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Original Article

Outcomes after stepwise ablation for persistent atrial fibrillation in patients with heart failure

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ABSTRACT

Background: There is limited data regarding the outcomes after stepwise ablation for persistent atrial fibrillation (AF) in patients with heart failure (HF).
Methods and results: Patients without structural heart disease undergoing stepwise ablation for persistent AF (continuous AF $\leq$ 1 year) were studied ($n=108$; age, 61 ± 10 years) and 32 patients had a history of HF. The HF patients were further grouped on the basis of left ventricular ejection fraction (LVEF) $\leq$ 45% ($n=15$) and $>$ 45% ($n=17$). During a median follow-up period of 2.2 years, repeated ablations were necessary in 65 patients. The proportion of patients that were arrhythmia free 1 year after the last ablation was 67% in patients with LVEF $\leq$ 45%, 86% in LVEF $>$ 45%, and 91% in no HF ($p=0.0009$). In patients with LVEF $\leq$ 45%, the AF burden was reduced to less than one paroxysmal episode per month, and patients with and without recurrences both showed significant increases in LVEF over the follow-up period (38 ± 7% to 60 ± 10% and 37 ± 6% to 53 ± 10%, respectively).
Conclusions: HF patients with LVEF $\leq$ 45% had lower chances to remain free from arrhythmias after stepwise ablation for persistent AF than those with LVEF $>$ 45%. Nevertheless, LVEF also improved in patients with recurrences, reflecting the observed reduction in AF burden and emphasizing the benefits of ablation.

1. Introduction

Atrial fibrillation (AF) often exacerbates heart failure (HF) and HF predisposes patients to the development and progression of AF [1,2]. This interplay between AF and HF significantly increases hospitalization and mortality. In patients with AF and HF, pharmacological rhythm control therapy was not found to be superior to rate control therapy [3], although it was reported that left ventricular (LV) function improved after catheter ablation for AF [4,5]. Catheter ablation for AF is therefore recommended for patients with HF [6]. However, some studies have shown that LV dysfunction is associated with poor clinical outcome of catheter ablation for AF [7–9].

In the last decade, ablation techniques and technologies have been developed for isolation of the pulmonary veins (PVs) [10,11]. In particular, the efficacy of PV isolation is limited for persistent AF. To improve clinical outcomes, ablation techniques for atrial substrate modification were also developed [12–14]. Stepwise ablation, which includes atrial substrate ablation in addition to PV isolation, is highly effective in treating persistent AF [15]. It is unknown whether LV dysfunction is a predictor of tachyarrhythmia recurrences, even with the stepwise ablation strategy. Furthermore, little is known about the association between tachyarrhythmia recurrence and changes in LV function after ablation for AF in HF patients.

The first aim of the present study was to assess arrhythmia-free rate after stepwise ablation for persistent AF in HF patients in comparison with patients without HF. The second aim was to assess changes in LV ejection fraction (LVEF) in HF patients with and without tachyarrhythmia recurrences over the course of the follow-up period.

2. Methods

2.1. Study population

Patients undergoing stepwise ablation for symptomatic and persistent AF were eligible for this study. Persistent AF was

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defined as continuous AF for >1 week and ≤ 1 year [6]. All patients with a prior history of HF underwent echocardiography and coronary angiography or coronary computed-tomography angiography for the assessment of structural heart disease before ablation. Exclusion criteria were New York Heart Association (NYHA) functional class III or IV at the time of the ablation, prior cardiac surgery, or structural heart disease, including prior myocardial infarction, ischemic cardiomyopathy, valvular disease, and hypertrophic cardiomyopathy. For the aims of this study, patients who were diagnosed with dilated cardiomyopathy were included because reduced LV dysfunction may be attributed to AF [4]. In patients with a prior history of HF, LV function was reassessed at least one month after conventional pharmacological therapy for HF, including rate control drugs. Based on the LV function reassessment results after one month of medical therapy, the patients were grouped by LVEF values of $\leq 45\%$ and $>45\%$. Patients without a history of HF served as controls. All patients provided informed written consent before undergoing the ablation protocol.

2.2. Electrophysiological study

All anti-arrhythmic drugs were discontinued at least 5 half-lives prior to ablation. No patients were taking amiodarone. Patients with a history of HF were treated with drugs, including diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, β-blockers, or digitalis, for at least one month. Warfarin was administered for at least one month prior to the procedure with a target international normalized ratio of 2.0–3.0 and was continued during the periprocedural period. Transesophageal echocardiography was performed one day before the procedure to confirm the absence of atrial thrombi.

A multielectrode catheter was deployed in the coronary sinus from the jugular vein. Two boluses of 50 IU/kg of heparin were administered, one prior to transseptal puncture and the second immediately after transseptal puncture. The activated clotting time was evaluated at least every 30 min and maintained at ≥ 300 s during the procedure. The surface ECG and bipolar intracardiac electrograms were monitored on a computer-based digital amplifier/recording system (Labsystem Pro, Bard Electrophysiology, Lowell, MA). The intracardiac electrograms were filtered with a bandpass of 30–500 Hz and measured with online calipers at a sweep speed of 100 mm/s.

2.3. Stepwise ablation for persistent AF

Ablation was performed using an irrigated-tip catheter (Navistar Thermocool, Biosense-Webster, Diamond Bar, CA) under the guidance of a 3D mapping system (CARTO, Biosense-Webster). Contrast-enhanced computerized tomography (CT) of the left atrium (LA) and PVs was performed before ablation and the CT image was integrated with a 3D navigation system during the procedure. Radiofrequency (RF) energy was delivered up to 35 W for the mitral isthmus line and cavotricuspid isthmus, and 30 W for other regions, respectively.

Catheter ablation was performed during ongoing AF as described previously [15,16]. The goal of the procedure was termination of AF (conversion to atrial tachycardia [AT] or restoration of sinus rhythm) by ablation. First, PV isolation was performed, guided by a circumferential decapolar electrode catheter. If isolation of all PVs failed to terminate AF, electrogram-based ablation in the LA or coronary sinus was performed. Characteristics of local electrograms targeted in the LA or coronary sinus were as follows: [1] continuous activity, [2] centrifugal activation pattern, [3] short cycle length activity (≥ 10 ms shorter than that in the surrounding area), and [4] activation gradient [17]. If AF continued after elimination of the electrograms with the characteristics mentioned above in all areas in the LA and coronary sinus, LA linear ablation at the roof and mitral isthmus were performed. If LA linear ablation failed to terminate AF, the sinus rhythm was restored by electrical cardioversion. No anti-arrhythmic drugs were administered to the patients during the procedure.

After restoration of the sinus rhythm, cavotricuspid isthmus linear ablation was performed in all patients. Regardless of whether AF was terminated by ablation or not, isolation of all PVs and conduction block of all linear lesions were validated during sinus rhythm or atrial pacing, as appropriate. If residual conduction gaps were identified, ablation was continued to achieve isolation of the PVs and conduction block of the line. For validation of conduction block of the roof line, a pacing catheter and the ablation catheter were deployed at the LA appendage and LA roof, respectively. For validation of mitral isthmus line block, a multielectrode catheter in the coronary sinus and ablation catheter in the LA were used for pacing and mapping.

During RF delivery in the posterior wall of the LA, esophageal temperature was monitored using a temperature probe. RF was discontinued when the esophageal temperature reached 41 °C [18]. Additional RF was not delivered at the same site until the esophageal temperature decreased to 39 °C.

2.4. Follow-up

Following the ablation, 100 mg of flecainide was administered for 2 months unless the patient had HF or sinus bradycardia. After this period, all anti-arrhythmic drugs were discontinued. Discovery of persistent or paroxysmal episodes of continuous AF/AT for >30 s after the 2-month blanking period was regarded as a recurrence of tachyarrhythmia. If required, a repeat procedure was performed after the blanking period.

The patient was monitored 2, 4, and 6 months after the procedure, and then at least every 6 months in our outpatient clinic. Electrocardiographic (ECG) recording was conducted during each follow-up, and 24-h Holter monitoring was performed at 4 and 6 months after the procedure, and every 6 months thereafter. Symptomatic patients were provided with a portable ECG monitor (Omron, Kyoto, Japan) for event monitoring in the study duration.

2.5. Statistical analysis

The data are presented as the mean $\pm$ standard deviation for normally distributed variables and as median and interquartile range for non-normally distributed variables. Continuous variables grouped by LVEF or HF were compared using one-way analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate. Comparison of proportions was performed by Fisher's exact test. Comparison of LVEF from before and one year after the ablation was performed using paired Student's *t* test. Freedom from tachyarrhythmias was analyzed using Kaplan–Meier method. A log-rank test was used to compare estimates of the arrhythmia-free rate across groups. Multivariable predictors were identified using Cox proportional hazard regression methods. Relative risks were expressed as a hazard ratio with 95% confidence interval. A p value less than 0.05 was considered to be statistically significant. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 15.0).

3. Results

Among 125 consecutive patients undergoing stepwise ablation for persistent AF, 17 patients (14%) were excluded because of prior cardiac surgery or structural heart disease (6 patients with prior myocardial infarction; 4, prior cardiac surgery; 4, hypertrophic cardiomyopathy; and 3, mitral valvular disease). Of the 108 patients studied, 15 (14%) had a history of HF and LVEF $\leq$ 45%, 17 (16%) had a history of HF and LVEF $>$ 45%, and 76 (70%) had no history of HF.

Baseline characteristics of the 108 patients are shown in Table 1. Regardless of LVEF, patients with a history of HF had shorter AF and continuous AF durations and higher $CHADS_2$ scores, and LA diameter than those in patients without a history of HF. All patients with history of HF and LVEF $>$ 45% showed improvement in NYHA functional class after rate control therapy; therefore, they were diagnosed as tachycardia-induced cardiomyopathy by the physicians who referred them.

3.1. The index procedure outcome

Baseline LA cycle length, defined as the average of 30 consecutive AF cycles at the LA appendage, was compared across the 3 groups (Fig. 1A). Patients with HF and LVEF $>$ 45% had the highest LA cycle length ($p=0.0001$).

In 47 patients (44%), AF was terminated by ablation during the index procedure. The AF termination rate of each group is shown in Fig. 1B. The rate of AF termination was highest in patients with HF and LVEF $>$ 45%, although it did not reach statistical significance ($p=0.057$). This trend was analogous to the LA cycle length of these 3 groups. Of these 47 patients, PV isolation terminated AF in only 7 patients (15%). In the remaining 40 patients (85%), electrogram-based ablation, in combination with PV isolation, terminated AF in 14 patients (30%), and further linear ablation terminated AF in 26 patients (55%). Fig. 2 shows the ablation techniques performed in each group. PV isolation alone did not terminate AF in any patient with HF and LVEF $\leq$ 45%. Procedural and RF duration and irrigation volume were similar across the 3 groups (Table 2).

Complications occurred in 2 patients (2%) during the periprocedural period. One patient without HF had a transient ischemic stroke 2 day after the ablation. The other patient with HF and LVEF $\leq$ 45% had gastric hypomotility, which spontaneously resolved in 5 day. No patient showed worsening of HF during the periprocedural period.

The median follow-up period from the index procedure was 2.2 years (interquartile range: 0.9–3.3 years). From the

Table 1
Baseline characteristics.

	Total ($n=108$)	HF and LVEF $\leq$ 45% ($n=15$)	HF and LVEF $>$ 45% ($n=17$)	No HF ($n=76$)	p value
Age (years)	61 ± 10	61 ± 10	64 ± 8	61 ± 10	0.5
Male (%)	77	73	65	80	0.3
AF duration (months)	10 (4–60)	4 (3–10.5)	7.5 (3–54)	12 (5.5–60)	0.04
Continuous AF duration (months)	4 (2–7)	3 (3–5)	2 (1.5–4.5)	4 (3–8)	0.02
Hypertension (%)	41	27	41	43	0.5
Diabetes (%)	11	20	12	9	0.4
History of stroke (%)	8	13	18	5	0.1
$CHADS_2$ score	1 (0–2)	1 (1–3)	2 (1–2)	0.5 (0–1)	< 0.0001
Left atrial diameter (mm)	42 ± 4	45 ± 4	44 ± 5	41 ± 4	0.001
LVEF (%)	59 ± 11	39 ± 7	58 ± 7	63 ± 7	< 0.0001
LV diastolic diameter (mm)	49 ± 6	56 ± 6	49 ± 5	47 ± 5	< 0.0001
BNP (pg/mL)	137 (74–210)	237 (86–358)	191 (140–315)	109 (70–180)	< 0.0001
Prior cardioversion (%)	19	33	18	16	0.3

Values are given as the mean ± standard deviation (SD) or as the median with interquartile range in parentheses.

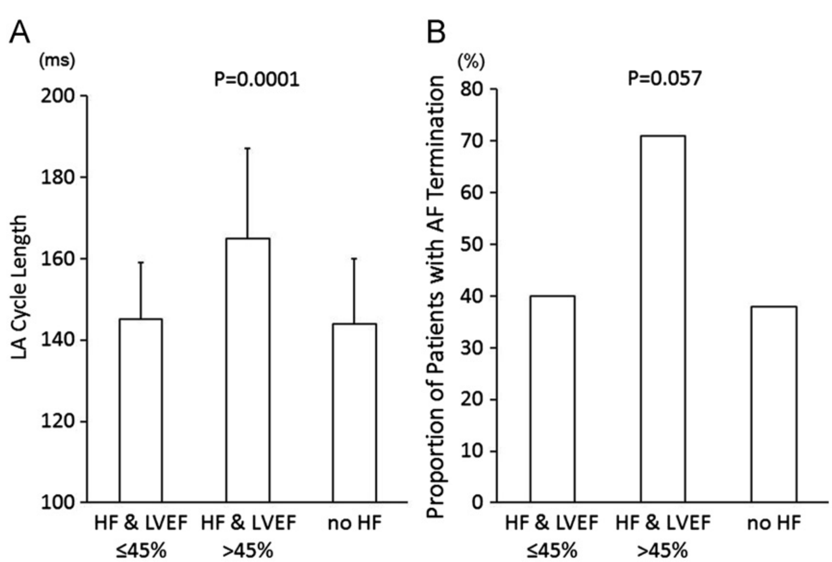

Fig. 1. Left atrial cycle length before ablation (A) and proportion of patients whose AF terminated (B) during the index ablation in each group. HF=heart failure; LVEF=left ventricular ejection fraction. Whiskers represent standard deviation of the mean.

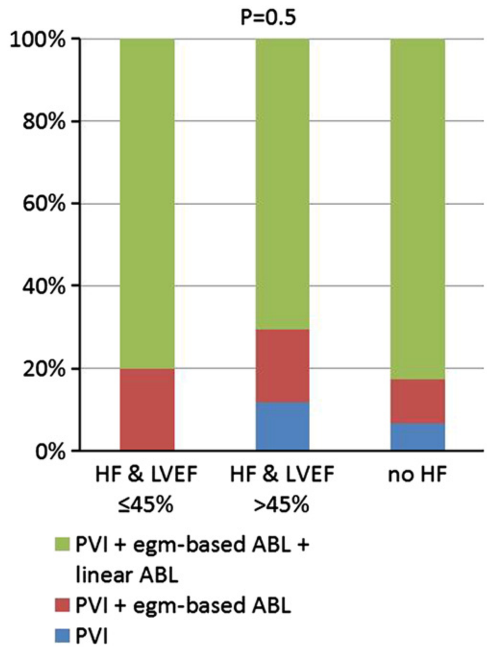

Fig. 2. Ablation techniques used in each group. PVI=pulmonary vein isolation; egm-based ABL=electrogram-based ablation; linear ABL=linear ablation.

Table 2
Procedural and radiofrequency duration and irrigation volume in the index procedure.

	HF and LVEF ≤ 45% (*n*=15)	HF and LVEF > 45% (*n*=17)	No HF (*n*=76)	*p* value
Procedural duration (min)	224 ± 35	208 ± 51	224 ± 45	0.4
RF duration (min)	80 ± 16	84 ± 29	84 ± 23	0.8
Irrigation volume (L)	1.99 ± 0.31	1.86 ± 0.54	1.85 ± 0.54	0.5

Values are given as the mean ± standard deviation (SD).

Kaplan–Meier curve, arrhythmia-free rates at the 1-year follow-up were estimated to be 36% in patients with HF and LVEF ≤ 45%, 27% in patients with HF and LVEF > 45%, and 40% in patients with no HF (log-rank test, $p=0.12$; Fig. 3).

3.2. Repeat ablation outcome

A second ablation was performed in 65 patients (60%) a median of 2.9 months (interquartile range: 2.3–4.5 months) after the index procedure. Eight patients (7%) underwent the second ablation > 1 year after the index ablation because of very late recurrence. The recurrent arrhythmia observed in these patients was AT in 31 patients (48%), AT and AF in 12 patients (18%), and AF in the remaining 22 patients (34%). In the 34 patients who presented with AF after the index procedure, conduction recovery was demonstrated in a median of 2 PVs during the repeat ablation. Of the 34 patients, 6 patients (18%) did not show conduction recovery in any PVs. In all patients with AF recurrence after the index procedure, electrogram-based ablation was performed because re-isolation of the PVs failed to terminate AF.

Of the 65 patients, 17 patients underwent a third ablation. The recurrent arrhythmia was AT in 8 patients, AT and AF in 4 patients, and AF in 5 patients. Of the 9 patients who presented with AF after the second ablation, 6 patients did not have conduction recovery in any PVs during the third ablation. In the remaining 3 patients, conduction recovery was found in a single PV. Electrogram-based ablation was performed in all patients with AF recurrence. Additionally, 3 patients underwent a fourth ablation (2 for AT, and 1 for AF, respectively). No complication occurred in any of the repeat ablations.

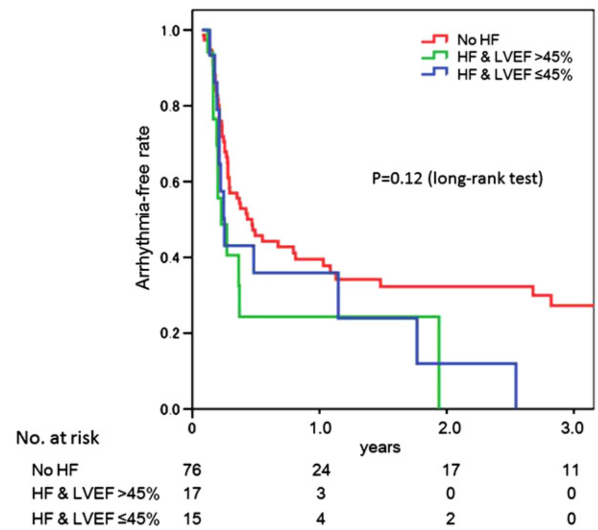

Fig. 3. Freedom from tachyarrhythmia after the index ablation procedure. Comparison of patients with heart failure (HF) and left ventricular ejection fraction (LVEF) ≤ 45%, those with HF and LVEF > 45%, and those without HF.

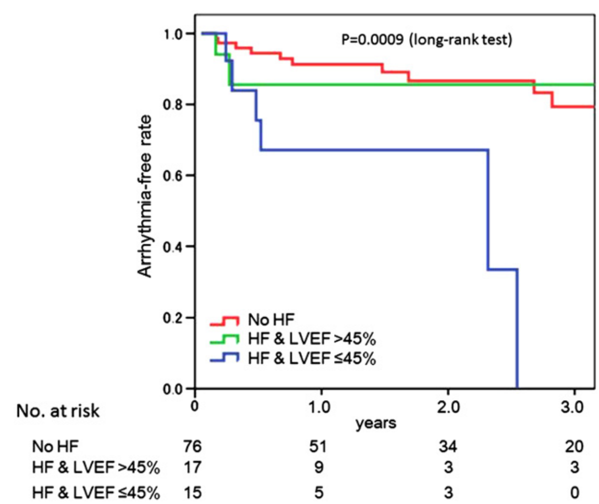

Fig. 4. Freedom from tachyarrhythmia after the last ablation. Comparison of patients with heart failure (HF) and left ventricular ejection fraction (LVEF) ≤ 45%, those with HF and LVEF > 45%, and those without HF.

The median follow-up period from the last ablation was 1.5 years (interquartile range: 0.8–2.7 years). The total number of ablations performed was similar across the 3 groups (HF and LVEF ≤ 45%: 1.9 ± 0.2; HF and LVEF > 45%: 1.8 ± 0.2; no HF: 1.8 ± 0.1; $p=0.8$). From the Kaplan–Meier curve, the arrhythmia-free rate at 1-year follow-up was 67% in patients with HF and LVEF ≤ 45%, 86% in patients with HF and LVEF > 45%, and 91% in patients with no HF (log rank test: $p=0.0009$; Fig. 4). The arrhythmia-free rate in patients without HF declined slightly to 87% at 2-year follow-up, but did not change in the other 2 groups (LVEF, ≤ 45% and > 45%). After adjustment for age, gender, and duration of continuous AF, HF and LVEF ≤ 45% group was associated with a 6- to 7-fold increased risk of tachyarrhythmia recurrence (Table 3).

Table 3
Multivariate analyses for recurrence of atrial tachyarrhythmias.

	Hazard ratio (95% CI)	*p* value
Age	0.98 (0.93–1.03)	0.5
Male	0.37 (0.12–1.26)	0.11
Duration of continuous AF (months)	0.95 (0.8–1.11)	0.5
HF and LVEF ≤ 45%		
vs. HF and LVEF > 45%	6.05 (1.25–44.2)	0.025
vs. no HF	7.03 (2.23–21.1)	0.0015

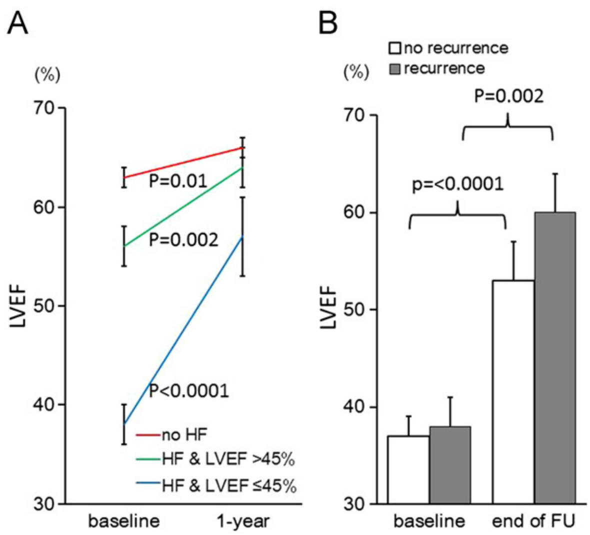

Fig. 5. Changes in left ventricular ejection fraction (LVEF). LVEF at baseline and at the 1-year follow-up are shown in patients with heart failure (HF) and LVEF ≤ 45%, those with HF and LVEF > 45%, and those without HF (A). LVEF at baseline and the end of the follow-up period are shown in patients with tachyarrhythmia recurrence and those free from recurrence (no recurrence) for patients with HF and LVEF ≤ 45% at baseline (B). $p=0.13$ for comparison of the increase in LVEF (LVEF at the end of follow-up minus baseline) between the 2 groups. Whiskers represent standard error of the mean.

At the end of the follow-up period, 19 of 108 patients (18%) had recurrent tachyarrhythmias. The recurrent tachyarrhythmia was paroxysmal AF or AT in 15 of the 19 patients (79%), and persistent AT in the remaining 4 patients. No patient had persistent AF. All 15 patients who had a paroxysmal form of recurrent tachyarrhythmia had less than one symptomatic episode per month. Of the 89 patients free from tachyarrhythmias, 83 patients (93%) were not taking antiarrhythmic drugs.

3.3. Left ventricular function after the ablation

In all 3 groups, LVEF increased from baseline to the 1-year follow-up (Fig. 5A). Patients with LVEF ≤ 45% showed the highest increase in LVEF.

In patients with LVEF ≤ 45% at baseline, the increase in LVEF was compared between the subgroups with and without tachyarrhythmia recurrence (Fig. 5B). In all patients with tachyarrhythmia recurrences, the clinical form of the recurrent tachyarrhythmia was paroxysmal, and the frequency of tachyarrhythmia episode was less than one per month. Over the follow-up period, LVEF increased in both groups (tachyarrhythmia recurrence: $38 \pm 7\%$ to $60 \pm 10\%$, $p=0.002$; no recurrence: $37 \pm 6\%$ to $53 \pm 10\%$, $p<0.0001$). The increase in LVEF in patients with and without recurrence was $22 \pm 9\%$ and $16 \pm 5\%$, respectively ($p=0.13$).

4. Discussion

There is only limited data available on the outcomes after catheter ablation for AF in HF patients. Our results may be helpful in selecting patients for catheter ablation, determining ablation strategy, and postprocedural management. The major finding of this study was that LVEF ≤ 45% at the time of ablation was associated with low arrhythmia-free rate after multiple ablations, but having history of HF was not. Furthermore, during index ablation, patients with LVEF ≤ 45% had shorter AF cycle length and lower rate of AF termination than those in patients with LVEF > 45%. These findings may suggest that the fibrillatory process was more advanced in patients with reduced LVEF.

A stepwise ablation strategy was used in the present study. In this ablation strategy, electrogram-based ablation or linear ablation was performed in combination with PV isolation, and the desired procedural endpoint was termination of AF [15,16]. All atrial regions except the sinus node and atrioventricular node are candidates for ablation. Stepwise ablation is, therefore, considered to be optimal for patients with persistent AF, because AF substrates are ubiquitously distributed in the atria and PVs in these patients. In fact, the efficacy of stepwise ablation for patients without HF was 91% at the 1-year follow-up in this study, which is comparable to rates for paroxysmal AF. However, patients with reduced LVEF showed worse clinical outcome even after undergoing stepwise ablation strategy. This is consistent with previous reports in which different ablation strategies were used [8,9]. It remains possible that more extensive ablation with a high rate of AF termination may result in improved clinical outcomes for patients with LV dysfunction. Further studies are required to address this issue.

The arrhythmia-free rate was 67%–91% at 1-year after multiple ablations depending on HF and LVEF status, although repeat ablations were required for more than half of the patients. One of the mechanisms responsible for tachyarrhythmia recurrences was conduction recovery in the PVs or linear lesions. Elimination of the dormant conduction unmasked by administration of ATP can reduce conduction recovery between the PVs and LA [19–21], but even with this approach, conduction recovery in the PVs was still observed. Prevention of conduction recovery in linear lesions is more challenging. Delivery of greater RF power may reduce conduction recovery, but there are risks of complications such as PV stenosis, steam pop, atrioesophageal fistula, and pericarditis. Thus, development of new ablation technologies is necessary for both safety and efficacy issues. However, prevention of conduction recovery in the PVs may not be the sole solution for improvement of efficacy. Our study group included some patients who had AF recurrences that did not show conduction recovery in any PV during repeat ablation. This fact clearly indicates incremental efficacy of ablation targeting the atrial tissue in persistent AF.

As reported previously [4,5], this study showed that elimination of AF improved LVEF significantly. In addition, patients with tachyarrhythmia recurrence also had a significant increase in LVEF after the ablation. This may highlight the benefit of catheter ablation for AF in HF patients. We note that all tachyarrhythmia recurrences consisted of occasional paroxysmal episodes (< 1/month), suggesting that infrequent episodes of tachyarrhythmias are unlikely to reduce LV function.

In clinical practice, the form of AF presentation in HF patients is often persistent, presumably because paroxysmal AF is likely to rapidly progress to the persistent form in these patients [2]. Thus, we focused on persistent rather than paroxysmal AF in this study. We also chose to exclude long-standing persistent AF. Because the duration of continuous AF is a predictor of a clinical outcome after ablation for persistent AF [16], association of LV function with clinical outcome would likely be obscured if patients with long-standing persistent AF were included.

4.1. Clinical implication

This study suggests that AF ablation targeting the atrial substrate, in combination with PV isolation, can be a therapeutic option for patients with LV dysfunction even after appropriate rate control. Furthermore, catheter ablation at earlier stages may be more favorable for HF patients, because fibrillatory substrate progresses rapidly in this cohort.

4.2. Limitations

Antiarrhythmic drugs were administered to patients without HF for a short-term after the ablation, but not to patients with reduced LVEF. This may contribute to the high arrhythmia-free rate in patients without HF. It has been reported that in patients with normal LV function, short-term antiarrhythmic drug therapy failed to improve mid-term clinical outcome after ablation [22]. However, it is unknown whether this result also applies to HF patients.

To exclude the effects of a potential link between AF and structural heart disease, patients with ischemic heart disease, valvular disease, or hypertrophic cardiomyopathy were not included in the present study.

The complication rate in patients with HF or reduced LVEF seemed modest, but a greater number of patients are required to assess the incidence of infrequent events. Finally, we did not study the efficacy and safety of AF ablation in HF patients in the NYHA functional class III or IV.

5. Conclusion

In our study, only two-thirds of HF patients with LVEF $\leq$ 45% remained free of arrhythmia after ablation for persistent AF, unlike the much higher success rates for patients with LVEF $>$ 45%. Nevertheless, in these LVEF $\leq$ 45% patients, LVEF improved in both arrhythmia-free and non-arrhythmia patients, reflecting the reduction in the AF burden and highlighting the benefits of stepwise ablation for persistent AF in HF patients.

Conflict of interest

None.

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