Safety and efficacy outcomes of atrial fibrillation ablation in patients with rheumatoid arthritis

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BACKGROUND Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease associated with atrial fibrillation (AF) and stroke.

OBJECTIVE The purpose of this study was to evaluate the safety and efficacy of AF ablation in patients with RA.

METHODS All patients with RA undergoing AF ablation at our institution from 2010 to 2021 were propensity matched to patients without RA using 9 baseline characteristics. The primary outcome was procedural efficacy defined by clinical AF recurrence, the need for antiarrhythmic drugs (AADs), and repeat catheter ablation. Secondary outcome was safety.

RESULTS A total of 45 patients with RA (age 66.3 ± 7.7 years) were matched to 45 patients without a history of RA (age 68.0 ± 7.3 years). Both groups had similar procedural and periprocedural characteristics. Before ablation, RA patients had statistically higher C-reactive protein (CRP) levels ($P \leq .01$) and erythrocyte sedimentation rates (ESRs) ($P < .05$) compared to non-RA patients. After ablation, RA patients had statistically significant higher rates of AF recurrence ($P = .006$), were more likely to be taking AADs ($P < .05$), and more likely to undergo repeat ablations ($P < .05$). The use of immunosuppression or corticosteroids at the time of ablation did not influence the primary endpoint of AF recurrence, AADs, or repeat ablation. Multivariate regression analysis showed CRP and ESR were independent predictors of AF recurrence. CRP was an independent predictor of repeat ablation.

CONCLUSION Patients with RA are at higher risk of clinical AF recurrence, and are more likely to be taking AADs and require repeat ablation. Preablation CRP and ESR are independent predictors of AF recurrence, and CRP is an independent predictor of repeat catheter ablation.

KEYWORDS Atrial fibrillation; Atrial fibrillation recurrence; Catheter ablation; Pulmonary vein isolation; Rheumatoid arthritis; Safety

(Heart Rhythm O2 2022;3:261–268)

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated inflammatory disease characterized by polyarthropathy and high-grade systemic inflammation, which is associated with several extra-articular complications.[1] Patients with RA have increased morbidity and mortality associated with cardiovascular disease, including an increased incidence of atrial fibrillation (AF).[2] A recent longitudinal nationwide study found that patients with RA had a 40% increased risk of developing AF and a 30% increased risk of stroke compared to the general population.[3] The pathophysiological relationship between RA and AF is complex and remains poorly understood. Inflammation is hypothesized to be a common driver of both disease processes.[4] The immune response associated with inflammation plays an important role in the initiation, maintenance, and recurrence of AF as well as in the development of thromboembolic complications.[4]

Current AF guidelines endorse catheter ablation with pulmonary vein isolation (PVI) as an effective option for treatment of AF.[5] The evidence for catheter ablation of AF in RA is largely unknown, with only 1 previous prior study performed in 15 RA patients.[6] In that cohort, catheter ablation was found to be reasonably safe, with success rates similar to those of patients without RA, but RA patients had a propensity for early AF recurrence.[6]

This study aimed to evaluate the safety and efficacy outcomes of catheter ablation of AF in a large contemporary cohort of patients with RA compared to a non-RA control group to evaluate for predictors of outcomes based on

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2666-5018/

https://doi.org/10.1016/j.hroo.2022.03.001

KEY FINDINGS

- This propensity-matched study sought to investigate the safety and efficacy of catheter ablation for atrial fibrillation (AF) in patients with rheumatoid arthritis (RA).
- Among the 45 patients with RA and 45 patients without a history of RA, the study found an increased postablation risk of AF recurrence, need for antiarrhythmic drugs, and requirement for repeat catheter ablation within 1 year postablation in the RA group. The safety profile of ablation in both groups was not statistically different.
- Preprocedural C-reactive protein (CRP) level and erythrocyte sedimentation rate were found to be independent predictors of AF recurrence and CRP an independent predictor of repeat ablation within 1 year. Of note, use of immunosuppression or corticosteroids for RA at the time of ablation was not associated with higher rates of recurrence, antiarrhythmic drug use, or repeat catheter ablation.

inflammatory markers, anti-inflammatory therapy, and RA disease activity at the time of ablation.

Methods

Study cohort

All consecutive patients aged 18 years or older with and those without RA undergoing primary radiofrequency catheter ablation for AF at our institution from January 2010 to December 2021 were retrospectively reviewed. Patients with RA were propensity matched using a logistic regression model in a 1:1 fashion with patients without RA. The diagnosis of RA was made according to the 2010 American College of Rheumatology/European League Against Rheumatism Collaborative Initiative.[7] In the RA cohort, patients with a diagnosis of RA after catheter ablation were excluded. Clinical, imaging, procedural, and follow-up data were reviewed from the electronic health records. The study was approved by the institutional review board of our institution (IRBe: 21-001149). Only patients consented to be included in research studies were included, and the research reported adhered to the Helsinki Declaration as revised in 2013.

Study outcomes

The primary outcome was procedural efficacy. This was defined as AF recurrence, the need for antiarrhythmic drugs (AADs), and/or repeat ablation by 3-month and 1-year postablation follow-up visits. This was determined by retrospective chart review and diagnostic testing performed at follow-up visits at 3 months and 1 year. All patients had undergone 12-lead electrocardiography (ECG) and Holter monitoring before this visit. AF recurrence was defined as documented AF on this diagnostic testing or on any additional ECGs that may have been recorded postablation, irrespective of symptoms. Predictors of primary outcomes based on baseline characteristics, inflammatory markers, anti-inflammatory therapy, and RA disease activity at the time of ablation were evaluated.

The secondary outcome of this study was safety. This was defined as a composite endpoint of 8 postablation complications, including the development of cardiac tamponade, pericarditis, phrenic nerve damage, atrioesophageal fistulas, stroke, myocardial infarction, clinically relevant bleeding, and postablation infections. Clinically relevant bleeding was defined according to the International Society on Thrombosis and Hemostasis criteria.[8]

Propensity-score matching

We derived a propensity score using multinomial logistic regression with 9 baseline characteristics: age, gender, history of heart failure, diabetes mellitus, transient ischemic attack/stroke, hypertension, peripheral vascular disease, hyperlipidemia, and coronary artery disease. These variables were chosen to ensure both cohorts had similar risk factors when evaluating for primary and secondary outcomes.

RA and non-RA patients were matched in a 1:1 fashion based on the propensity score. The nearest-neighbor matching with caliper width of 0.2 of the pooled standard deviation of the logit of the propensity score was used. With this method, the first randomly selected RA subject was matched to a non-RA patient with the closest propensity score within the specified caliper width. If multiple non-RA patients were equally close to this RA subject, then 1 of the non-RA patients was randomly selected for matching. This process was repeated until all possible matches were executed.

Statistical analysis

Continuous variables are given as mean ± SD and compared using the *t* test. Categorical variables are given as frequency (proportion) and compared using a the χ^2 test. If any expected cell count was <5, a Fisher exact test was used. Univariate analysis was applied to both continuous and categorical variables. Variables that were statistically significant at univariate analysis were included in the multivariate analysis (logistic regression) to identify variables independently associated with the primary outcomes of this study. Two-sided $P < .05$ was considered significant. All statistical analyses were performed using JMP software Version 14 (SAS Institute Inc., Cary, NC).

Results

Clinical and procedural characteristics

The clinical characteristics of patients in the RA study group and the non-RA control group are summarized in Table 1. In a total cohort of 90 patients, 45 patients with RA (age 66.3 ± 7.7 years) were propensity matched to 45 patients with no history of RA (age 68.0 ± 7.3 years). Both groups shared similar baseline characteristics and risk factors.

Table 1 Baseline characteristics before index catheter ablation for AF in RA patients compared to patients with no history of RA

Variable	Non-RA patients (n = 45)	RA patients (n = 45)	*P* value
Age (y)	68.0 ± 7.3	66.3 ± 7.7	.29
Male/female (n/n)	15/30	15/30	
BMI (kg/m^2)	31.0 ± 6.78	30.6 ± 5.44	.79
CHA_2DS_2 VASc score	3.18 ± 2.05	2.73 ± 1.80	.27
HAS-BLED score	3.73 ± 1.50	3.47 ± 1.24	.36
eGFR	56.9 ± 5.7	58.9 ± 4.6	.07
History of HTN	33 (73)	28 (62)	.26
History of DM	11 (24)	10 (22)	.80
History of smoking	18 (40)	16 (36)	.66
AAD	18 (40)	20 (44)	.67
Amiodarone	2	5	
Dofetilide	1	5	
Dronedarone	0	2	
Sotalol	8	5	
Flecainide	5	2	
Propafenone	2	1	
RF (IU/mL)			
Median [IQR]	—	29.5 [28–34]	
Negative (<15)	—	35 (78)	
Anti-CCP (U/mL)			
Median [IQR]	—	52.5 [39–250]	
Negative (<5)	—	33 (73)	
CRP (mg/L)	2 [0.7–3.0]	5 [3.0–11.5]	<.01
ESR (mm/1 h)	3.5 [3.0–6.0]	10 [3.0–23.0])	.05
Immunosuppressive agents	0	17 (38)	<.01
Steroids	0	6 (13)	.01
LA volume index (mL/m^2)	38.6 ± 12.3	38.0 ± 10.3	.77
LV EF (%)	58.7 ± 5.92	57.9 ± 8.37	.60
Valvular heart disease	7 (16)	11 (24)	.29
Type of AF			
Paroxysmal	28 (62)	27 (60)	
Persistent	17 (38)	16 (36)	
Long-standing persistent	0	2 (4)	
Duration of AF from diagnosis to ablation (y)	4.66 ± 4.95	3.67 ± 3.82	.29

Values are given as mean ± SD, n (%), n, or median [IQR] unless otherwise indicated.

AAD = antiarrhythmic drug; AF = atrial fibrillation; anti-CCP = anticyclic citrullinated peptide antibodies; BMI = body mass index; CRP = C-reactive protein; DM = diabetes mellitus; EF = ejection fraction; eGFR = estimated glomerular filtration rate; ESR = erythrocyte sedimentation rate; HTN = hypertension; IQR = interquartile range; LA = left atrium; LV = left ventricle; RA = rheumatoid arthritis; RF = rheumatoid factor.

Mean time from diagnosis of RA to catheter ablation of AF was 5.67 ± 6.92 years. Within 2 weeks before the index ablation, 40% (18/45) of the RA group was receiving some combination of immunosuppressive therapy. One RA patient was taking steroids, 12 were taking immunosuppressive agents (7 methotrexate, 3 hydroxychloroquine, 1 mycophenolate, 1 infliximab), and 5 were taking a combination of immunosuppression and steroids (3 methotrexate, 1 mycophenolate, 1 hydroxychloroquine). Patients with RA had higher levels of C-reactive protein (CRP) (median 5 [interquartile range 3.0–11.5] mg/L vs 2 [0.7–3.0] mg/L; $P < .01$) and erythrocyte sedimentation rate (ESR) (median

Table 2 Procedural characteristics of the index catheter ablation for AF in RA patients and patients with no history of RA

Variable	Non-RA patients (n = 45)	RA patients (n = 45)	*P* value
PVI	15 (33)	16 (36)	.82
PVI + lines	7 (16)	6 (13)	.76
PVI + CTI	17 (38)	14 (31)	.51
PVI + lines + CTI	6 (13)	9 (20)	.40
Baseline study (min)	72.3 ± 73.9	52.3 ± 29.0	.09
Ablation time (min)	126.1 ± 74.3	109.4 ± 61.1	.25
Total procedural time (min)	259.5 ± 84.2	231.5 ± 75.1	.10
Total energy delivery time (min)	3073 ± 2123	2375 ± 1433	.07

Values are given as n (%) or mean ± SD unless otherwise indicated.

CTI = cavotricuspid isthmus; PVI = pulmonary vein isolation; other abbreviations as in Table 1.

Table 3 Catheter ablation efficacy for AF in patients with RA compared to patients with no history of RA

	Non-RA patients (n = 45)	RA patients (n = 45)	*P* value
<3 months post index ablation			
AF recurrence	6 (13)	15 (33)	.02
AAD	16 (36)	26 (58)	.04
Amiodarone	5	11	
Dofetilide	2	6	
Dronedarone	0	1	
Sotalol	6	4	
Flecainide	2	3	
Propafenone	1	1	
3 months to 1 year post index ablation			
AF recurrence	8 (18)	20 (44)	.006
AAD	4 (9)	11 (24)	.05
Amiodarone	0	5	
Dofetilide	1	3	
Dronedarone	0	1	
Sotalol	3	2	
Flecainide	0	0	
Propafenone	0	0	
Reablation	1 (2)	6 (13)	.05
PVI	1	3	
PVI + CTI	0	1	
PVI + lines	0	2	

Values are given as n (%) or n unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

10 [interquartile range 3.0–23] mm/1 h vs 3.5 [3.0–6.0] mm/1h; $P < .05$) as measured 1.56 ± 1.04 days before the index AF ablation.

Both non-RA and RA patients were similar in age at the time of ablation (64.2 ± 7.66 years vs 64.2 ± 7.98 years; $P = .62$), and procedural endpoints were ascertained in all patients. All patients were referred for catheter ablation of AF and underwent PVI with wide area circumferential ablation. Adjuvant ablation lines were used in 6 RA patients (5 carinal lines, 1 left atrial [LA] roof line) and 7 non-RA patients (3 carinal lines, 2 LA roof lines, 2 mitral isthmus lines). Concomitant right-sided cavotricuspid isthmus (CTI) ablation for typical atrial flutter was performed in 14 RA patients and 17 non-RA patients. Adjuvant ablation lines and right-sided CTI were performed in 9 RA patients (6 carinal line, 1 mitral isthmus line, 1 LA roof line, 1 LA inferior line) and 6 non-RA patients (4 carinal line, 1 LA roof line, 1 LA inferior line) (Table 2). Five of the 45 patients with RA (11%) were prescribed colchicine after ablation compared with 3 of the 45 patients (6%) in the control group ($P = .46$).

Primary and secondary outcomes

The primary outcomes of this study are given in Table 3. After PVI, patients with RA had statistically higher rates of AF

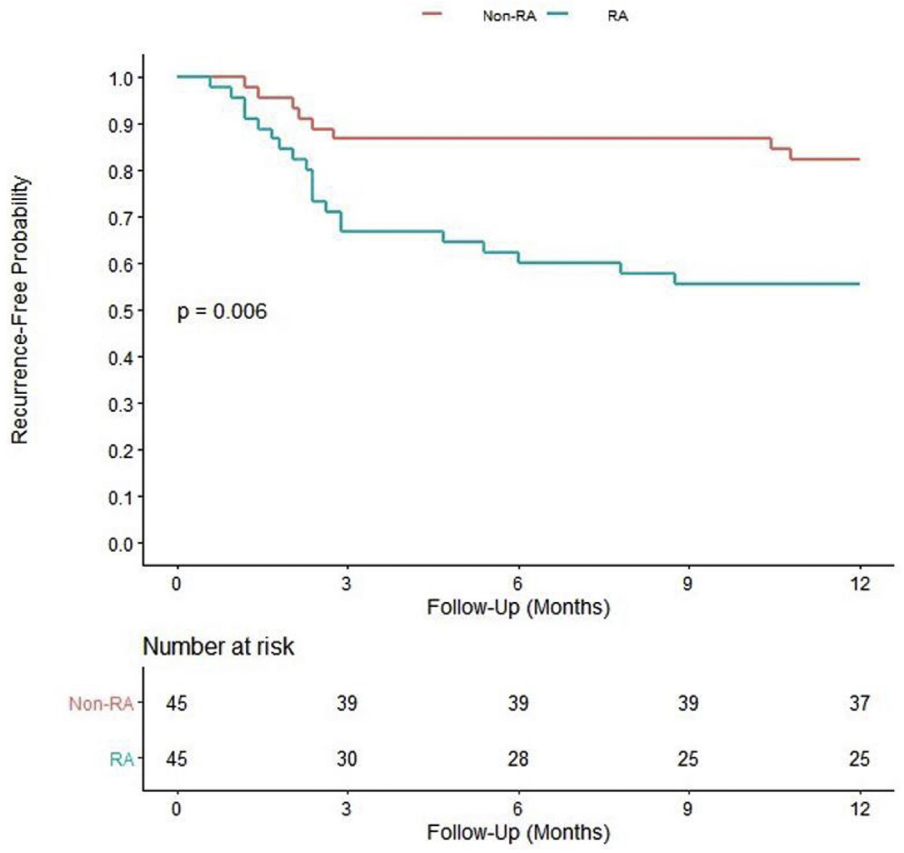

Figure 1 Kaplan-Meier curve for atrial fibrillation (AF) recurrence after index catheter ablation for AF.

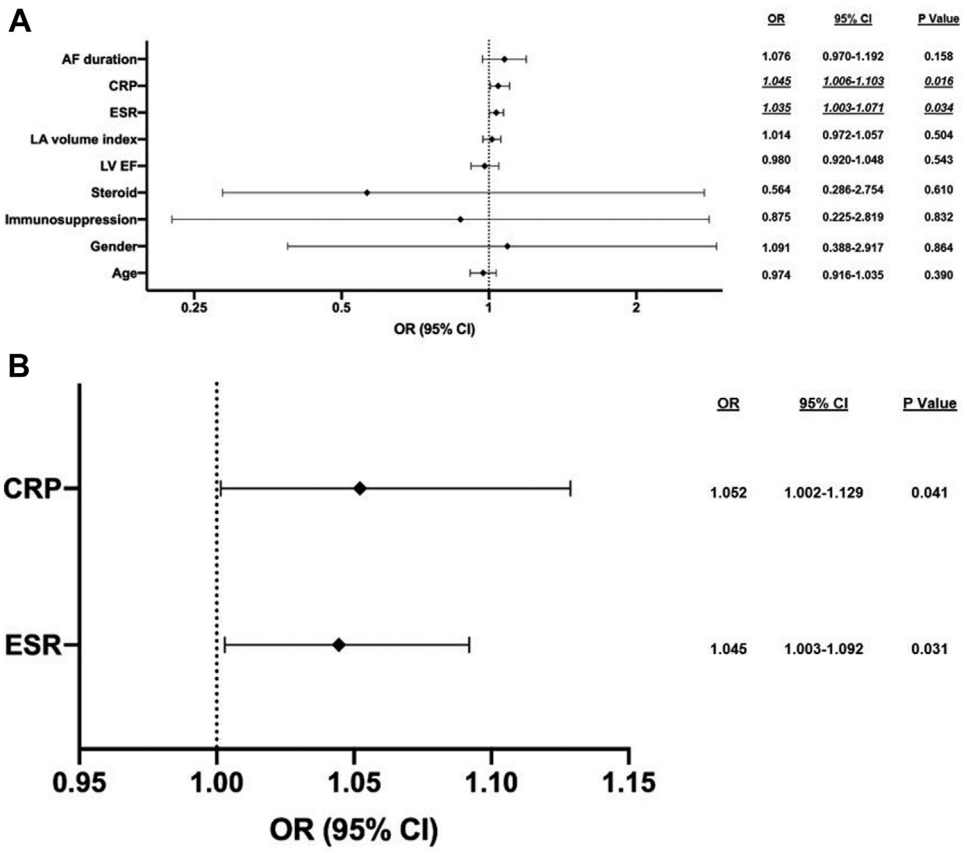

Figure 2 Univariate (**A**) and multivariate (**B**) logistic regression analysis for predictors of atrial fibrillation (AF) recurrence 1 year post index catheter ablation. CI = confidence interval; CRP = C=reactive protein; EF = ejection fraction; ESR = erythrocyte sedimentation rate; LA = left atrium; LV = left ventricle; OR = odds ratio.

recurrence by their 3-month (33.3% [15/45] vs 13.3% [6/45]; $P = .02$) and 1-year postablation follow-up visits (44.4% [20/45] vs 17.7% [8/45]; $P = .006$) (Figure 1). In the study group, 6 RA patients underwent repeat PVI <1 year after the index ablation compared to 1 non-RA patients in the control group ($P = .049$). During the redo procedure, conduction gaps between the pulmonary veins and LA were identified in all these patients, and PVI was re-achieved during the second ablation. In the RA study group, 1 patient also underwent CTI ablation for typical atrial flutter, and 2 patients underwent LA roof and mitral isthmus adjuvant lines for atypical atrial flutter. Rheumatoid factor and anticyclic citrullinated peptide antibodies titers were positive in 4 of the 6 RA patients (66.7%) who underwent repeat ablation.

Before the index catheter ablation, there was no statistical difference between the AAD profiles of the study and control groups. However, higher rates of patients in the RA group needed AAD by the 3-month (57.8% [26/45] vs 35.6% [16/45]; $P = .04$) and 1-year postablation follow-up visits (24.4% [11/45] vs 8.9% [4/45]; $P = .048$). After ablation, 80% of patients (16/20) with RA continued their AAD therapy and 5% (1/20) changed from sotalol to amiodarone compared with 50% (9/18) of patients in the control group who continued their regimen and 6% (1/18) who changed from propafenone to flecainide. After ablation, new AADs were initiated in 9 patients with RA compared to 6 patients in the control group.

The secondary outcomes of the study were equivalent, with only 2 episodes of groin hematomas in the RA study group and 1 episode in the control arm. No stroke or transient ischemic attack occurred periprocedurally or during follow-up in either group.

Predictors of primary outcome

Based on previous studies and expected clinical relevance, the following variables were entered into a Cox logistic regression model: age, gender, immunosuppression, steroid use, left ventricular ejection fraction, LA volume index, ESR, CRP, and duration of AF.[4,6]

Univariate analysis found ESR (odds ratio [OR] 1.035; 95% confidence interval [CI] 1.003–1.071; $P = .034$) and CRP (OR 1.045; 95% CI 1.006–1.103; $P = .016$) were predictors of AF recurrence. Moreover, CRP (OR 1.052; 95% CI 1.002–1.129; $P = .041$) and ESR (OR 1.045; 95% CI 1.003–1.092; $P = .031$) were also independent predictors of AF recurrence on multivariate analysis (Figure 2). Univariate analysis found CRP (OR 1.032; 95% CI 1.002–1.077; $P = .038$) to be a risk factor for repeat ablation within 1 year. Multivariate analysis found CRP (OR 1.038; 95% CI

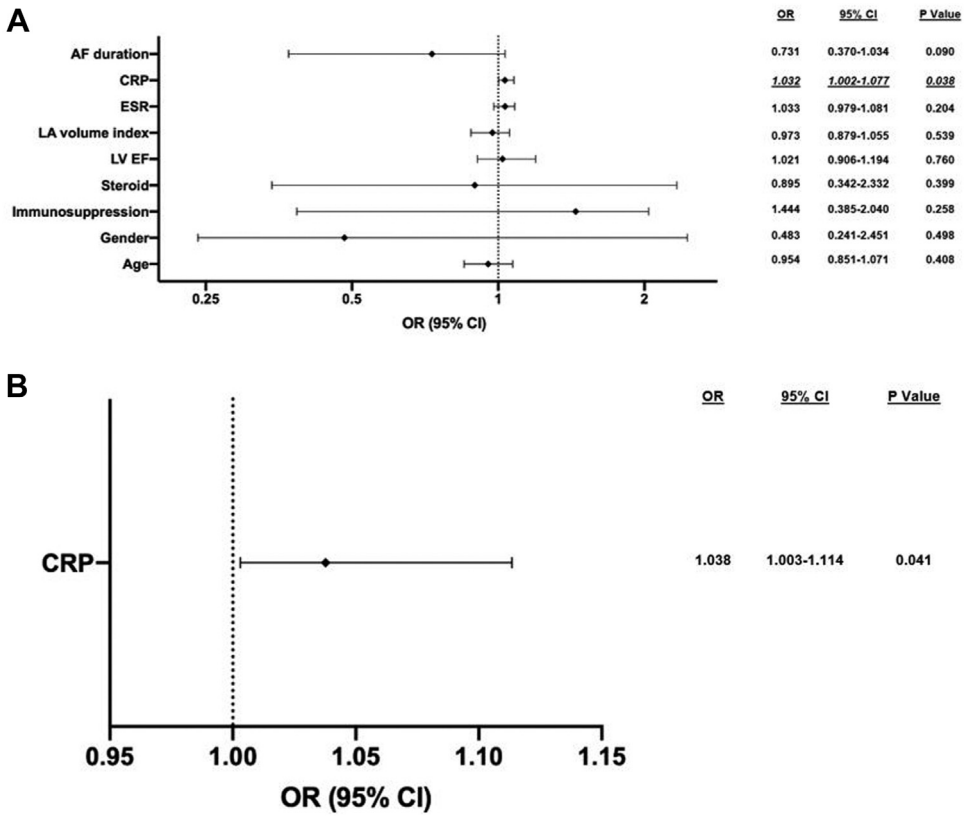

Figure 3 Univariate **(A)** and multivariate **(B)** logistic regression analysis for predictors of repeat catheter ablation 1 year post index catheter ablation. Abbreviations as in Figure 2.

1.003–1.114; $P = .041$) to be an independent risk factor for repeat ablation within 1 year (Figure 3). Univariate analysis indicated ESR (OR 1.040; 95% CI 1.003–1.088; $P = .031$) was associated with the need for AAD postablation, but multivariate analysis failed to identify ESR as an independent predictor for requiring AAD postablation (Figure 4).

Discussion

To our knowledge, this is the largest study to date evaluating catheter ablation of AF in patients with RA. The major findings of this study are as follows. (1) There is an increased postablation risk of RA patients having a higher rate of AF recurrence, the need for AADs, and requiring repeat catheter ablation within 1-year post index ablation. (2) Preprocedural CRP and ESR are independent predictors of AF recurrence, and CRP is an independent predictor of repeat ablation within 1 year. (3) The use of immunosuppression or corticosteroids for RA at the time of ablation was not associated with higher rates of recurrence, AAD use, or repeat catheter ablation. (4) The safety profile of catheter ablation in RA patients is not statistically different from that seen in non-RA patients.

Our propensity-matched study found catheter ablation to be safe in patients with RA, with no major complications reported. Moreover, the intraprocedural technical difficulties of ablation in both groups were similar. These findings are consistent with an earlier smaller study that also found catheter ablation to be safe in patients with RA.[6]

In our study, patients with RA had significantly higher levels of inflammatory biomarkers before catheter ,ablation and CRP and ESR were found to be independent predictors of AF recurrence. We hypothesize that patients with RA had more systemic inflammation at the time of catheter ablation, which in turn led to a higher incidence of AF recurrence. This may also reflect a more advanced state of RA as well as continued inflammation throughout the postablation window; however, this remains speculative.

The pathophysiological relationship between RA and AF is complex and remains poorly understood. Inflammation is hypothesized to be a common driver of both disease processes, and it is well established that inflammatory pathways contribute to structural and electrical atrial remodeling.[4] Inflammation can initiate AF, which in turn generates an inflammatory response that can perpetuate arrhythmias through electrical remodeling, believed to occur through the modulation of calcium homeostasis and connexins.[9] CRP is an acute-phase reactant, synthesized in the liver, that serves as a sensitive and objective marker for inflammation.[10] Several large, prospective cohort studies have found elevated CRP levels can predict the development of new onset of AF as well as AF recurrence after catheter ablation or cardioversion.[11–13] CRP *per se* does not increase the risk of AF, but it is a

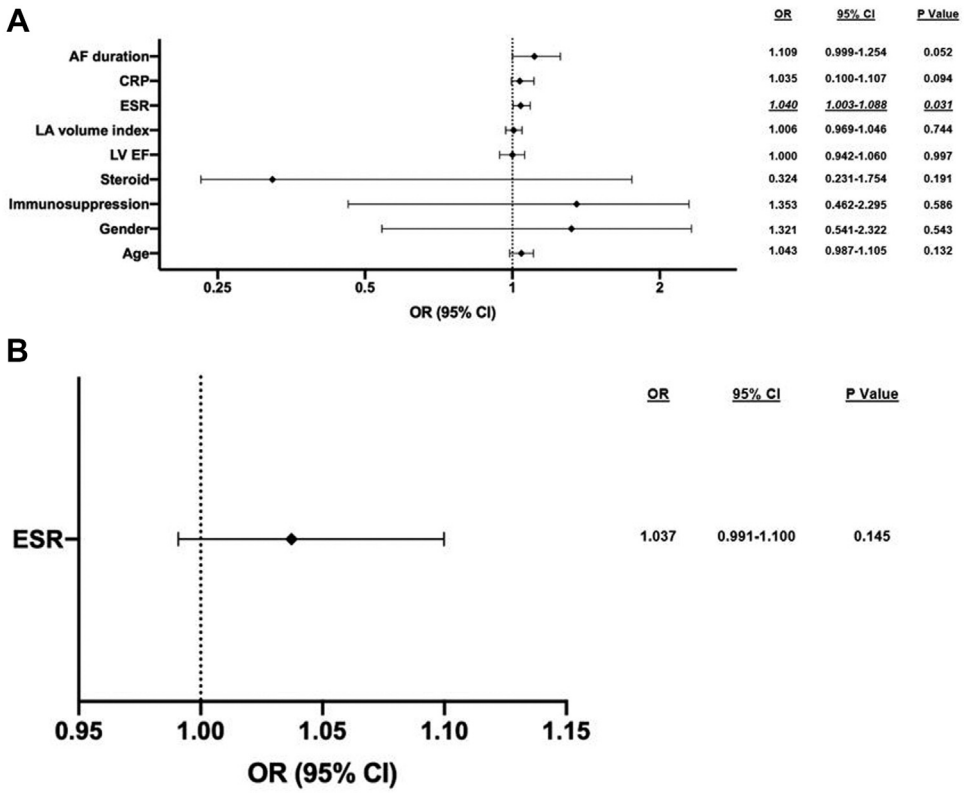

Figure 4 Univariate **(A)** and multivariate **(B)** logistic regression analysis for predictors for the need for antiarrhythmic drugs 1 year post index catheter ablation. Abbreviations as in Figure 2.

surrogate marker for an underlying inflammatory process.[14,15]

Given the increasing evidence of the pathogenic role of inflammation in the pathophysiology of AF, it has been suggested that therapies mitigating inflammation may reduce the risk of AF.[16] A double-blind, placebo-controlled trial of 104 patients with symptomatic AF found steroid administration at the time of electrical cardioversion reduced the risk of subsequent AF recurrence.[17] However, in our study, the use of immunosuppression or corticosteroids for RA at the time of ablation was not associated with the primary outcomes of the study on univariate and multivariate analyses.

Another potential mechanism to explain the development of AF recurrence postablation in RA patients is autoimmunity.[18] Emerging evidence indicates the role of autoantibodies and autoimmunity in the pathogenesis of AF.[19] Our study found 6 RA patients who had undergone repeat ablation <1 year post index ablation had conduction gaps between the pulmonary veins and LA. Four of these 6 patients had a positive autoantibody titer measured within 2 weeks of the index ablation, raising the possibility that the altered immune response in RA patients may lead to the presence of these conduction gaps postablation. However, other autoimmune markers, such as matrix metalloproteinase-3, were not studied in this study, and this would need further study.

Study limitations

Several limitations are attributed to the retrospective observational design of our study. Our study was performed within a single academic center and thus is subject to the limitations associated with a highly homogeneous patient population. Therefore, the generalizability of our study is limited. Likewise, although population demographics were similar between the RA and non-RA groups, there is a high degree of variability between the specific ablation methodology and technique implemented by individual operators given their current practice of AF ablation. This includes, but is not limited to, differences in energy settings, the use of continuous vs interrupted lesions, contact force, mapping systems, and integration of additional linear ablation lines in combination with PVI. In all cases, conventional PVI with wide area circumferential ablation was performed. The use of adjuvant ablation lines was not standardized and was utilized at the discretion of the operator based on the specific clinical circumstances. Our study was further limited by its low power and the possibility that the multivariate model was overfitted with possible misleading associations. Lastly, our study was limited by our finite follow-up duration, which inadvertently excludes safety and efficacy outcomes that extend beyond our time frame of interest. Such technical variability coupled with the nonstandardized follow-up evaluation yields potential confounders.

Conclusion

Patients with RA are at higher risk for clinical AF recurrence, are more likely to be taking AADs, and require repeat ablation after catheter ablation of AF. Preablation inflammatory markers (CRP and ESR) are independent predictors of AF recurrence, and CRP is an independent predictor of repeat catheter ablation. These findings merit further analysis in a large, multicenter prospective trial.

Funding Sources: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosures: The authors have no conflicts to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: Only patients who had consented to be included in research studies were included.

Ethics Statement: The study was approved by the institutional review board of our institution (IRBe: 21-001149). The research reported in this paper adhered to the Helsinki Declaration as revised in 2013.

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