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Original article

Catheter ablation of atrial fibrillation in patients with rheumatoid arthritis

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ABSTRACT

Background: Rheumatoid arthritis (RA) is associated with an increased incidence of atrial fibrillation (AF). This study evaluated the safety and efficacy of catheter ablation (CA) in the treatment of AF in patients with RA, which has not been previously reported.

Methods: A total of 15 RA patients with AF who underwent CA were enrolled. For each RA patient, we selected 4 individuals (control group, 60 patients in total) who presented for AF ablation in the absence of structural heart or systemic disease and matched the RA patients with same gender, age (±2 years), type of AF, and procedure date.

Results: Patients with RA had a significantly higher C-reactive protein level (1.81 ± 2.35 mg/dl vs. 4.14 ± 2.30 mg/dl, $p = 0.0320$), white blood cell count (5632 ± 1200 mm^3 vs. 6361 ± 1567 mm^3, $p = 0.0482$), and neutrophil count (3308 ± 973 mm^3 vs. 3949 ± 1461 mm^3, $p = 0.0441$). At 2-year follow-up, atrial tachyarrhythmia (ATa) recurrence rate in the RA group (33.3%, 5/15) was similar to that in the control group (31.7%, 19/60; $p = 0.579$) after single procedure. In all the five patients from the RA group who developed recurrence, ATa relapsed within 90 days following index procedure (median recurrence time 18 days vs. 92 days in control group; $p = 0.0373$). Multivariate Cox regression analysis showed that hypertension and left atrial diameter but not RA, C-reactive protein, white blood cell count, and neutrophil count were independent predictors of ATa recurrence.

Conclusions: Catheter ablation of AF can be safely performed in patients with RA, with a success rate comparable to that of patients without RA. RA patients tend to develop early ATa recurrence after AF ablation.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with an estimated worldwide prevalence of 1–2%. The incidence of atrial fibrillation (AF) is 40% higher in RA patients than in the general population, and RA has its own associated morbidity and mortality [1,2]. Atrial fibrillation can occur at any time during the course of RA, although it may present as the first manifestation of the disease [2]. The risk of AF in patients with RA is known to be increased by several factors including heart failure and ischemic heart disease [3]. Catheter ablation (CA) has been proven successful in the treatment of AF in patients with or without structural heart disease [4]. This approach might be considered as the first-line therapy in patients with AF and systemic disorders as use of antiarrhythmic drugs (AAD) in this population is either contraindicated, scarcely effective, or associated with more adverse effects. For instance, RA is commonly accompanied by other autoimmune rheumatic diseases such as systemic sclerosis or vasculitis and pulmonary hypertension where β-blocker use should be avoided [5]. This study evaluated the safety and efficacy of CA in the treatment of AF in patients with RA.

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Methods

Study population

Between April 2008 and March 2013, 15 RA patients with AF underwent their primary CA at our center (RA group, 9 paroxysmal AF and 6 persistent AF). The diagnosis of RA in these 15 patients followed the American Rheumatism Association Guidelines [6]. For each RA patient, we selected four control patients from our database. These 60 individuals (control group) presented for AF ablation in the absence of structural heart or systemic disease including RA and matched the 15 RA patients with same gender, age (±2 years), type of AF, and procedure date.

Laboratory analyses

Full blood samples were collected on the second morning following hospitalization after overnight fasting. All samples were immediately cooled on ice and centrifuged twice at 2000 × *g* for 15 min. Plasma was stored at −80 °C. Quantitative determination of plasma C-reactive protein (CRP) levels was performed by a high sensitivity CRP assay using a nephelometer (Dade Behring Inc., Newark, DE, USA). The inter-assay coefficient of variation was 6.4%. Plasma white blood cell (WBC) counts and differential leukocyte counts were measured with a hematology analyzer (Serono-Baker Diagnostics System 9000, Allentown, PA, USA). The normal range of WBC counts at our central laboratory was 4.0–12.0 × 10^9/L.

Electrophysiology study and AF ablation

All AAD except for amiodarone were stopped for at least five half-lives and amiodarone was stopped for at least 2 months before ablation. Before the procedure, the presence of a left atrial thrombus was excluded by transesophageal echocardiography. All patients provided written informed consent. After overnight fasting, the procedure was performed with patients under conscious sedation. Our technique for AF ablation has been previously described [7]. Briefly, a deflectable decapolar catheter was positioned in the coronary sinus (CS). After a successful single transseptal puncture, a 3.5-mm irrigated ablation catheter (NAVISTAR® THERMOCOOL®, Biosense-Webster Inc., Diamond Bar, CA, USA) was advanced to the LA for mapping and subsequent ablation that was guided by a three-dimensional electroanatomic mapping system (CARTO, Biosense-Webster Inc.). In patients with paroxysmal AF, complete pulmonary vein isolation (PVI) was achieved by continuous circular lesions around ipsilateral pulmonary vein antrum. Cavo-tricuspid isthmus (CTI) ablation was added in patients with electrocardiogram (ECG)-documented typical atrial flutter. Ablation strategy in patients with persistent AF included PVI and linear ablation across the left atrial (LA) roofline, mitral isthmus (MI) and CTI. If AF was sustained or converted to an organized atrial tachyarrhythmia, cardioversion was applied. Achievement of PVI and complete conduction block of the three linear lesions were used as the procedural end-point in persistent AF patients. Radiofrequency energy was delivered with a maximum temperature of 45 °C, a power up to 35 W, and a flow rate of 17 mL/min. When ablating inside CS, the maximum power was decreased to 25 W while the flow rate was increased to 30 mL/min. At each site, the ablation time was restricted to 30–60 s but no more than 30 s when ablating on the LA posterior wall and inside CS.

Follow-up

All patients were put on previously ineffective AAD which was discontinued 3 months after the procedure. Follow-up was scheduled at 1, 3, 6, and 12 months after the procedure when 12-lead ECG and 24 h Holter monitoring were obtained. In addition, at any time when a patient experienced symptoms suggesting arrhythmia, an ECG was recorded. Telephone interview was conducted monthly by a research associate. Arrhythmia recurrence was defined as any kind of atrial tachyarrhythmia (AF, atrial flutter, or atrial tachycardia) of >30 s duration in the absence of AAD, documented by ECG or Holter monitoring. The duration of the follow-up was counted from the day of index ablation procedure. No blanking period was applied [8]. AF recurrence within 3 months post-ablation was defined as early recurrence; otherwise, it was defined as late recurrence.

Statistical analysis

Variables are expressed as the mean ± SD or number and percentage, as appropriate. For patient characteristics, continuous variables were compared with a linear mixed-effects regression model in which the group variable (the RA or control group) was considered as a fixed effect and the subject identification variable as a random effect. Categorical variables were compared with a conditional Cox regression model. Variables that were statistically significant in univariate Cox regression models (p-value <0.1) were included in a multivariate regression model using an "enter" method to determine whether they remained significant after adjustment for potential confounders. T test was used to compare total procedural time and fluoroscopy time between two groups, if their distribution did not deviate significantly from the normal distribution (tested with the Kolmogorov–Smirnov test). Chi-square test was used to compare the AF recurrence between two groups. Kaplan–Meier curves were plotted to assess recurrence-free survival, and the log-rank test was used to make comparisons between groups. The time to recurrence of AF was compared with a stratified Cox proportional hazards regression model, to estimate the independent predictors of AF recurrence. A p-value of <0.05 was considered statistically significant. Data were analyzed with SPSS (version 18.0, SPSS Inc., Chicago, IL, USA).

Results

Clinical characteristics

The clinical characteristics of patients in the RA group are summarized in Table 1. History of RA was 17.6 ± 13.8 (range 3–50) years. Patients 6, 7, 8, 10, 12, 13, and 15 had moderate or severe deformity in the proximal interphalangeal and metacarpophalangeal joints of the hands; while joints of shoulders, elbows, knees, and ankles were also affected in these patients and the lesions were destructive. In other patients joint deformity was mild. Specifically, none of the patients presented with residual joint swelling prior to the AF ablation procedure. All patients' X-rays of the spine and thoracic cage were normal. Patients 14 and 15 were complicated with Sjögren's syndrome and mitral valve insufficiency on echocardiogram. No evidence of coronary vasculitis, pericarditis/myocarditis, cardiomyopathy, cardiac amyloidosis, or congestive heart failure was documented in any subject. None of the RA patients showed anemia, neutropenia, thrombocytopenia, thrombocytosis, eosinophilia, or dysfunction of neurological, renal, endocrinal, or gastrointestinal systems. Five patients were taking methylprednisolone and/or immunosuppressive agents (Table 1) while the other 10 patients had not received any anti-RA treatment since at least 2 weeks before AF ablation.

The demographics of patients between the RA group and the control group were comparable except for the pre-procedural WBC/neutrophil count and CRP level (Table 2). Patients with RA had significantly higher CRP levels (1.81 ± 2.35 mg/dl vs. 4.14 ± 2.30 mg/dl, $p = 0.0320$), WBC count (5632 ± 1200 mm^3 vs. 6361 ± 1567 mm^3, $p = 0.0482$), and neutrophil count (3308 ± 973 mm^3 vs. 3949± 1461 mm^3, $p = 0.0441$).

Table 1
Clinical characteristics of each patient with rheumatoid arthritis.

Patient no.	Type of AF	Gender	Age	RA duration (year)	Previous stroke	Comorbidity	Anti-RA treatment	Pre-procedural CRP (mg/L)	LAD (mm)	LVEF	Free from ATa	Recurrent time (day)
1	PeAF	F	62	3	N	–	N	4.90	33	0.58	Y	N
2	PeAF	F	72	30	N	HTN	N	3.54	45	0.53	Y	N
3	PAF	F	65	5	N	HTN	Y	5.50	36	0.68	Y	N
4	PAF	M	77	50	N	HTN	N	2.80	38	0.65	Y	N
5	PAF	F	59	8	N	–	Y	3.26	33	0.57	N	1
6	PeAF	F	71	20	Y	HTN	N	4.96	32	0.63	Y	N
7	PAF	F	76	10	N	HTN	N	5.20	38	0.68	N	81
8	PAF	F	55	5	N	–	Y	4.23	32	0.65	Y	N
9	PAF	F	76	10	Y	HTN	N	3.36	35.5	0.70	Y	N
10	PeAF	F	60	8	N	HTN	N	4.04	46	0.57	Y	N
11	PAF	M	67	30	N	–	N	2.79	41	0.60	N	14
12	PAF	M	62	20	N	–	Y	3.20	34	0.65	Y	N
13	PAF	F	59	30	N	HTN	N	4.37	37	0.71	Y	N
14	PeAF	F	72	30	Y	DM	Y	3.98	45	0.62	N	18
15	PeAF	F	52	5	N	–	N	6.54	57	0.55	N	45

AF, atrial fibrillation; CRP, C-reactive protein; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; PAF, paroxysmal atrial fibrillation; PeAF, persistent atrial fibrillation; F, female; M, male; N, no; Y, yes; HTN, hypertension; DM, diabetes mellitus; RA, rheumatoid arthritis; ATa, atrial tachyarrhythmia.

Procedural outcome

Procedural endpoints were achieved in all patients. There was no difference in terms of total procedural time (161 ± 69 min vs.147 ± 66 min, $p = 0.46$) and fluoroscopy time (27 ± 16 min vs. 32 ± 30 min, $p = 0.60$) between the RA group and the control group. None of the patients in either group experienced a major complication except one in the RA group (Patient 12) who developed groin hematoma that resolved with manual and bandage compression. In the RA group, five patients (33.3%; Patients 5, 7, 11, 14, and 15) developed atrial tachyarrhythmia (ATa) recurrence. Among them, three patients (Patients 5, 7, and 11) with paroxysmal AF prior to the index procedure received a repeat ablation after recurrence. During the redo procedure, conduction gaps between PVs and LA were identified in all these patients and PVI was re-achieved during the second procedure. Patients 14 and 15 with persistent AF prior to index procedure had ATa recurrence 18 and 45 days after the initial ablation. Both patients developed severe mitral regurgitation during follow-up and were treated with mitral valvuloplasty plus surgical ablation 3 years later. The other 10 patients in the RA group remained in sinus rhythm at 2-year follow-up. In the control group, ATa relapsed in 19 patients (31.7%; $p = 0.579$ vs. RA group). Apparently, AF patients with RA were prone to develop early recurrence (median recurrent time 18 days) compared to those without RA (median recurrent time 92 days in the control group, $p = 0.0373$). Specifically, in those patients (5 in the RA group and 9 in the control group) who had early ATa recurrence following the index ablation procedure, the recurrent tachycardia sustained beyond 90 days until they were retreated or the end of follow-up. The Kaplan–Meier curves showed that ATa-free survival between the two groups was borderline significant (log rank $p = 0.062$) within the first 90 days (Fig. 1A) with AAD but not (log rank $p = 0.807$) when the follow-up was extended to 2 years (Fig. 1B) after a single procedure.

Table 2
Comparison of patients' demographics between the RA group and the control group.

	Control group ($n = 60$)	RA group ($n = 15$)	p-Value
Male/female, n	12/48	3/12	–
Age (years)	63.57 ± 9.19	63.67 ± 8.02	–
Paroxysmal, n (%)	36 (60.00)	9 (60.00)	–
Persistent, n (%)	24 (40.00)	6 (40.00)	–
AF duration (years)	5.03 ± 5.22	5.67 ± 5.19	0.6717
Hypertension, n (%)	37 (61.67)	8 (53.33)	0.5623
Diabetes mellitus, n (%)	5 (8.33)	1 (6.67)	0.8020
Stroke, n (%)	15 (25)	3 (20)	0.8020
LVEF (%)	63.06 ± 9.25	63.13 ± 6.79	0.9775
LAD (mm)	39.29 ± 7.16	38.83 ± 6.92	0.8236
Statin	16 (26.67)	5 (33.33)	0.6180
Methylprednisolone	0 (0%)	4 (26.67)	0.0011
Immunosuppressive agents	0 (0%)	2 (13.33)	0.0378
CRP	1.81 ± 2.35	4.14 ± 2.30	0.0320
Body temperature (°C)	36.3 ± 0.2	36.3 ± 0.1	0.2110
White blood cell count (#/mm^3)	5632 ± 1200	6361 ± 1567	0.0482
Neutrophils (#/mm^3)	3308 ± 973	3949 ± 1461	0.0441
Lymphocytes (#/mm^3)	1867 ± 525	1963 ± 557	0.5201
Monocytes (#/mm^3)	309 ± 102	337 ± 147	0.3870
Neutrophil/lymphocyte ratio	1.94 ± 0.94	2.16 ± 1.23	0.4290
Hemoglobin (g/dl)	13.1 ± 1.7	12.6 ± 1.8	0.3200
Platelet count (×10^3)	198 ± 44	196 ± 59	0.8880

RA, rheumatoid arthritis; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; LAD, left atrial diameter; CRP, C-reactive protein.

Predictor of AF recurrence after a single procedure

Based on prior knowledge or expected clinical relevance [9,10], the following potential confounders were entered into a Cox regression model which was established in all study subjects: age, gender, AF type, AF duration, left atrial diameter (LAD), left ventricular ejection fraction (LVEF), hypertension, RA, WBC count, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), monocyte count, and CRP level. Univariate analysis indicated that hypertension, LAD, WBC count, and neutrophil count were significantly associated with ATa recurrence (Table 3). Specifically, pre-procedural CRP level and the presence of RA were not demonstrated as risk factors of arrhythmia recurrence after AF ablation. Multivariate Cox regression analysis showed that hypertension [hazard ratio (HR) 0.233, 95% confidence interval (CI) 0.072–0.755, $p = 0.015$] and LAD (HR 1.113, 95% CI 1.022–1.213, $p = 0.014$) were independent predictors of ATa recurrence following CA. Univariate analysis indicated that RA (HR 0.371, 95% CI 0.124–1.109, $p = 0.076$), neutrophil count (HR 1.487, 95% CI 0.939–2.354, $p = 0.091$), and NLR (HR 2.435, 95% CI 1.187–4.995, $p = 0.015$) were associated with early ATa recurrence ($p < 0.1$); however, multivariate Cox regression failed to identify any independent predictor of early ATa recurrence.

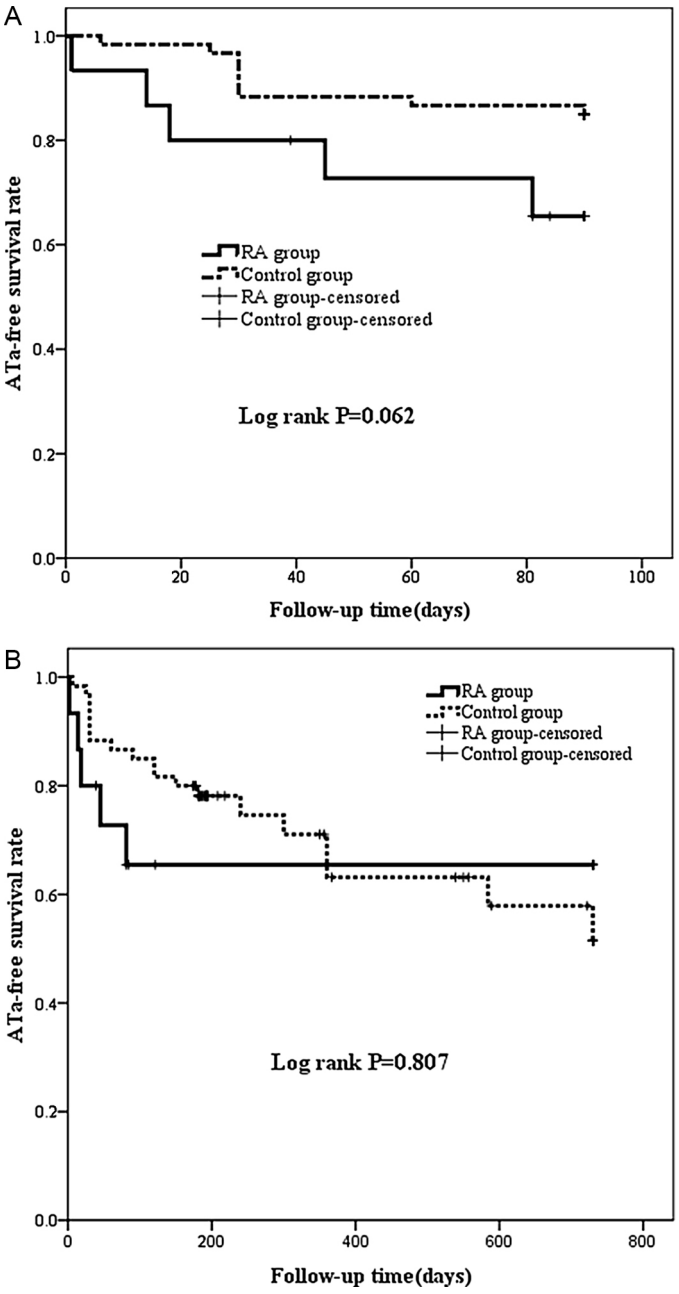

Fig. 1. Kaplan–Meier analysis of ATa-free survival in the RA and the control group at 90-day (A) and 2-year (B) follow-up. ATa, atrial tachyarrhythmia; RA, rheumatoid arthritis.

Table 3
Cox regression analysis for predictors of atrial tachyarrhythmia recurrence.

Variables	HR	95% CI	*p*-Value
Age	1.025	0.914–1.149	0.6770
Gender	1.245	0.354–4.376	0.7327
AF type	1.040	0.172–6.298	0.9660
AF duration	1.037	0.967–1.112	0.3074
LAD	1.045	0.999–1.094	0.0160
LVEF	0.906	0.770–1.066	0.2340
Hypertension	0.416	0.185–0.938	0.0340
RA	1.065	0.339–3.341	0.9143
WBC count	1.370	0.857–2.191	0.0880
Neutrophil count	1.487	0.939–2.354	0.0910
Lymphocyte count	0.212	0.020–2.266	0.1990
NLR	1.209	0.823–3.874	0.1620
Monocyte count	1.239	0.314–2.827	0.1180
CRP	1.044	0.921–1.183	0.4996

HR, hazard ratio; CI, confidence interval; AF, atrial fibrillation; LAD, left atrial diameter; LVEF, left ventricular ejection fraction; RA, rheumatoid arthritis; WBC, white blood cell; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

Discussion

The major findings of this study were (1) CA of AF can be safely performed in patients with RA and has a success rate comparable to that of patients without RA, and (2) RA patients tend to develop early ATa recurrence after AF ablation.

Rheumatoid arthritis is the most common inflammatory joint disease, affecting 1–2% of the population worldwide with more than two thirds of patients being female. It has been reported that over 25% of the women with AF have an underlying rheumatologic condition [11]. However, the relation between these two diseases remains controversial. Recently, published data from a Danish cohort showed a 40% increase of the risk of AF in patients with RA compared to the general population [1]. Although the pathophysiology of AF in the presence of RA is complex and poorly understood, several lines of evidence support the fact that AF is a common comorbidity in RA [1]. However, Kim et al. failed to demonstrate such an association in their study [12]. The safety and effectiveness of CA of AF in patients with RA have not been reported. Therefore, we performed a retrospective study to investigate the effect of CA on the outcome of patients with RA who underwent AF ablation. We found that CA could be safely performed in patients with RA and had a success rate comparable to that of patients without RA.

Systemic inflammation plays an important role in the initiation, maintenance, and recurrence of AF [13]. Elevated level of CRP has been suggested to be related to the initiation or maintenance of AF. The WBC count and subtypes, such as neutrophil, lymphocyte, monocyte, and NLR, are readily available biomarkers of systemic inflammation and associated with AF. After CA, an increased level of inflammatory biomarkers was correlated with the amount of radiofrequency delivery and was associated with early recurrence [14]. In the present study, patients with RA had a significantly higher CRP level, WBC count and neutrophil count, but Cox regression analysis showed that none of them was an independent predictor of ATa recurrence. Actually, a recent cohort study found an independent association between CRP and AF risk in men, but not in women [15]. Rheumatoid arthritis is more prevalent in women and 80% of the patients in the RA group were females. Interestingly, all recurrent patients in the RA group experienced ATa relapse within 90 days following CA. In all the RA patients involved in the present study, it appeared that the disease was clinically inactive either spontaneously or under drug control. They presented with a relative lower level of inflammatory biomarkers compared to a previous report [16]. So the pre-procedural status of systemic inflammation might no longer contribute to the outcome (early or late ATa recurrence) after AF ablation. However, we speculated that these patients may have robust local and systemic inflammatory responses to CA, which led to a high incidence of early recurrence even with AAD in the RA group.

Given the pathogenic role of inflammation in AF recurrence and maintenance after ablation, it has been postulated that therapies aggressively targeting peri-procedural inflammation might reduce the risk of development of AF. A recent meta-analysis demonstrated that intravenous corticosteroid therapy before and/or after cardiopulmonary bypass and cardiac surgery was associated with a significant reduction in incidence of post-operative AF [17]. The model of post-operative AF resembles that of AF recurrence after CA, because in both of these clinical scenarios, a strong inflammatory reaction comes into play [8]. Previously, Koyama

et al. [14] also found that hydrocortisone combined with oral prednisolone resulted in a significant reduction in peri-procedural inflammatory biomarkers and a reduced rate of immediate AF recurrence after CA. However, in the present study, five RA patients were under steroids and/or immunosuppressive agents therapy but two of them developed early recurrence. Although no statistical analysis was applied due to the small sample size, it appeared that the regular anti-inflammatory treatment is not preventing early ATa relapse in the RA patients as they may have pronounced inflammatory reaction immediately after ablation. In fact, a few studies have indicated that use of non-aspirin non-steroidal antiinflammatory drugs or glucocorticoids was associated with an increased risk of AF or flutter [18,19]. Whether the current anti-RA therapy will produce favorable or unfavorable effects on the outcome of AF ablation in RA patients remains unclear.

Although recurrence in blanking period usually is not considered as treatment failure, their prognostic value for later AF recurrence is high [20]. The initial extensive myocardial damage caused by radiofrequency CA is followed by a local and systemic inflammatory response [14]. So, numerous studies have found that inflammatory responses appeared shortly after CA and that those responses were closely associated with early AF recurrence, usually within the first 3-month "blanking period" [21]. Actually, in Deftereos's study [8] the authors did not apply a blanking period when they investigated the effect of colchicine on preventing early AF recurrence after CA. Similarly, in our study patients with RA have a strong background of systemic inflammation. So we did not apply a blanking period when evaluating procedural outcome and found that RA patients were more prone to develop early ATa recurrence compared to the control subjects. Of note, in both groups none of the early recurrent ATa (occurring within 90 days after ablation) spontaneously terminated during follow-up.

The study also revealed that LAD is another independent risk factor for recurrence, consistent with previous studies [22]. Increased LA size might be a consequence, at least in part, of chronic inflammatory state and atrial myocardial fibrosis under condition of RA.

Our study had some limitations. This was an observational study of a cohort of patients from a single center. The number of patients with RA enrolled in our study was small. Finally, we did not have data of inflammatory biomarkers after ablation or during follow-up, making the comparison to the pre-procedural data impossible.

In conclusion, CA of AF can be safely performed in patients with RA, with an overall success rate comparable to that in patients without RA. Patients with RA tend to develop early ATa recurrence within 3 months following an ablation procedure, which might be attributed to an immediate, robust inflammatory reaction induced by CA in this specific population.

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Conflict of interest

The authors declare that there is no conflict of interest.

Authors' contribution

Study was designed by Song-Nan Wen, Nian Liu, Rong Bai, and Chang-Sheng Ma. Data collection was done by Song-Nan Wen, Nian Liu, Song-Nan Li, Jun-Ping Kang, Man Ning, Jia-Hui Wu, Rong-Hui Yu, De-Yong Long, Ri-Bo Tang, Cai-Hua Sang, Chen-Xi Jiang, Jian-Zeng Dong, Xiao-Hui Liu, Yue Wang, and Rong Hu. Data were analyzed by Qian Yan, Xiao-Yan Wu, Song-Nan Wen, Yan-Fei Ruan, and Xin Du. Manuscript was prepared by Song-Nan Wen, Nian Liu, Rong Bai, and Salim Mohamed. Critical revision to the manuscript was done by Rong Bai, Nian Liu, Xiao-Hui Liu, and Chang-Sheng Ma. All authors read and approved the manuscript.

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