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Inflammatory Response after Different Ablation Strategies for Paroxysmal Atrial Fibrillation

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ABSTRACT

Background: Catheter ablation for atrial fibrillation (AF) has been gaining popularity; however, the trend of inflammatory response markers in patients treated with different catheter ablation strategies over time and their predictability of AF recurrence remain unknown.

Methods: A total of 210 patients with AF were enrolled and grouped according to surgical mode as follows: freeze group, RF group, and freeze3D group. The subjects were tested for related indexes before and after surgery. To determine AF recurrence during follow up, 24-h ambulatory electrocardiography was performed at two, three, six, and 12 months after surgery.

Results: The inflammation indexes of the three groups peaked between one and three days after surgery but fell at different time points ($P < .05$). The recurrence rate of paroxysmal atrial fibrillation (PAF) was positively correlated with the increase in the percentage of white blood cells and neutrophils after surgery ($P < .05$).

Conclusions: The postoperative inflammation indices peaked and fell at different time points after different catheter ablation methods. In addition, the recurrence rate of AF in patients treated with freeze3D is lower.

INTRODUCTION

Atrial fibrillation (AF) is one of the most common types of arrhythmia in clinics and is known as the cardiovascular epidemic of the 21st century. The increase in morbidity and mortality associated with AF is concerning, and the variability of AF is twice as high as that of normal people. The main cause of disability among patients with AF is stroke [Wolf 1991; Krijthe 2013]. With the development of cardiac electrophysiological technologies, catheter ablation has become an important method for radical treatment of AF and has greatly improved the life quality of patients with AF.

Pulmonary vein isolation (PVI) is the cornerstone of paroxysmal atrial fibrillation (PAF) treatment. However, early radiofrequency ablation has limited clinical application, due to its long learning curve and complicated operation procedures. The emerging frozen balloon atrial isolation technique can achieve the isolation effect of pulmonary vein potential by filling and freezing the balloon, which causes transmural damage of the target myocardial. A recent "Fire and Ice" study on the comparison between cryoablation and radiofrequency ablation [Kuck 2016] showed that cryoablation has a therapeutic effect on PAF that is similar to radiofrequency ablation. Furthermore, cryoablation has fewer postoperative complications than radiofrequency ablation. However, there is still a certain chance of recurrence after catheter ablation for PAF. Studies have shown that AF recurrence is related to various factors, including the size of the left atrium, duration of AF, and the age of patients [An 2018]. In addition, catheter ablation for AF often is accompanied by various inflammatory reactions and myocardial damage [Lim 2014; Antolič 2016]. There is a certain correlation between the inflammatory response and AF recurrence after catheter ablation [Richter 2012; Antolič 2016; Mukherjee 2016; Jin 2018]. However, there currently is no consensus on the change in the trend of inflammation indexes after cryoablation, radiofrequency ablation, or cryoablation combined with 3D ablation over time. Furthermore, it is unclear whether there are differences in postoperative inflammatory indexes among the above three surgical methods and whether there is a correlation between the inflammation indexes and AF recurrence. The current study observed the changes in postoperative inflammatory indexes by the three different ablation methods for AF and further compared the differences in inflammatory indexes among the three groups. This study aimed to explain the correlation between AF recurrence and inflammatory indexes with the intention to provide guidance for clinical treatment.

MATERIALS AND METHODS

Study objects: Patients who underwent catheter ablation for AF in the Department of Cardiology, Second Hospital of Hebei Medical University from March 1, 2016 to March 1, 2017, were enrolled. The inclusion criteria were as follows: (1) Patients with at least two episodes of PAF confirmed by electrocardiogram (ECG) in the past six months; (2) patients

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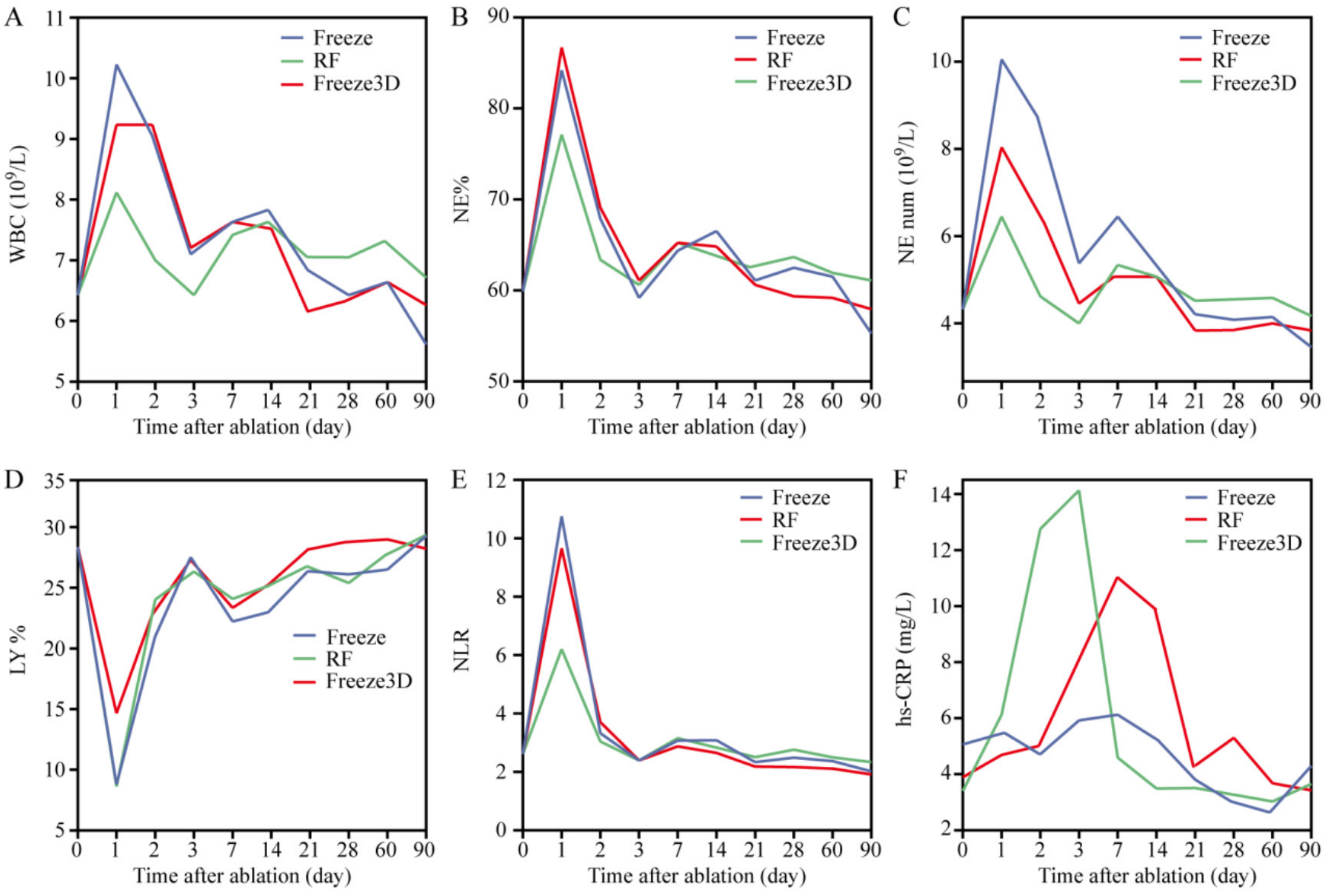

The trend of WBC, NE%, NE num, LY%, NLR and hs-CRP in groups.

with poor treatment effect and intermittent occurrence of AF after the use of class I or III antiarrhythmic drugs; and (3) patients aged <80 years old who signed the informed consent form and actively required catheter ablation. The exclusion criteria were as follows: (1) patients who previously had undergone catheter ablation for AF; (2) patients with left atrial thrombus; (3) patients with severe stenosis or incomplete heart disease; (4) patients with a left atrial diameter of >50 mm; (5) patients with liver/kidney dysfunction, malignant tumor, or blood system disease; and (6) patients with an acute or chronic infection.

Grouping: Patients with AF were randomized to receive radiofrequency ablation, cryoablation, or 3D-guided cryoablation and divided into the freeze, RF, and freeze3D groups. Patients in the freeze group were treated with a first- or second-generation frozen balloon (Medtronic) during catheter ablation; during this period, each pulmonary vein was cryoablated until the pulmonary vein potential was isolated. Patients in the RF group were treated with "point-to-point" radiofrequency ablation of the pulmonary veins by SmartTouch radiofrequency ablation catheter (Johnson & Johnson, USA) until the pulmonary veins were isolated; during this period, no frozen balloon was used for ablation. Patients in the freeze3D group were treated with frozen balloon cryoablation; during this period, each pulmonary vein was frozen up to two times. If the pulmonary vein potential still was not isolated after cryoablation, a radiofrequency ablation catheter was used for supplemental ablation until the pulmonary vein potential was isolated. The patients' clinical data and blood biochemical indicators were reviewed before surgery, and only the clinician knew the patients' grouping situations. The operation was performed by a single surgeon. Furthermore, the patients were divided into recurrence-free, early-recurrence, and long-term recurrence groups based on AF recurrence after surgery. Early recurrence was defined as any atrial arrhythmia ≥30 s that was recorded by ECG and dynamic ECG within the three months after ablation. Long-term recurrence was defined as any atrial arrhythmia ≥30 s that occurred three months after surgery, namely clinical recurrence. Total recurrence was defined as all atrial arrhythmias ≥30 s that occurred after catheter ablation. If the enrolled patients had both early and long-term recurrence, the situation was defined as one case considered total recurrence.

Surgical procedures: In all patients, CT reconstruction of the left atrial pulmonary vein was performed to understand the venous structure of the pulmonary veins. Furthermore,

Table 1. Baseline characteristics of population of the three groups

	Freeze group (N = 70)	RF group (N = 70)	Freeze3D group (N = 70)
Age, y	58.96 ± 12.54	57.61 ± 10.77	63.07 ± 11.07
Male sex	37(52.9%)	39(55.7%)	42(60.0%)
Current or ex-smoker	8(11.4%)	16(22.9%)	13(18.6%)
Alcohol user	8(11.4%)	10(14.3%)	6(8.6%)
Comorbidities			
Congestive heart failure	7(10.0%)	6(8.6%)	9(12.9%)
Hypertension	42(60%)	30(42.9%)	42(60%)
Diabetes mellitus	10(14.3%)	13(18.6%)	13(18.6%)
Coronary artery disease	15(21.4%)	11(15.7%)	21(30%)
CHA2DS2 score	2.06±1.58	1.80 ± 1.82	2.33 ± 1.71
Statin therapy	35(50%)	35(50%)	35(50%)
Echocardiographic parameters			
LA size, mm	35.63 ± 4.39	35.37 ± 4.34	34.77 ± 4.39

Note: Results are mean±SD or n (%), among the three groups P value>0.05. CHA2DS2: congestive heart failure, hypertension, age ≥75 year old, diabetes mellitus, and previous stroke/TIA. LA: left atrial. LVEF: left ventricular ejection fraction.

transesophageal echocardiography was performed to exclude left atrial thrombosis.

The procedures of cryoablation were as follows. A 23-mm or 28-mm diameter frozen balloon (Medtronic, USA) was selected based on each patient's preoperative left atrial pulmonary vein CT results. After the lower extremity femoral vein was punctured and catheterized, one long sheath was introduced through the venous system, and one IAS needle (Medtronic, USA) was used to complete the IAS puncture. Later, the cryoablation balloon and a measuring electrode (Achieve, Medtronic, USA), which could be built into the balloon, were introduced into the right atrium through the femoral vein and the inferior vena cava and inserted into the left atrium through the IAS puncture site. The measuring electrode was placed at each pulmonary vein opening to detect and monitor the changes in pulmonary vein potential. The balloon then was pushed forward along the measuring electrode, placed at the pulmonary vein opening position, and filled to block the vestibule of the left atrial pulmonary vein. Cryoablation was performed after the pulmonary vein and the left atrium were confirmed to have sealed by contrast agent infusion. Generally, the first-generation frozen balloon has a single freezing time of up to 240 s, and the second-generation balloon has a single freezing time of up to 180 s. Before performing the right pulmonary vein cryoablation, the surgeon placed a pacing electrode above the superior vena cava for routine pacing and monitored the phrenic nerve pacing to prevent paralysis of the sacral nerve injury. Cryoablation should be stopped immediately once the diaphragm contraction has either weakened or stopped during the operation. The cryoablation procedures can be repeated until the pulmonary vein potential disappears, and two-way pacing stimulation should be used to clarify the left atrial-pulmonary vein bidirectional block.

The procedures of radiofrequency ablation were as follows. After the IAS puncture, a radiofrequency ablation catheter (SmartTouch, Johnson & Johnson, USA) and a measuring electrode (Lasso®, Johnson & Johnson, USA) were placed in the left atrium. One Lasso was used to complete the 3D building of the left atrium and the pulmonary vein under the supervision of a 3D electroanatomic mapping system (Carto 3, Johnson & Johnson, USA). Linear ablation of the left atrial pulmonary vein was then performed at the vestibule of the left atrial pulmonary vein using an ablation catheter. The endpoint of the surgery was set as the appearance of afferent and efferent block of the pulmonary venous potential. After observing for 20–30 min after the afferent and efferent block of the pulmonary vein potential appeared, the pulmonary vein potential conduction was detected again, and if there was recurrence, ablation was continued.

The procedure of 3D-guided cryoablation was as follows. After the IAS puncture, a circular measuring catheter (Achieve, Medtronic, USA) was used to construct the left atrium and pulmonary vein structures under Ensite 3D guidance, and frozen ball cryoablation was performed, according to the 3D results. The number of cryoablations of each pulmonary vein was less than two. If the pulmonary vein potential still showed conduction after two instances of cryoablation, radiofrequency ablation was performed to achieve complete pulmonary vein potential isolation and two-way block of the pulmonary vein.

Sample collection and examination: The white blood cell count (WCC) and high-sensitivity C-reactive protein (hs-CRP) levels were measured on day 1, 2, and 3, week 1, 2,

Table 2. Time course of changes in inflammation among the three groups

Variables	Groups	Baseline	1Day	2 Days	3 Days
WBC(10^9/L)	Freeze group	6.31 ± 2.04	10.10 ± 3.19$^{\Delta}$	8.86 ± 2.54$^{\Delta}$	7.04 ± 2.07$^{\Delta}$
	RF group	6.53 ± 1.43	8.25 ± 1.92$^{\Delta}$	7.17 ± 1.73$^{\Delta}$	6.46 ± 1.40*
	Freeze3D group	6.54 ± 1.61	9.56 ± 2.57$^{\Delta}$	9.01 ± 2.42$^{\Delta}$	7.18 ± 1.62$^{\Delta}$
	Freeze versus RF	0.453	0	0	0.052
	Freeze versus Freeze3D	0.436	0.238	0.705	0.656
	RF versus Freeze3D	0.975	0.006	0	0.019
NE%	Freeze group	59.87 ± 10.92	84.13 ± 14.66$^{\Delta}$	64.60 ± 15.88$^{\Delta}$	57.39 ± 16.61*
	RF group	59.15 ± 13.48	76.32 ± 11.33$^{\Delta}$	64.01 ± 7.72$^{\Delta}$	61.14 ± 8.45*
	Freeze3D group	59.66 ± 9.70	86.75 ± 4.34$^{\Delta}$	68.11 ± 7.86$^{\Delta}$	61.88 ± 8.56$^{\Delta}$
	Freeze versus RF	0.719	0	0.758	0.71
	Freeze versus Freeze3D	0.917	0.167	0.71	0.03
	RF versus Freeze3D	0.797	0	0.034	0.724
LY%	Freeze group	30.15 ± 9.83	8.34 ± 5.99$^{\Delta}$	23.78 ± 9.98$^{\Delta}$	27.80 ± 9.03$^{\Delta}$
	RF group	30.90 ± 13.08	14.85 ± 5.56$^{\Delta}$	25.43 ± 7.30$^{\Delta}$	27.14 ± 7.22$^{\Delta}$
	Freeze3D group	30.67 ± 9.28	10.42 ± 5.70$^{\Delta}$	24.32 ± 7.29$^{\Delta}$	27.45 ± 7.97$^{\Delta}$
	Freeze versus RF	0.688	0	0.249	0.640
	Freeze versus Freeze3D	0.780	0.037	0.706	0.805
	RF versus Freeze3D	0.94	0	0.438	0.826
NLR	Freeze group	2.52 ± 2.00	10.65 ± 5.02$^{\Delta}$	3.19 ± 1.67$^{\Delta}$	2.37 ± 1.11*
	RF group	2.81 ± 2.60	6.41 ± 3.59$^{\Delta}$	2.90 ± 1.71$^{\Delta}$	2.61 ± 1.91*
	Freeze3D group	2.37 ± 2.05	9.96 ± 3.96$^{\Delta}$	3.37 ± 1.88$^{\Delta}$	2.51 ± 1.20$^{\Delta}$
	Freeze versus RF	0.447	0	0.340	0.346
	Freeze versus Freeze3D	0.701	0.35	0.549	0.579
	RF versus Freeze3D	0.253	0	0.121	0.698
hs-CRP(mg/L)	Freeze group	3.46 ± 4.96	3.77 ± 5.50$^{\Delta}$	2.97 ± 2.90$^{\Delta}$	4.97 ± 6.52$^{\Delta}$
	RF group	2.08 ± 3.25	4.99 ± 4.60$^{\Delta}$	17.35 ± 17.81$^{\Delta}$	15.95 ± 15.82$^{\Delta}$
	Freeze3D group	2.53 ± 5.50	3.54 ± 5.14$^{\Delta}$	3.73 ± 4.55$^{\Delta}$	6.69 ± 9.88$^{\Delta}$
	Freeze versus RF	0.091	0.187	0	0
	Freeze versus Freeze3D	0.253	0.794	0.684	0.39
	RF versus Freeze3D	0.567	0.117	0	0

3, and 4, and month 2 and 3 after surgery. The analysis was performed immediately after blood sample collection.

The WCC was detected using a Sysmex XN2000 automatic blood cell analyzer, and the hs-CRP level was determined by latex-enhanced immunoturbidimetry (normal reference range for WCC and hs-CRP: 3.5–9.5 [$\times 10^9$/L] and 0–0.08 mg/L, respectively).

Patients with PAF routinely were treated with conventional braking, fluid replacement, and continuous ECG monitoring for three days. Outpatient follow up was planned for month 2, 3, 6, and 12 after surgery. Follow up started one month after surgery, and patients underwent electrocardiography and dynamic electrocardiography twice per month to record the recurrence of arrhythmia.

Statistical methods: Data analysis was performed using SPSS13.0 statistical software. The measurement data with normal distribution were expressed as mean ± standard deviation and compared using the Student t-test, and data with non-normal distribution were expressed in quartiles and analyzed using the Mann–Whitney U test. The count data were expressed in terms of frequency and percentage and analyzed using the χ^2 test or Fisher's exact test. The intra- and inter-group comparison of inflammatory indexes after AF ablation was performed using a repeated measurement mixed linear model. The Spearman correlation coefficient was used to analyze the relationship between two continuous variables. A *P*-value of <0.05 was considered statistically significant.

Table 2. Time course of changes in inflammation among the three groups (continous)

Variables	Groups	1 Week	2 Weeks	3 Weeks	4 Weeks	2 Months	3 Months
NE%	Freeze group	62.42 ± 14.51$^{\Delta}$	63.21 ± 15.03$^{\Delta}$	57.97 ± 14.69*	58.10 ± 15.81*	56.27 ± 16.99*	52.60 ± 17.96*
	RF group	64.62 ± 8.14$^{\Delta}$	64.08 ± 7.62$^{\Delta}$	62.31 ± 8.01*	63.20 ± 8.71*	60.45 ± 8.29*	59.99 ± 8.56*
	Freeze3D group	64.94 ± 6.51$^{\Delta}$	65.82 ± 6.08$^{\Delta}$	60.51 ± 6.14*	59.41 ± 5.54*	58.63 ± 7.59*	57.27 ± 7.22*
	Freeze versus RF	0.25	0.662	0.026	0.015	0.078	0.003
	Freeze versus Freeze3D	0.178	0.184	0.195	0.521	0.291	0.05
	RF versus Freeze3D	0.867	0.391	0.359	0.065	0.435	0.256
NE num(10^9/L)	Freeze group	5.90 ± 7.85$^{\Delta}$	6.20 ± 8.88$^{\Delta}$	5.15 ± 8.51*	5.06 ± 9.48*	4.97 ± 8.53*	3.47 ± 1.25*
	RF group	5.14 ± 3.03$^{\Delta}$	5.14 ± 2.18$^{\Delta}$	4.40 ± 1.23*	4.51 ± 1.36*	4.15 ± 1.18*	4.79 ± 5.46*
	Freeze3D group	4.79 ± 1.50$^{\Delta}$	5.05 ± 1.39$^{\Delta}$	3.83 ± 1.04*	3.80 ± 1.13*	3.82 ± 1.17*	3.58 ± 1.17*
	Freeze versus RF	0.409	0.309	0.435	0.605	0.421	0.044
	Freeze versus Freeze3D	0.216	0.262	0.169	0.226	0.233	0.856
	RF versus Freeze3D	0.698	0.935	0.554	0.494	0.735	0.060
LY%	Freeze group	23.26 ± 7.90$^{\Delta}$	23.43 ± 8.14$^{\Delta}$	27.69 ± 8.14*	27.09 ± 9.45*	28.40 ± 9.48*	29.54 ± 10.80*
	RF group	25.84 ± 7.59$^{\Delta}$	26.34 ± 7.43$^{\Delta}$	27.84 ± 7.37*	27.21 ± 8.07*	29.78 ± 7.53*	30.49 ± 8.23*
	Freeze3D group	24.93 ± 5.84$^{\Delta}$	25.41 ± 5.47$^{\Delta}$	29.13 ± 5.78*	29.62 ± 5.91*	30.53 ± 6.79*	30.76 ± 9.85*
	Freeze versus RF	0.051	0.031	0.915	0.939	0.392	0.625
	Freeze versus Freeze3D	0.198	0.134	0.333	0.090	0.169	0.515
	RF versus Freeze3D	0.489	0.490	0.392	0.106	0.637	0.886
NLR	Freeze group	3.02 ± 1.52$^{\Delta}$	3.05 ± 1.57$^{\Delta}$	3.68 ± 11.20*	2.43 ± 1.97*	2.22 ± 0.87*	2.19 ± 1.56*
	RF group	3.00 ± 1.78$^{\Delta}$	2.77 ± 1.42$^{\Delta}$	2.46 ± 1.05*	2.66 ± 1.34*	2.27 ± 1.03*	2.45 ± 2.01*
	Freeze3D group	2.67 ± 0.95$^{\Delta}$	2.78 ± 1.06$^{\Delta}$	2.18 ± 0.69*	2.13 ± 0.68*	2.09 ± 0.76*	1.83 ± 0.65*
	Freeze versus RF	0.946	0.285	0.332	0.283	0.800	0.391
	Freeze versus Freeze3D	0.188	0.300	0.233	0.150	0.438	0.239
	RF versus Freeze3D	0.221	0.959	0.822	0.012	0.310	0.038
hs-CRP(mg/L)	Freeze group	4.88 ± 7.23$^{\Delta}$	3.26 ± 5.77*	2.41 ± 4.99*	1.37 ± 1.26*	1.35 ± 1.40*	2.95 ± 6.44*
	RF group	3.62 ± 4.55$^{\Delta}$	1.75 ± 1.91*	1.70 ± 1.95*	1.41 ± 1.24*	1.45 ± 1.67*	1.59 ± 2.49*
	Freeze3D group	5.49 ± 8.36$^{\Delta}$	3.33 ± 3.84*	2.75 ± 4.11*	2.74 ± 4.89*	1.81 ± 2.28*	2.03 ± 2.62*
	Freeze versus RF	0.329	0.055	0.337	0.948	0.780	0.112
	Freeze versus Freeze3D	0.625	0.934	0.651	0.60	0.196	0.272
	RF versus Freeze3D	0.149	0.052	0.164	0.74	0.331	0.586

Data presented as mean ± SD, compared to baseline values, *$P > .05$, $^{\Delta}P < .05$

RESULTS

Characteristics of baseline clinical data: A total of 210 patients with AF (59.9 ± 11.68 years old) were enrolled in the trial and divided into three groups, with 70 patients in each group. The three groups were matched in age, sex, comorbidities, and CHADS2 scores ($P > .05$). The freeze group had 29 cases (41.4%) treated with the first-generation balloon, and the freeze3D group had eight cases (11.4%) treated with the first-generation balloon. All the enrolled patients had completed pulmonary vein isolation. There were no complications such as left atrial esophageal fistula or pericardial tamponade during surgery (Table 1).

WCC: In the RF group, the WCC began to rise after surgery, peaked on day 1 ($P < .05$), gradually decreased, and finally fell back to the preoperative level during month 2 after surgery. In the freeze and freeze3D groups, the WCC also began to increase after surgery, peaked on day 1 ($P < .05$), began to decrease on day 2 and 3 but remained higher than the preoperative level ($P < .05$), then gradually decreased, and finally fell back to the preoperative level ($P > .05$) in week 3 after surgery.

Table 3. Comparison of AF recurrence among the three groups

	Early recurrence	Late recurrence	Recurrence
Freeze group	7(10%)	14(20%)	14(20%)
RF group	7(10%)	15(21.4%)	16(22.9%)
Freeze3D Group	5(7.1%)	5(7.1%)	9(12.9%)

Data presented as n(%)

Comparison among the three groups showed that the peak WCC was higher in the freeze groups and the freeze3D groups after surgery (P < 0.05), and the highest in the freeze group; however, there was no statistical difference between these two groups. In the freeze and freeze3D groups, the WCC fell faster and fell back to the preoperative level in week 3 after surgery. The postoperative inflammatory indexes in group RF lasted longer and fell back to the preoperative level in month 2 after surgery (Figure 1 and Table 2).

Percentage of neutrophils (NE%): In the RF group, the NE% level peaked on day 1 after surgery (*P* < .05), fell back to the preoperative level on day 3 after surgery (*P* > .05), then rose again on day 7 after surgery, and fell back to the preoperative level in week 3 (*P* > .05).

In the freeze group, the NE% level also peaked on day 1 after surgery (*P* < .05) and fell back to the preoperative level on day 3 after surgery (*P* > .05); following this, the NE% continued to decline, and finally fell back to the preoperative level in week 3 (*P* > .05). In the freeze3D group, the NE% peaked on day 1 after surgery, decreased slightly on days 2 and 3 after surgery (while still higher than the preoperative level), and fell back to the preoperative level in week 3 after surgery (*P* > .05).

Comparison among the three groups showed that the peak NE% was the highest in the freeze3D group and the lowest in the RF group. There was no significant difference between the freeze3D group and freeze group (*P* > .05). The NE% level in the three groups all fell back to the preoperative level at week 3 after surgery (Figure 1 and Table 2).

Neutrophil absolute value (NE num): In the RF group, the NE num peaked on day 1 after surgery (*P* < .05), then continued to decline, and finally fell back to the preoperative level in week 3 after surgery. In the freeze and freeze3D groups, the NE num also peaked on day 1 after surgery (*P* < .05), showed a slight decrease on days 2 and 3 after surgery (while still higher than the preoperative level) (*P* < .05), and fell back to the preoperative level in week 3 after surgery (*P* > .05).

Comparison of NE num among the three groups showed that the NE num was the highest in the freeze group (*P* < .05). The NE num fell back to the preoperative level on day 3 in the RF group; namely the NE num elevation duration was shorter in the RF group than on the other groups. The NE num in the freeze and freeze3D groups fell back to the preoperative level in week 3 after surgery (Figure 1 and Table 2).

Percentage of lymphocytes (LY%): The LY% in all three groups began to decrease after surgery, reached the lowest on day 1 after surgery (*P* < .05), increased on days 2 and 3 after surgery (while still lower than the preoperative level, *P* < .05), decreased again in week 1 after surgery, and eventually rose to the preoperative level in week 3 after surgery.

Comparison among the three groups showed that the LY% reduction was the most significant in the freeze group, followed by the freeze3D and RF groups. The comparison between the two groups was statistically significant (*P* < .05). The LY% in all three groups reached the lowest on day 1 after surgery and eventually recovered to the preoperative level in week 3 after surgery (Figure 1 and Table 2).

Neutrophil-to-lymphocyte ratio (NLR): The NLR in the three groups peaked on day 1 after surgery (*P* < .05), after which the NLR level fluctuated and eventually fell back to the preoperative level in week 3 after surgery.

Comparison among the three groups showed that the peak NLR was the greatest in the freeze group, followed by the freeze3D group and RF group. However, there was no significant difference in the comparison between the two groups. The NLR in the three groups returned to the preoperative level in week 3 after surgery (Figure 1 and Table 2).

hs-CRP: The hs-CRP level in the RF group RF peaked on day 3 after surgery (*P* < .05), gradually decreased, and fell back to the preoperative level in week 2 (*P* > .05). The overall level of hs-CRP in the freeze group was lower than that in the RF group, peaked on day 3 after surgery (*P* < .05), and finally fell back to the preoperative level in week 2 after surgery. The hs-CRP level in the freeze3D group began to rise on day 1 after surgery, peaked in week 1 after surgery (*P* < .05), and fell back to the preoperative level in week 2 after surgery.

Comparison among the three groups showed that the peak hs-CRP level was greatest in the RF group, followed by the freeze and freeze3D groups. As for the peaking time, the freeze and RF groups peaked at day 3 after surgery. However, the freeze3D group peaked in week 1, which was delayed compared to the other two groups. As for the duration, the postoperative decrease in inflammatory indexes was most rapid in the RF group, and all three groups recovered to the preoperative level by week 2 after surgery (Figure 1 and Table 2).

AF recurrence: The patients with early recurrence in the freeze group included seven cases of early recurrence (10.0%) and 14 cases of long-term recurrence (20.0%), and the total recurrence was 14 cases (20.0%). In the freeze3D group, five patients (7.1%) had early postoperative recurrence and five patients (7.1%) had long-short postoperative recurrence, and the total recurrence was nine cases (12.9%). In the RF group, there were seven cases (10.0%) of early recurrence and 15 cases (21.4%) of long-term recurrence, and the total recurrence was 16 cases (22.9%). There was no significant difference in early recurrence rate among the three groups (*P* = .793). The long-term recurrence rate and the total recurrence rate in the freeze3D group were lower than in the freeze and RF groups (*P* < .05), but there was no significant difference between the freeze and RF groups (*P* > .05) (Table 3).

Relationship between inflammatory indexes and AF recurrence: In this study, the elevation degree of the inflammatory indexes was taken as the observation indicator, namely the

Table 4. Extent of elevation in biomarkers and AF recurrence

	WBC elevation	NE% elevation	NE num elevation	LY% elevation	NLR elevation	Hs-CRP elevation
Early recurrence	2.25 ± 4.05	38.58 ± 19.81	5.07 ± 3.36	-24.46 ± 17.13	6.74 ± 6.91	8.41 ± 16.38
No early recurrence	2.91 ± 2.69	23.18 ± 12.50	4.74 ± 2.78	-18.12 ± 10.69	6.58 ± 4.58	8.48 ± 12.87
P for groups	*P* = 0.33	*P* < 0.001	*P* = 0.63	*P* = 0.02	*P* = 0.89	*P* = 0.98
Late recurrence	3.81 ± 3.72	32.53 ± 16.79	4.63 ± 3.37	-24.48 ± 13.49	6.55 ± 5.69	9.24 ± 13.53
No late recurrence	3.99 ± 2.71	22.96 ± 12.86	3.82±2.79	-27.90 ± 10.96	6.62 ± 4.65	9.10 ± 13.11
P for groups	*P* = 0.74	*P* < 0.001	*P* = 0.14	*P* = 0.11	*P* = 0.93	*P* = 0.95
Recurrence	3.93 ± 3.55	32.88 ± 16.11	4.79 ± 3.23	-23.26 ± 13.15	6.53 ± 4.66	8.21 ± 12.90
No recurrence	2.83 ± 2.71	22.55 ± 12.74	3.85 ± 2.79	-26.53 ± 10.84	6.87 ± 5.52	8.26 ± 13.30
P for groups	*P* = 0.03	*P* < 0.001	*P* = 0.06	*P* = 0.10	*P* = 0.72	*P* = 0.98

Data presented as mean ± SD

difference between the peaks of the inflammatory response indexes and the preoperative levels. The elevation degree of the WCC, NE%, NE num, LY%, and NLR was the difference between the level on day 1 after surgery and the preoperative level. The elevation degree of hs-CRP was the difference between the level on day 3 after surgery and the preoperative level. The results showed that the total recurrence rate was positively correlated with the postoperative increase of WCC and NE% ($P < .05$). In addition, there was a positive correlation between early recurrence and postoperative increase of NE% ($P < .001$), and a negative correlation with the postoperative increase of LY% ($P = .02$). The long-term recurrence was positively correlated with the postoperative increase of NE% ($P < .001$) (Table 4).

DISCUSSION

AF can increase the incidence of thromboembolic disease, stroke, and the morbidity and mortality of heart failure, thus seriously affecting the life quality of patients with AF. Catheter ablation techniques play an increasingly important role in the clinical treatment of AF. At present, two main types of catheter ablation methods are used for AF. One is traditional radiofrequency ablation, which achieves pulmonary vein potential isolation through "point-to-point" circumferential pulmonary vein ablation, and the other is the frozen balloon atrial isolating surgery that recently has emerged and achieves two-way isolation of the atrial pulmonary venous potential through the balloon's frostbiting to the pulmonary vein. Different catheter ablation procedures often produce different clinical outcomes. In 2016, the "Fire and Ice" study conducted by Kuck et al showed that for PAF, cryoablation has the same clinical effect as radiofrequency ablation [Kuck 2016]. However, even in PAF, there are certain chances of postoperative recurrence, mainly related to the age of the patient, the left atrial size, and the onset time of AF [An 2018]. Furthermore, the inflammatory response after catheter ablation may affect the AF recurrence. Jin et al found that the hs-CRP level peaked on day 3 after AF catheter ablation and was associated with early postoperative AF recurrence [Jin 2018]. Subsequently, Martin et al compared the myocardial enzymes and inflammation indicators after different catheter ablation methods and found that, compared to cryoablation, the increase in hs-CRP level after radiofrequency ablation was more significant; however, there was no statistical difference in the duration of postoperative inflammation between the two methods [Martin 2012]. Moreover, Rienstra et al followed up >900 patients with AF for five years and found that patients with high WCCs were more likely to have AF [Reinstra 2012]. However, there are no definitive conclusions about the changing trend of inflammation indexes after catheter ablation in patients with AF, whether there are differences in the inflammation index after different catheter ablation methods, and whether inflammation has a correlation with postoperative AF recurrence. The current study found that the inflammation indexes in the three groups all peaked on day 1 until week 1 after surgery. The changes in WCC, NE%, LY%, and NLR were the most significant in the freeze group and relatively moderate in the RF group, which lay in the middle of the freeze3D group. The change in hs-CRP was most obvious in the RF group, and there was statistical significance in hs-CRP change between the freeze and RF groups, which can be considered to be caused by the significant pain and intraoperative stress response following radiofrequency ablation.

The relationship between AF and the inflammatory response first was proposed by Bruins et al by observing the relationship between the postoperative inflammatory response and the incidence of perioperative AF in patients undergoing coronary artery bypass grafting [Bruins 1997]. Following this observation, it was pointed out that the peak incidence of AF appeared on day 2–3 after surgery, which also was the peak period of the CRP level. Subsequently, Mukherjee found that AF and supraventricular tachycardia after radiofrequency ablation increased CRP, which was more significant in the AF group; postoperative inflammatory response and operative time, number of discharges, and area of myocardial damage were positively correlated [Mukherjee 2016]. In contrast to radiofrequency ablation, cryoablation achieves the effect of pulmonary vein isolation by cryo-frostbite and necrosis of the target, and as a result can cause obvious myocardial injury response after surgery. After comparing the myocardial injury after AF ablation and radiofrequency ablation, Schmidt et al found that the myocardial injury was more significant in the cryoablation group, but that there was no significant difference in postoperative CRP [Schmidt 2012]. Lim et al found that CRP after catheter ablation peaked to a greater extent on day 2-3 days after surgery [Lim 2014]. Postoperative CRP elevation is affected by various factors, such as intraoperative stress and pain [Afari 2011]. In recent years, inflammatory response indexes, such as WCC, neutrophils, and lymphocytes also have received increasing attention. Korantzopoulos et al found that the occurrence of AF was closely related to WCC [Korantzopoulos 2005]. Furthermore, Rienstra et al also found that the rise in the WCC was associated with the AF recurrence after catheter ablation [Rienstra 2012]. Subsequently, Weymann et al found that the WCC was associated with recurrence of atrial fibrillation, and that the ratios of neutrophils and lymphocytes, as well as the ratio between these two, were more predictive of AF recurrence [Weymann 2017]. This study found that the recurrence of postoperative AF was associated with a higher degree of postoperative WCC and NE%.

Catheter ablation procedures play an extremely important role in predicting AF recurrence. Studies have shown that the AF recurrence after catheter ablation is mostly related to the reconnection of left atrial pulmonary venous potential [Gerstenfeld 2003; Nanthakumar 2004; Mesas 2006], which is related to factors such as age, onset time of AF, left atrial anteroposterior diameter, and left atrial structural remodeling. Therefore, how permanent potential isolation can be achieved is the ultimate goal of catheter ablation. At present, the most representative catheter ablation methods against AF are radiofrequency ablation and cryoablation. Recently, the combination of cryoablation and 3D ablation has become increasingly popular. Radiofrequency ablation mainly involves the construction of a 3D model of the left atrial pulmonary vein in a 3D electroanatomic mapping system, searches for the bidirectional potential of the pulmonary vein and the left atrium at the junction of the pulmonary vein vestibule and the left atrium, and performs energy release through "point-to-point" radiofrequency ablation. The catheter performs ablation around the pulmonary vein to ultimately achieve pulmonary vein potential isolation. However, radiofrequency ablation has its limitations. First, radiofrequency ablation performs "point-to-point" circumferential pulmonary vein isolation during surgery. In this regard, there are certain possibilities of point-missing during surgery, and in thicker myocardial tissue, transmural damage may occur as a result of insufficient energy. On the other hand, the radiofrequency ablation procedure is relatively complex, has a long learning curve, and the surgical outcome is closely related to the proficiency of the surgeon; together, these represent some of the causes of postoperative AF recurrence [Chierchia 2009]. Cryoablation mainly causes transmural damage to the myocardium at the left atrial pulmonary vein junction through a decrease in the temperature of the frozen balloon, thereby achieving bidirectional isolation of the left atrial pulmonary vein potential. Studies have shown that [Chierchia 2009; Kuck 2016] cryoablation against PAF has the same effectiveness as radiofrequency ablation; however, cryoablation also has its limitations. Certain patients may have poor sealing effects of the frozen balloon due to an abnormal anatomic structure of the pulmonary vein and the left atrium, by which point the temperature of the balloon is not sufficient to achieve the effect of transmural injury, thus resulting in reconnection of pulmonary vein potential [Tzeis 2016]. Similarly, in cryoablation at the right pulmonary vein, the sacral nerve injury caused by the ablation often forces termination of the ablation, thus affecting the isolation effect of pulmonary vein potential. The emerging cryo-3D ablation technique combines the advantages of both cryoablation and radiofrequency ablation and can isolate the circumferential pulmonary vein and perform complementary ablation against the hypertrophic site of the myocardium simultaneously, thereby reducing the recurrence rate of AF. A meta-analysis by Shao et al showed that compared with simple cryoablation, cryo-3D ablation has advantages in terms of surgical effectiveness and safety [Shao 2018]. In this trial, there was no statistical significance in the early- and long-term recurrence between the RF and freeze groups, but the freeze3D group had a large advantage in the long-term and total recurrence rate.

Martin et al compared the changes of postoperative inflammatory indexes in different catheter ablation methods and found that there were certain correlations among the level of inflammatory indexes after catheter ablation, myocardial injury indexes, and ablation range; the greater the ablation range, the stronger the postoperative inflammatory response [Martin 2012]. In this trial, the WCC, NE%, LY%, and NLR in the RF group peaked on day 1 after surgery, but the hs-CRP level peaked on day 3. The mechanism was considered to be the inflammatory response around the necrotic myocardium caused by energy release through the radiofrequency ablation catheter. Deneke et al, through the cardiac anatomy of seven patients who died after radiofrequency ablation, found that the myocardial and surrounding tissues had obvious indexes of inflammatory response [Deneke 2005]. Hence, they believed that the increase in the inflammation indexes after catheter ablation were directly related to myocardial injury and necrosis and that the postoperative inflammatory response was associated with myocardial cell injury, necrosis, and entry of a large number of cytokines in the blood during postoperative myocardial reperfusion [Stein 2008]. This experiment also found that the inflammatory indexes after cryoablation and cryo-3D ablation increased on days 1 and 2 after surgery, and the hs-CRP level peaked on day 3 after surgery. Compared with radiofrequency ablation, the peak inflammatory response in the freeze and freeze3D groups were higher, and the changes in inflammatory indexes were more significant. Thus, it can be speculated that the range of freezing ablation may be larger. Furthermore, the transmural effect of freezing was more obvious, thus resulting in more significant myocardial damage and more obvious postoperative inflammatory response and duration. These finding were in agreement with those demonstrated by Martin et al. [Martin 2012].

Tselentakis et al found that inflammatory mediators can produce reversible heterogeneous inhibition toward the cardiac conduction system [Tselentakis 2006]. Consequently, they suggested that the systemic inflammatory response can lead to the occurrence, maintenance, and AF recurrence. At the same time, studies have shown that the inflammatory response can promote the secretion of adhesion factors in the epithelium of blood vessels and capture WBC in the bloodstream, thereby increasing the risk of AF recurrence [da Silva 2017]. In this study, early recurrence of PAF after catheter ablation was positively correlated with the postoperative elevation of NE%, and the total recurrence was positively correlated with the postoperative elevation of WBC and NE%. The degree of postoperative inflammatory index elevation was associated with the AF recurrence and may have predictive value for the recurrence after AF catheter ablation.

This study had several limitations. The study was a single-center observational study, and the sample size of each group was small. Therefore, some indexes may have deviations. Multicenter studies with larger sample sizes are needed to verify the study results. Moreover, the follow-up time of this study was short; hence, the relationship between inflammation and AF recurrence after catheter ablation needs to be clarified further.

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