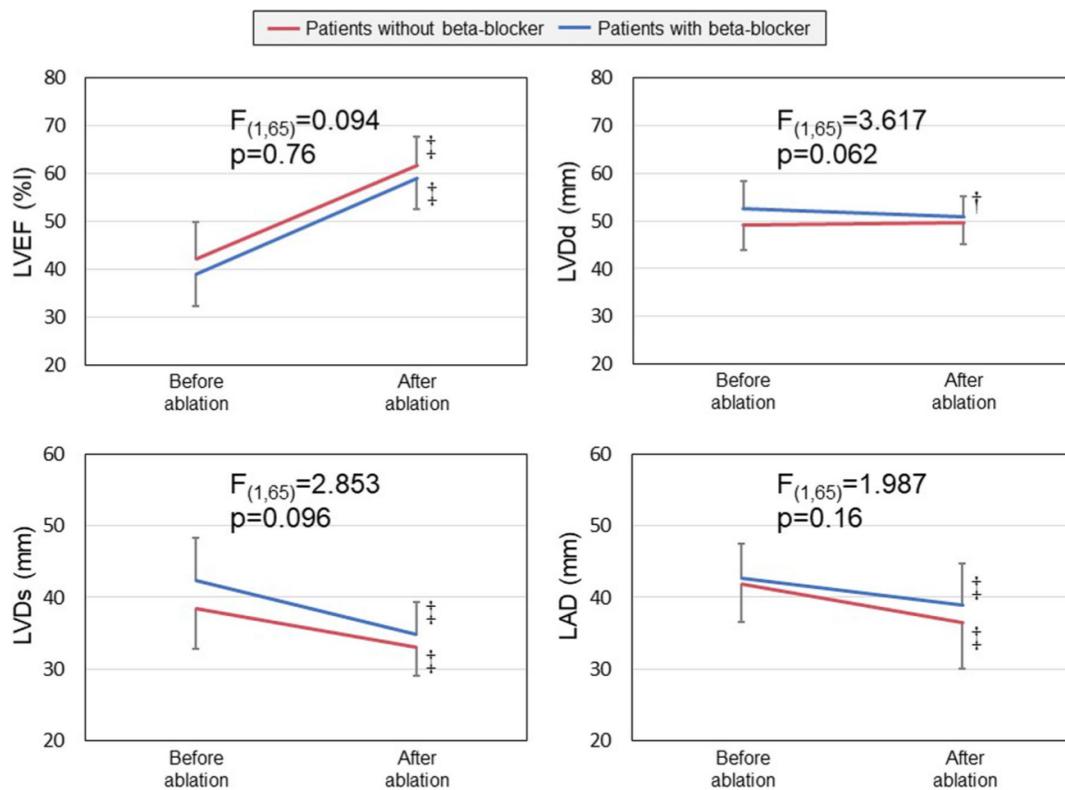


Fig. 3 Serial changes in the echocardiographic parameters before and after the procedure in patients treated with or without beta-blockers. Serial changes in pre- and post-procedural echocardiographic parameters are analyzed using repeated measures ANOVA. The blue and red lines indicate patients treated with and without beta-

blockers, respectively. $\dagger p$ value <0.05 versus pre-procedure analyzed by a paired t -test. $\ddagger p$ value <0.001 versus pre-procedure analyzed by a paired t -test. LAD, left atrial diameter; LVDD, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction

[3]. However, other patients with LV systolic dysfunction, including those with DCM, may show substantial or complete recovery of LV systolic function after receiving drug therapy. In a previous prospective randomized trial that investigated withdrawal of heart failure treatment in patients deemed to have heart failure with recovered LVEF, treatment was withdrawn successfully in only 50% of patients, while 40% had a relapse of their dilated cardiomyopathy within 6 months [18]. Conversely, in patients with peripartum cardiomyopathy whose LVEF had recovered after delivery, none had a deterioration in LVEF over a median follow-up of 29 months if the pharmacological treatment was withdrawn [19]. Similar to peripartum cardiomyopathy, a good prognosis for patients with AIC is expected after eradication of the cause, which is the termination of arrhythmia.

Significant differences in baseline characteristics were observed between patients with AIC with and without beta-blocker usage. Therefore, it is difficult to evaluate whether beta-blockers should be used. However, since no differences in baseline, except for LV chamber size and use

of cryoballoon, were observed between patients with and without RAS inhibitors use, treatment without RAS inhibitors was not likely to have contributed to the increased adverse events. Because RAS inhibitors were frequently used in patients with LV dilatation, the LV end-diastolic diameter in patients with RAS inhibitors may have been significantly reduced after catheter ablation. It is unclear whether this reduction was due to the effect of the RAS inhibitor or the maintenance of sinus rhythm.

Taken together, it may be reasonable not to use RAS inhibitors after catheter ablation in patients without comorbidities of other cardiomyopathies and LV dilatation if the patients have trouble with the side effects of RAS inhibitors or wish to reduce their medications. Furthermore, catheter ablation in patients with AF and LV dysfunction may be preceded by waiting to determine the efficacy of the pharmacological therapy for heart failure when AIC is probable. Future prospective studies are needed to further clarify treatment recommendations for patients with AIC after the procedure.

Limitations

First, this was a retrospective observational study with a relatively small sample size and a limited follow-up period. Second, each attending physician decided to administer RAS inhibitors and/or beta-blockers. Therefore, treatment with using neither RAS inhibitors nor beta-blockers at the same time was not evaluated, and there were several differences in the backgrounds of patients treated with or without beta-blockers. Prospective studies are required to confirm these findings.

Conclusion

Catheter ablation in patients with AIC due to AF is associated with a good post-procedural prognosis. Additional studies are required to consider this strategy without concomitant pharmacological treatment for heart failure after catheter ablation.

Funding Hiroshi Tada received honoraria (lecture fees) from Daiichi-Sankyo Co., Ltd.; Biotronik Japan, Inc.; Bristol-Myers Squibb; Boehringer Ingelheim; Bayer Yakuhin, Ltd.; Japan; Boehringer Ingelheim Japan; ALVAUS Co., Ltd.; Novartis Pharmaceuticals Japan; ONO PHARMACEUTICAL CO., LTD; Takeda Pharmaceutical Company, Ltd. Shinsuke Miyazaki received honoraria (lecture fees) from Boehringer Ingelheim, Bristol-Myers Squibb, Medtronic Japan, Boston Scientific Co., and Daiichi-Sankyo Co., Ltd. and a scholarship from Johnson & Johnson. Daisetsu Aoyama belong to endowed department by Biotronik Japan, Inc., DVx Inc., ALVAUS Co., Ltd.

Data availability The deidentified participant data will not be shared, except for a considerable useful request.

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