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CLINICAL INVESTIGATIONS

Predictors of arrhythmia recurrence in patients with heart failure undergoing left atrial ablation for atrial fibrillation

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Background: Atrial fibrillation (AF) ablation is increasingly used in patients with reduced left ventricular ejection fraction (LVEF). The aim of the present study was to evaluate the long-term results of a single radiofrequency catheter ablation procedure in heart failure (HF) patients with AF.

Hypothesis: We tested the hypothesis that left atrial ablation is an effective therapeutic modality in patients with heart failure.

Methods: Our study included HF patients with LVEF <50% who underwent catheter ablation for AF at our department between January 2010 and March 2017. All patients underwent our institution's protocol for follow-up post-ablation.

Results: The study enrolled a total of 38 patients (mean age, 54.1 ± 12.2 years; 28 [73.7%] males; mean LVEF, 38.2% ± 6.3%). After a mean follow-up period of 38.2 months (range, 5–92 months), 28 patients (73.7%) were free from arrhythmia recurrence. In multivariate analysis, early arrhythmia recurrence (P = 0.03) and amiodarone antiarrhythmic drug administration (P = 0.003) remained independent predictors of arrhythmia recurrence.

Conclusions: The main findings of this study are that (1) a single radiofrequency catheter ablation procedure is an effective and safe modality for AF in patients with concomitant HF; (2) after a mean 3.3 years of follow-up, 73.7% of HF patients remained in sinus rhythm; and (3) early arrhythmia recurrence was a significant predictor of arrhythmia recurrence after the blanking period.

KEYWORDS

Atrial Fibrillation, Catheter Ablation, Heart Failure

1 | INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) often coexist. AF is associated with an approximate 9.5-fold increase in mortality within the first 4 months when accompanied by HF.[1] Data from the Framingham Heart Study show that HF was one of the strongest predictors for AF, with the risk nearly 5-fold for men and 6-fold for women.[2] Catheter ablation is recommended as a first-line therapeutic approach in patients with symptomatic paroxysmal AF (PAF) that is refractory to antiarrhythmic therapy.[3,4] However, it has lower success rates in patients with nonparoxysmal AF (NPAF; persistent and long-standing persistent AF).[3,4] Based on the current expert consensus document on catheter ablation for AF, the long-term success rate of the method is defined as freedom from AF following the 3-month blanking period through a minimum of 36 months.[5] AF ablation is increasingly used in patients with reduced left ventricular ejection fraction (LVEF), but predictors of long-term outcomes are still unknown. The aim of the present study was to evaluate the long-term results of a single

radiofrequency catheter ablation procedure in HF patients with PAF and NPAF.

2 | METHODS

Our study included HF patients with LVEF <50% who underwent catheter ablation at our department for AF between January 2010 and March 2017. Catheter ablation was performed under intravenous sedation with midazolam and remifentanil by 2 experienced operators (M.E. and K.P.L). Complete pulmonary vein (PV) antrum isolation was confirmed after a waiting period of 30 minutes. The patients were anticoagulated using acenocoumarol with a target international normalized ratio of 2.0 to 3.0 or direct oral anticoagulants at least 4 weeks before and 3 months after the procedure. All patients underwent our institution's protocol for follow-up post-ablation. Patients were seen every week at the dedicated arrhythmia outpatient clinic of our institution for the first month. Patients had follow-up visits with a 24-hour Holter electrocardiogram at 1, 3, 6, 9, and 12 months, and for every 6 months thereafter, or whenever they developed symptoms consistent with recurrent AF.

2.1 | Statistical analysis

Continuous variables were presented as mean ± SD, whereas categorical variables were presented as absolute and relative frequencies (percentages). Continues variables were tested for normal distribution using the Kolmogorov–Smirnov test. Continuous variables with and without normal distribution were compared using Student *t* test or the Mann–Whitney *U* test, respectively. Pearson χ^2 or Fisher exact test were used to test for any associations between 2 categorical variables. We examined univariate models and multivariate models with forward selection of variables per likelihood ratio criteria. Analyses were done with SPSS version 17.0 (SPSS Inc., Chicago, IL), and all reported *P* values are 2-tailed.

3 | RESULTS

The study enrolled a total of 38 patients (mean age, 54.1 ± 12.2 years; 28 (73.7%) males; mean LVEF, 38.2% ± 6.3%) with reduced LVEF (<50%). The baseline characteristics of patients are shown in Table 1. Of the total population, 16 patients (42.1%) underwent catheter ablation for PAF and 22 (57.9%) for NPAF. There were no procedure-related complications. The mean duration of the procedure was 191.6 ± 29.3 minutes, and the mean fluoroscopy time was 16.4 ± 4.98 minutes.

After a mean follow-up period of 38.2 ± 33.6 months (range, 5–92 months), 28 patients (73.7%) were free from late arrhythmia recurrence (Table 2). Sinus rhythm (SR) was maintained in 12 (75%) and 16 (72.7%) patients with PAF and NPAF, respectively. During the blanking period, which was defined as the 3-month period after the ablation procedure, 6 (15.8%) patients presented with early arrhythmia recurrence (EAR). Univariate analysis revealed that EAR during the blanking period (*P* = 0.027) and amiodarone medication before the procedure (*P* = 0.002) were statistically significant predictors of late arrhythmia recurrence. In multivariate analysis, EAR (*P* = 0.03) and amiodarone antiarrhythmic drug administration (*P* = 0.003) remained independent predictors of late arrhythmia recurrence (Table 3).

Moreover, we performed a separate analysis to find predictors of EAR (during the blanking period; Table 4). Univariate analysis revealed that treatment with β-blockers before or after ablation and baseline LVEF were significant predictors of EAR. However, none of the variables that were significant in univariate analysis remained a significant predictor following multivariate adjustment.

TABLE 1 Baseline characteristics of the 38 patients included in this study

Variable	
Follow-up, mo	38.2 ± 33.6
Age, y	54.1 ± 12.2
Male sex	28 (73.7)
BMI, kg/m^2	29.2 ± 5.3
Type of AF	
Paroxysmal	16 (42.1)
Persistent	22 (57.9)
Early AF recurrence	6 (15.8)
Cr levels, mg/dL	0.82 ± 0.23
HTN	20 (52.6)
DM	8 (21.1)
Dyslipidemia	8 (21.1)
CAD	8 (21.1)
Duration of history of AF, y	5.0 ± 4.45
AADs before AF ablation	
Amiodarone	8 (21.1)
β-Blockers	36 (94.7)
AADs after AF ablation	
Amiodarone	4 (10.5)
β-Blockers	18 (47.4)
Anticoagulation	
Acenocoumarol	20 (52.6)
Dabigatran	4 (10.5)
Apixaban	6 (15.8)
Rivaroxaban	8 (21.1)
Echocardiography	
LAD, mm	43.6 ± 4.5
LVEF, %	38.2 ± 6.3
IVSd, mm	9.1 ± 1.01
LVEDD, mm	47.9 ± 4.82
PWD, mm	9.32 ± 0.66
Procedural characteristics	
Procedure time, min	191.6 ± 29.3
Fluoroscopy time, min	16.4 ± 4.98
Radiation dose, mGy/m^2	2532.8 ± 1450.9

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; Cr, creatinine; DM, diabetes mellitus; HTN, hypertension; IVSd, intraventricular septum thickness at systole; LAd, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PWD, posterior wall thickness; SD, standard deviation. Data are presented as n (%) or mean ± SD.

TABLE 2 Baseline characteristics of the included patients stratified by late AF recurrence following a single catheter ablation procedure

Characteristics	Late Recurrence		*P* Value
	Yes, n = 10 (26.3)	No, n = 28 (73.7)	
Age, y	55.2 ± 7.1	53.7 ± 13.6	0.737
Male sex	10 (35.7)	18 (64.3)	1.00
BMI, kg/m^2	29.5 ± 4.0	29.1 ± 5.7	0.856
Paroxysmal AF	4 (25)	12 (75)	0.875
AF duration, y	6.0 ± 2.58	4.64 ± 4.94	0.412
Early recurrence	4 (66.7)	2 (33.3)	0.027
HTN	6 (30)	14 (70)	0.588
DM	2 (25)	6 (75)	0.924
Dyslipidemia	4 (50)	4 (50)	0.100
CAD	4 (50)	4 (50)	0.100
AADs before the procedure			
Amiodarone	6 (75)	2 (25)	0.002
β-Blockers	10 (27.8)	26 (72.2)	1.00
AADs after the procedure			
Amiodarone	2 (50)	2 (50)	0.279
β-Blockers	2 (11.1)	16 (88.9)	0.067
Echocardiographic parameters			
IVSd, mm	9.4 ± 1.07	8.93 ± 0.98	0.209
LVEDD, mm	46.2 ± 3.43	48.5 ± 5.15	0.199
PWD, mm	9.4 ± 0.52	9.29 ± 0.71	0.636
LVEF, %	35.2 ± 8.57	39.29 ± 5.04	0.087
LAd, mm	43.4 ± 2.55	43.71 ± 5.08	0.848
Procedure characteristics			
Fluoroscopy time, min	17.71 ± 5.42	15.86 ± 4.82	0.312
Duration of procedure, min	220 ± 29.81	181.43 ± 21.72	0.003
Radiation dose, mGy/m^2	3784.6 ± 2132.9	2085.7 ± 761.9	0.029

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; IVSd, intraventricular septum thickness at systole; LAd, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PWD, posterior wall thickness; SD, standard deviation. Data are presented as n (%) or mean ± SD.

TABLE 3 Predictors of AF recurrence (multivariate analysis)

	OR (95% CI)	*P* Value
Early recurrence	13.35 (1.29-138)	0.03
Amiodarone before the procedure	26.3 (3.01-229.2)	0.003

Abbreviations: AF, atrial fibrillation; CI, confidence interval; OR, odds ratio.

Subgroup analysis according to the cause of HF (ischemic vs nonischemic) was also performed. In our study, 8 ischemic HF patients and 30 nonischemic HF patients (valvular heart disease, dilated cardiomyopathy, and hypertrophic cardiomyopathy) were included. In those with ischemic HF (mean age, 56 years; 75% males), 4 patients (50%) had late AF recurrence, whereas 4 patients (50%) remained free from arrhythmia recurrence during the follow-up period. The patients with AF recurrence were older, had longer AF duration, higher prevalence of dyslipidemia, and thicker posterior wall diameter than did patients without AF recurrence. By contrast, in those with nonischemic HF (mean age, 53.6 years; 73.3% males), 6 patients (20%) had late AF recurrence, whereas 24 patients (80%) remained free from arrhythmia recurrence. There were not any significant differences in baseline characteristics between the 2 groups.

TABLE 4 Baseline characteristics of the included patients stratified by early AF recurrence following a single catheter ablation procedure

Characteristics	Early Recurrence		*P* Value
	Yes, 6 (15.8)	No, 32 (84.2)	
Age, y	50 ± 8.2	54.9 ± 12.7	0.375
Male sex	6 (21.4)	22 (78.6)	0.168
BMI, kg/m^2	32.5 ± 4.93	28.6 ± 5.19	0.297
Paroxysmal AF	4 (25)	12 (75)	0.217
AF duration, y	5.0 ± 3.58	5.0 ± 4.64	0.807
HTN	4 (20)	16 (80)	0.663
DM	2 (25)	6 (75)	0.587
Dyslipidemia	2 (25)	6 (75)	0.587
CAD	2 (25)	6 (75)	0.587
AADs before the procedure			
Amiodarone	2 (25)	6 (75)	0.587
β-Blockers	4 (11.1)	32 (88.9)	0.021
AADs after the procedure			
Amiodarone	0 (0)	4 (100)	1.000
β-Blockers	0 (0)	18 (100)	0.021
Echocardiographic parameters			
IVSd, mm	9.33 ± 1.37	9.0 ± 0.95	0.614
LVEDD, mm	45.3 ± 3.14	48.4 ± 4.96	0.159
PWD, mm	9.33 ± 0.52	9.31 ± 0.69	0.929
LVEF, %	28.7 ± 4.93	40.0 ± 4.75	<0.001
LAd, mm	43.7 ± 1.03	43.6 ± 4.92	0.572
Procedure characteristics			
Fluoroscopy time, min	17 ± 5.37	16.2 ± 4.98	0.687
Duration of procedure, min	196.7 ± 33.86	190.6 ± 28.84	0.870
Radiation dose, mGy/m^2	3983 ± 2983.6	2260.9 ± 770.3	0.261

Abbreviations: AADs, antiarrhythmic drugs; AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; HTN, hypertension; IVSd, intraventricular septum thickness at systole; LAd, left atrial diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; PWD, posterior wall thickness; SD, standard deviation. Data are presented as n (%) or mean ± SD.

4 | DISCUSSION

The main findings of the present study are that (1) a single AF catheter ablation procedure is an effective and safe modality in HF patients with AF; (2) after a mean 3.3 years of follow-up, 73.7% of HF patients remained in SR; and (3) EAR and the use of amiodarone

before the procedure were significant predictors of arrhythmia recurrence after the blanking period.

Catheter ablation, when compared with direct current synchronized cardioversion followed by amiodarone, has been associated with significantly higher 1-year rates of SR maintenance and with improved cardiac function.[6] Additionally, patients who underwent catheter ablation were found to have significantly lower mortality, stroke/transient ischemic attack, and HF hospitalizations compared with patients who underwent cardioversion.[7] Another interesting finding is that patients with poorer cardiac function at baseline appear to benefit most from ablation in terms of cardiac function improvement at 1 year.[6] The Catheter Ablation vs Standard Conventional Treatment in Patients With Left Ventricular Dysfunction and Atrial Fibrillation (CASTLE-AF) trial included HF patients (LVEF ≤35%) who underwent AF catheter ablation or conventional care. The authors showed that catheter ablation led to significant improvement in the primary composite endpoint of all-cause mortality and worsening HF with a relative risk reduction of 38%, whereas LVEF increased by 8% at 5 years of follow-up in the catheter ablation group.[8] Recent meta-analyses showed that catheter ablation resulted in improved LVEF, cardiac function, exercise capacity, and quality of life in HF patients with AF compared with the medical rate-control strategy.[9–11] Additionally, PV isolation improves cardiac function in patients with PAF and impaired LVEF.[12] Furthermore, in patients with HF undergoing AF ablation, it was found that there is an initial short-term LVEF improvement related to baseline heart rate and a long-term LVEF improvement related to the rhythm outcome (improved in SR maintenance).[13] The efficacy of catheter ablation in patients with impaired LVEF is better when it is performed early in the natural history of AF and HF.[11] An interesting finding is that patients with and without left ventricular systolic dysfunction had similar risk for recurrent AF or atrial tachycardia after catheter ablation, but repeat procedures were required more often in those with left ventricular systolic dysfunction.[14] Another study showed that PV isolation in HF patients was associated with improved questionnaire score at 6 months, a longer 6-minute walk distance, and a higher LVEF compared with patients who underwent atrioventricular node ablation and biventricular pacing.[15]

The success rates of catheter ablation for AF differ between published studies. This can be attributed to different procedure techniques used and the differences in the follow-up duration. For example, Bhargava et al reported SR maintenance in 72.6% of patients (77.6% in PAF and 67.2% in NPAF) after a single ablation procedure during a mean follow-up of 57 ± 17 months[16]; and Weerasooriya et al, in a mixed population (PAF and NPAF), reported 40%, 37%, and 29% freedom of arrhythmia at 1, 2, and 5 years of follow-up, respectively.[17]

Interestingly, we identified different predictors of early and late arrhythmia recurrence. For EAR, they were the use of β-blockers before or after ablation and LVEF. By contrast, for late recurrence, they were use of amiodarone before the procedure and EAR. In other words, none of the factors significant for EAR remained a significant predictor for late recurrence.

Moreover, EAR is a well-known predictor of late AF recurrence in both PAF and NPAF patients.[18–22] This finding was similarly observed in our study. EAR events occurring in the initial 2 weeks following PV antral isolation may be related to inflammation that occurs post-ablation.[21] Beyond this period, EAR events, especially when multiple, probably are provoked by PV reconduction and other pathophysiological mechanisms of AF.[21]

Finally, age is a significant factor that is associated with disease progression in AF.[23,24] Bunch et al. reported that age was a significant factor in determining outcomes after catheter ablation for AF.[25] Furthermore, Kosiuk et al[26] with the DR-FLASH score (diabetes mellitus, renal dysfunction, persistent form of AF, left atrial diameter > 45 mm, age > 65 years, female sex, and hypertension) and Letsas et al[27] with the CHA_2DS_2-VASc score highlighted the importance of age as an independent predictor of arrhythmia recurrence after catheter ablation. This is partly explained by age-related fibrosis leading to conduction abnormalities[28,29]; however, in our study, age did not differ significantly between patients with and without arrhythmia recurrence.

Our data showed that amiodarone use before ablation is an independent predictor of late AF recurrence. This finding is attributable to the progression of AF that occurs during drug trials.[30] The presence of congestive HF was found to be a significant risk factor for complications after catheter ablation.[31] However, the existing data showed that there is no difference in the risk of complications in patients with and without HF.[14] Together, all of our findings support the notion that early intervention is needed to control AF due to its progressive nature.

4.1 | Study limitations

The present study has several limitations. First, it is a small, single-center study. Due to the lack of statistical power, separate analyses in patients with mid-range and reduced LVEF could not be performed. Second, although the baseline characteristics of all participants, the procedure details, and the events during the follow-up period were collected prospectively, the study is retrospective in nature. Third, the follow-up monitoring for the detection of arrhythmia recurrence was performed via 24-hour or 48-hour Holter recordings and 12-lead electrocardiograms. Thorough methods of monitoring (loop recorders, 7-day Holter monitoring) were not applied, and the percentage of recurrence may have been underestimated. Finally, the follow-up was not sufficiently long to detect the AF recurrence.

5 | CONCLUSION

The main findings of this study are that (1) a single AF catheter ablation procedure is an effective and safe modality in HF patients with AF; (2) after a mean 3.3 years of follow-up, 73.7% of HF patients remained in SR; and (3) EAR was a significant predictor of arrhythmia recurrence after the blanking period.

Conflicts of interest

The authors declare no potential conflicts of interest.

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