

Original Article

The efficacy and safety of radiofrequency ablation on the platelet activation and the inflammatory response in elderly atrial fibrillation patients

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Abstract: Background: Atrial fibrillation (AF) is the most common type of arrhythmia. AF is more common in the elderly population than in the young population. Radiofrequency ablation (RA) is the treatment option for drug-naïve AF; however, previous studies have focused on the young population. Therefore, it would be clinically valuable to compare the efficacy and safety of RA in both elderly and young patients with AF. Objective: This study intended to compare the efficacy and safety of RA in elderly and young patients with AF. Methods: Forty patients with drug-naïve AF who underwent RA at our hospital were retrospectively evaluated, of whom 20 were < 65 years old (group 1) and 20 were ≥ 65 years old (group 2). The treatment efficacy was evaluated by comparing the durations of the surgical procedures, the postoperative platelet activation, and the inflammatory factor levels. Results: The total operation times for RA (160.64 ± 7.25 vs. 160.64 ± 7.25 min, $P = 0.341$) and the fluoroscopy times (40.82 ± 5.93 vs. 39.89 ± 6.35 min, $P = 0.636$) did not differ between the elderly (74.1 ± 6.7 years) and the young (54.6 ± 7.9 years) groups. The postoperative platelet activation levels ($6.90\% \pm 0.64\%$ vs. $6.90\% \pm 0.70\%$, $P = 0.991$), the P-selectin expression levels (4.5 ± 1.3 vs. 4.9 ± 1.3 , $P = 0.333$) and the activated glycoprotein IIb/IIIa (0.5 ± 1.0 vs. 0.4 ± 1.1 , $P = 0.649$), and the inflammatory factor levels (C-reactive protein: 26.45 ± 6.66 vs. 25.72 ± 7.78 mg/L, $P = 0.750$) were elevated in both groups but did not differ between the two groups. Conclusion: RA is a safe and effective procedure in elderly and young patients with medically refractory AF.

Keywords: Radiofrequency ablation, atrial fibrillation, platelet activation, inflammatory response, elderly population

Introduction

Atrial fibrillation (AF), the most common type of arrhythmia, is defined as chaotic and disorganized electrical signals originating from the atria [1]. Instead of the sinus node directing the electrical rhythm, many different impulses are rapidly fired at once, resulting in a very fast, chaotic rhythm in the atria. In the United States, AF has a high incidence and mortality rate and is a medically expensive condition. It is estimated that more than 2 million people in the United States have AF, and it is speculated that the number will reach 5.6 million by 2050 [2]. AF increases the risk of stroke fivefold, accounting for 15% of all strokes [3]. It can affect all age groups but is more common in the elderly population.

The prevalence of AF is < 1% in the population aged 60-65 years, but it is 8%-10% in the population aged > 80 years [2]. However, previous studies have typically focused on the younger populations, and in-depth studies targeting the elderly patients are lacking.

Radiofrequency ablation (RA) has emerged as an effective therapeutic option for heart rate control in patients with symptomatic AF, which is often not controlled by drugs due to drug intolerance; drug intolerance is more common in elderly patients or in patients with advanced heart failure or obstructive pulmonary disease [4]. However, perioperative thromboembolism is an extremely worrisome complication. The incidence of thromboembolic events associated with RA for AF has been reported to range

from 0.9% to 5%, depending on the RA strategy and the perioperative anticoagulation protocol [5]. Low inflammatory response levels are thought to be one of the causes and consequences of AF [6], and AF has been reported to increase the levels of several inflammatory factors [7], and inflammation can promote arrhythmia and is also associated with a pre-thrombotic state.

To further evaluate the safety and efficacy of RA for the treatment of elderly patients with AF, we compared the coagulation activation and inflammatory response levels before and after RA in elderly and young patients with AF.

Materials and methods

Patients

This retrospective study enrolled 40 patients with AF who underwent RA at our hospital. All the patients had 12-lead electrocardiography (ECG)-recorded symptoms of AF episodes. The patients were divided into two groups according to their ages. Group 1 included 18 patients < 65 years old, and group 2 included 22 patients ≥ 65 years old. The inclusion criteria were: patients with AF recorded using a 12-lead electrocardiogram, the cardiac function of the heart failure patients returned to NYHA classifications I or II after treatment, patients 18-75 years old, patients with refractory paroxysmal or frequent AF, patients who agreed to undergo radiofrequency ablation, and patients who signed the surgical informed consent and completed the follow-up. The exclusion criteria were: patients with chronic AF for > 12 months, a left atrial internal diameter of > 55 mm, the presence of intracardiac thrombus confirmed through echocardiography, myocardial infarction or cardiac surgery 3 months prior to participating in the study, and a history of RA. This study was approved by the Ethics Committee of Beijing Chaoyang Hospital Affiliated to Capital Medical University. The patients and their families were informed of the study, and they signed the informed consent forms.

Electrophysiological study

The patients provided consent for the treatment prior to the electrophysiological studies. All the patients included in the study were medically ineffective and all preoperative antiar-

rhythmic drugs were discontinued for at least five half-lives, and the oral anticoagulants were discontinued for 2 days. The operation was performed according to the standard procedures. The patients were monitored for 3-6 h postoperatively and were then discharged on the same day. All antiarrhythmic drugs were discontinued and the patients were followed up.

Laboratory examinations

We collected peripheral blood samples (10 mL) from the patients before and after the surgery for analysis. Enzyme-linked immunosorbent assays (ELISA) were used to measure the patients' serum high-sensitivity C-reactive protein (hs-CRP) levels (SenBeijia, Nanjing, China). The platelet aggregation tests were performed using a Bio/Data PAP4 Aggregameter (Mölab, Hilden, Germany). The peripheral blood was injected into a sodium citrate centrifuge tube. After centrifugation at 1000 r/min for 10 min, the upper platelet-containing plasma was extracted, and the remaining blood was centrifuged at 3000 r/min for 20 min, and then the upper platelet-poor plasma was obtained. The final platelet concentration was adjusted to $100-200 \times 10^3/\mu\text{L}$, and 0.1 mmol/L adenosine diphosphate (ADP) was added to induce aggregation. The platelet aggregation rate after 5 min was recorded.

The surface expressions of the P-selection and activated GP IIb/IIIa were determined using flow cytometry (BD LSRFortessa). The blood platelets were stained with fluorescein-isothiocyanate labeled PAC-1 (activated GP IIb/IIIa receptors; Sigma-Aldrich, Shanghai, China), phycoerythrin-labeled anti-CD62P (Pselectin; Abcam, Shanghai, China) and phycoerythrin-cyanin 5.1 labeled anti-CD41 (total GP IIb/IIIa receptors; Abcam, Shanghai, China). The whole blood was incubated with antibodies for 30 min and analyzed using flow cytometry within 24 hours [8].

Follow-up

The follow-up data were obtained from the attending physician or the patients via questionnaires or over the telephone. When the patient-reported symptoms were consistent with those of arrhythmia recurrences, a prolonged ECG recording was recommended; repeat

Table 1. Patient characteristics

Clinical data	Group 1	Group 2	P value
Number	18	22	-
Mean age (year)	54.6 ± 7.9	74.1 ± 6.7	2.6903E-10
Males	8	12	0.525
History of AF (years)	3.6 ± 1.4	3.4 ± 1.3	0.556
Organic heart disease (%)	6 (33.3%)	10 (45.5%)	0.781
	CHD 2	CHD 4	-
	HOCM 1	HCMP 2	-
	Tachymyopathy 2	Tachymyopathy 1	
	Valvular 1	Valvular 2	-
		DCMP 1	-
Hypertension (%)	7 (38.9%)	11 (50%)	0.482

CHD: coronary heart disease; HOCM: hypertrophic cardiomyopathy; HCMP: hypertensive cardiomyopathy; DCMP: idiopathic dilated cardiomyopathy.

Table 2. Procedural parameters

Parameters	Group 1	Group 2	P value
Mean procedural time (min)	163.06 ± 8.61	160.64 ± 7.25	0.341
Mean fluoroscopy time (min)	39.89 ± 6.35	40.82 ± 5.93	0.636
Complications	0	1	-

ablation was performed if a recurrence was confirmed.

Statistical analysis

The statistical analysis was performed using SPSS version 24.0 (SPSS Inc., Chicago IL, United States). The statistical graphs were prepared using GraphPad Prism 8.0 software (GraphPad Software Inc., La Jolla, CA, United States). Continuous variables were presented as the mean and standard deviation (mean ± SD). FlowJo (version 10.0.7, Tree Star, Ashland, OR, USA) was used to analyze the flow cytometry results. The qualitative variables were indicated as frequencies or percentages. The differences in the two groups' baseline data were evaluated using Student's t-tests for quantitative variables and chi-squared tests for the qualitative variables. A *P* value of < 0.05 was considered to indicate a significant difference.

Results

Clinical characteristics of the study population

A total of 40 patients with drug-naïve AF were included in this retrospective study, with 18 patients (< 65 years) in group 1 [(54.6 ± 7.9)

years] and 22 patients (≥ 65 years) in group 2 [(74.1 ± 6.7) years]. There were no statistically significant differences between the two groups in terms of sex, history of AF, or underlying cardiovascular disease (*P* > 0.05) (**Table 1**); this result indicates that the two groups were comparable.

Procedural parameters

There was no difference in the operation times between the two groups (163.06 ± 8.61 vs. 160.64 ± 7.25 min, *P* = 0.341), indicating that the efficiency of the RA in the elderly patients was similar to the efficiency of the RA in the young patients. Further, there was no difference in the fluoroscopy times (39.89 ± 6.35

vs. 40.82 ± 5.93, *P* = 0.636). Regarding the acute postoperative complications, one patient in group 2 complained of pain in the precordial region, with no pericardial friction sounds on the physical examination and no pericardial effusion or other anomalies on the ECG (**Table 2**; **Figure 1A**).

Platelet activation and the inflammatory response

Both groups had significant platelet activation after the operations; however, there was no difference between the two groups in this regard. In particular, the two groups showed no significant differences in their ADP-induced optical aggregometry or in their P-selectin expressions or activated glycoprotein IIb/IIIa levels (*P* > 0.05) (**Table 3**; **Figure 1B**). These results indicated that RA triggered the same level of platelet activation in the elderly and young AF patients.

Both groups exhibited a significant inflammatory response after their operations, as evidenced by a significant increase in the patients' hs-CRP levels. However, there was no significant difference between the two groups in this regard (*P* > 0.05) (**Table 3** and **Figure 1C**).

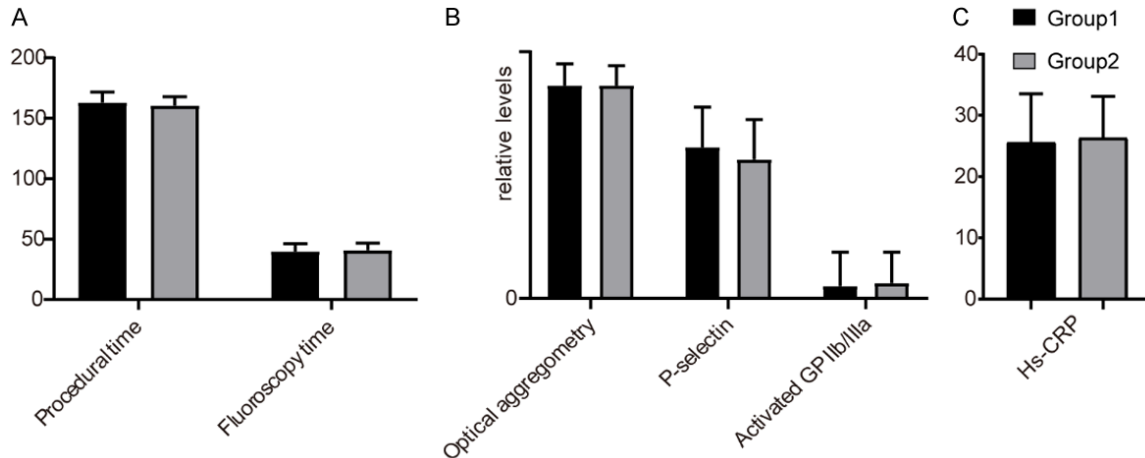


Figure 1. Comparison of the procedural parameters, the platelet activation parameters, and the inflammatory parameters. The comparisons of the procedural parameters (A), the increased platelet activation parameters (B), and the increased inflammatory parameters (C) showed no significant differences between the two groups ($P > 0.05$).

Table 3. Increased levels of platelet activation and inflammatory parameters

Parameters	Group 1	Group 2	P value
Optical aggregometry (%)	6.90 ± 0.70	6.90 ± 0.64	0.991
Surface expression of P-selectin	4.9 ± 1.3	4.5 ± 1.3	0.333
Surface expression of activated GP IIb/IIIa	0.4 ± 1.1	0.5 ± 1.0	0.649
High-sensitive C-reactive protein (mg/L)	25.72 ± 7.78	26.45 ± 6.66	0.75

ed Western countries than in developing countries [10]. Therefore, clinicians and epidemiologists in developing countries should conduct better AF investigations in their own populations [11].

Discussion

Our study demonstrates that using RA to treat AF leads to platelet activation and an increased inflammatory response. More importantly, the platelet activation and inflammatory response levels are similar in elderly and young patients. Further, the operation times are similar in elderly and young patients. Therefore, we can conclude that the safety and efficiency of RA in elderly patients are similar to the safety and efficiency of RA in young patients. This provides a basis for promoting the use of RA in elderly patients with AF.

AF is the most common type of arrhythmia in adults [9] and affects an estimated 33.5 million patients worldwide (excluding clinically asymptomatic patients). The incidence of AF is expected to increase threefold over the next 30 years [10]. Based on its high prevalence and potentially serious consequences, we should seek optimal decisions for AF management and treatment. The epidemiological observations of AF are more clearly established in develop-

Age is an important risk factor for AF, and the risk of AF doubles with each decade of age. For example, it has been reported that the annual incidence of AF in a population aged < 65 years old in the United States is 1.9 per 1000 population for women and 3.1 per 1000 population for men; in contrast, the annual incidence of AF in a population aged > 85 years old is 31.4 per 1000 population for women and 38 per 1000 population for men [12]. Similar results were obtained in a European cohort study, where the incidence of AF was 1.1 per 1000 person-years in patients aged 55-59 years old and 20.7 per 1000 person-years in patients aged ≥ 80 years old [13]. Therefore, we should pay particular attention to elderly patients with AF.

In recent years, RA has been used more widely in patients with AF. However, its efficacy and safety still need to be confirmed [14]. The complexity of the procedure and its dependence on the skills of the operator expose patients to a considerable number of potential complications [15]. Thromboembolism is a severe complication of AF because of its long-

term impact on the patient's health. Symptomatic cerebral embolisms have been reported in approximately 14% of patients after their operations [16]. A study has confirmed that RA triggers early platelet activation [17]; however, the exact mechanism remains inconclusive. Our study is the first to confirm the level of platelet activation in the early stage of the postoperative period. More importantly, this state of platelet activation does not differ between the elderly and young populations, indicating that despite the higher prevalence of AF in the elderly population, RA remains a safe treatment modality that does not cause high levels of postoperative or intraoperative thromboembolisms.

Inflammation is involved in the initiation and maintenance of AF [18, 19]; however, AF can further exacerbate inflammation. Therefore, the activation status of the inflammatory pathways plays a key role in the pathology of AF. RA can induce elevated inflammatory levels [20]. High postoperative inflammatory levels may lead to the recurrence of AF and are associated with poor prognosis. In an animal model of canine aseptic pericarditis, the increase in inflammation induced by the operation was confirmed; however, after anti-inflammatory treatment, the risk of AF recurrence was reduced by 60% [21]. The inflammatory response during RA is mainly caused by thermal injury [22]. Elevated postoperative CRP levels have been reported to be associated with an increased risk of AF recurrence [23]. A clinical study involving 40 patients treated with AF after RA found that the patients with AF had high CRP levels and that the increase in CRP levels predicted the likelihood of early AF recurrence within 3 days of the operation but not recurrence after 3-6 months [24, 25]. Therefore, we measured elevated CRP levels after the operations in both groups; however, we observed no difference in the elevation levels between the two groups. This indicates that the safety of RA in the elderly population is equivalent to the safety in the young population.

The main limitations of our study are the small number of patients included, the short follow-up period, and the lack of an effective follow-up for the long-term postoperative outcomes. Another unavoidable limitation is the higher prevalence of underlying cardiovascular disease

in elderly patients than in young patients. In the future, we will conduct a clinical study with a larger sample size and long follow-up period to better prove the efficacy and safety of RA in elderly patients with AF as well as to provide a better treatment option for elderly patients with medically refractory AF.

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Disclosure of conflict of interest

None.

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