Original Article
Risk factors for atrial fibrillation recurrence after cryoballoon catheter ablation in patients with paroxysmal atrial fibrillation

Jin Zhou[1,2], Jing Xu[2], Shan Sun[2], Aijuan Cheng[2], Peng Li[2], Jun Ding[2], Peigen Yang[2], Zhiyuan Zhang[2], Tao Fang[2], Yingchuan Yan[2], Hongliang Cong[1,2]

[1]*Tianjin Medical University, Tianjin, China;* [2]*Department of Cardiology, Tianjin Chest Hospital, Tianjin, China*

Abstract: *Objective:* This retrospective study aimed to analyze the risk factors for post-surgical atrial fibrillation (AF) recurrence in paroxysmal AF patients who underwent cryoballoon catheter ablation. *Methods:* We selected a total of 98 patients with paroxysmal AF who were treated with frozen balloon catheter ablation in Tianjin Chest Hospital from January to December in 2016. A three-dimensional (3-D) electroanatomical mapping system was used to guide the cryoballoon catheter ablation surgery. According to whether the AF recurred during postoperative follow-up (starting from 3 months after surgery), the patients were divided into AF recurrence group and sinus rhythm maintenance group. Risk factors for AF recurrence were analyzed by both univariate and multivariate logistic regression model. *Results:* Of the 98 patients, 17 were in AF recurrence group and 81 were in sinus rhythm maintenance group. Univariate analysis showed that there was significant difference between two groups in the incidence of coronary heart disease, the level of hypersensitive C-reactive protein, B-type natriuretic peptide precursor and the duration of AF (all *P* < 0.05). Multivariate logistic regression analysis identified hypersensitive C-reactive protein, type B natriuretic peptide and AF duration as the factors influencing the recurrence of AF (all *P* < 0.05). *Conclusion:* The concentration of hypersensitive C-reactive protein, B-type natriuretic peptide and the duration of AF are independent risk factors for postoperative AF recurrence in paroxysmal AF patients who undergo cryoballoon catheter ablation.

Keywords: Atrial fibrillation recurrence, cryoballoon catheter ablation, paroxysmal atrial fibrillation, multivariate logistic regression, risk factor

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia with an incidence rate of 3%-4% in the general population [1, 2]. Major serious complications of AF include heart enlargement, heart failure, organ embolism, cognitive dysfunction and dementia [3]. For AF patients who are unresponsive to antiarrhythmic drugs, AF ablation is an effective treatment [4]. There are currently two main surgical procedures for ablation therapy: radiofrequency catheter ablation (RFCA) and cryoballoon catheter ablation (CBCA) [5]. While the former is a conventional technique, the latter is a new treatment that is primarily used for patients with paroxysmal AF [6]. During the surgery, the pulmonary vein connected to the left atrium is blocked with a bal-

loon, which then releases liquid nitrogen monoxide for rapid cryogenic cooling of the surrounding tissues. As a result, the necrotic tissue causes pulmonary venous potential isolation, leading to the ablation of arrhythmia [7]. CBCA has several advantages over RFCA, such as reliable outcome, a low incidence rate of pulmonary vein stenosis and thromboembosis, and short operation time [8]. In the North American Arctic Front (STOP AF) Pivotal Trial, 13.6% of the 136 paroxysmal AF patients had recurrence during the 12-month follow-up [9]. Currently, the risk factors for AF recurrence have not been fully investigated. In this retrospective study, we therefore analyzed the risk factors for postoperative AF recurrence in paroxysmal AF patients who underwent cryoballoon catheter ablation.

Patients and methods

Patients

This retrospective study included a total of 98 paroxysmal AF patients who underwent CBCA in Tianjin Chest Hospital from January to December in 2016. There were 49 males and 49 females with an average age of 59.54±8.98 years (range: 28 to 77 years). The study was approved by the Research Ethics Committee at the Tianjin Chest Hospital. All patients had signed the informed consent for the use of clinical data.

Inclusion and exclusion criteria

Patients were selected based on the following inclusion criteria: (1) paroxysmal AF patients without valvular disease aged between 18 and 80 years; (2) no left atrial appendage thrombosis as confirmed by preoperative esophageal ultrasonography; and (3) unresponsive to anti-arrhythmic drugs. Exclusion criteria were as follows: (1) cerebrovascular attacks within six months prior to this study; (2) heart diseases such as congenital heart disease, cardiomyopathy, heart valve disease, and infective endocarditis; (3) left ventricular ejection fraction (LVEF) < 40%, and/or left atrium end diastolic diameter (LAEDD) < 50 mm; and (4) thyroid dysfunction, severe liver and kidney dysfunction, malignancy, active bleeding, and allergy to contrast agents.

Surgical procedure

Before the surgery, blood was collected from each patient for routine blood test, coagulation, and biochemical analysis. Electrocardiogram and cardiac color Doppler ultrasound was performed. During the surgery, the patients were kept in supine position, and a 6F sheath was perforated through the right internal jugular vein. A coronary sinus lead was inserted as the reference electrode. An arterial pressure monitoring catheter was placed into the left radial artery. A 6F sheath was inserted into the right femoral vein, followed by the insertion of the right ventricular electrode catheter. Guided by a J-shaped tip guidewire, a Swartz long sheath was pierced into the right femoral vein, followed by the insertion of an atrial transseptal puncture needle. Atrial transseptal puncture

was performed and left and right pulmonary vein angiography was conducted to locate the position of the pulmonary vein orifice. Under the guidance of a CARTO three-dimensional mapping system (Biosense Webster Inc., Diamond Bar, CA, USA) and a ring Achieve electrode (Medtronic Inc., Minneapolis, MN, USA), the ablation catheter was perfused with cold 0.9% saline for electric isolation. Circumferential pulmonary vein isolation (PVI) ablation was performed 1-2 times until sinus rhythm was restored and AF could no longer be induced. The patients received anticoagulant drugs for 3 months after the surgery.

Follow-up visits

After the surgery, patients underwent clinic or phone call follow-ups each month, and 24-hour Holter ECG every 3 months. ECG and 24-hour Holter ECG was performed at the earliest convenience in patients with postoperative clinical symptoms such as palpitations. Postoperative AF recurrence was defined as sustained atrial arrhythmia (AF, atrial flutter, and atrial tachycardia) lasting 30 seconds or above during any ECG test since 3 months after AF ablation. According to whether the AF recurred during postoperative follow-up, the patients were divided into AF recurrence group (AF group, n=17) and sinus rhythm maintenance group (SR group, n=81).

Statistical analysis

Statistical analysis was performed using SPSS 24.0 software (IBM SPSS., Chicago, IL, USA). Measurement data were expressed as mean ± standard deviation, and compared by student's t-tests. Enumeration data were analyzed by X^2 tests. Multivariate logistic regression was used to analyze the risk factors for AF recurrence. $P < 0.05$ was considered statistically significant.

Results

General patient characteristics

The general patient characteristics of AF and SR groups were compared. As shown in **Table 1**, there were no significant differences in the age, gender, incidence rate of hypertension and diabetes mellitus, or history of smoking and drinking between the two groups (all $P > 0.05$).

Table 1. Comparisons of basic clinical data between Comparisons of basic clinical data between AF recurrence (AF) and sinus rhythm maintenance group (SR)

Group	Case number	Age (year)	Male [n (%)]	Coronary heart disease [n (%)]	Hypertension [n (%)]	Diabetes [n (%)]	Smoking [n (%)]	Drinking [n (%)]	AF duration (year)
AF	17	57.5±9.2	9 (53)	6 (23.5)	4 (23.5)	1 (5.9)	5 (29)	3 (17.6)	11.6±7.2
SR	81	59.9±8.9	40 (49)	7 (8.6)	44 (54)	9 (11.1)	16 (19.8)	6 (7.4)	4.0±3.4
X^2 (t) value		-1.02	0.07	8.68	5.33	0.011	0.78	1.77	6.64
p value		0.312	0.790	0.028	0.208	0.922	0.381	0.178	0.009

Table 2. Comparisons of cardiac color Doppler ultrasound data between AF recurrence (AF) and sinus rhythm maintenance group (SR)

Group	Case number	LA (mm)	LV (mm)	EF (%)
AF	17	38.76±4.16	49.82±3.73	60.94±4.21
SR	81	37.75±3.73	50.56±3.64	59.96±8.93
t value		1.08	-0.77	-0.45
p value		0.281	0.442	0.646

However, the incidence rate of coronary heart disease and duration of AF (in years) in AF group was significantly higher compared with SR group (both *P* < 0.05, **Table 1**).

Both groups had similar cardiac ultrasound index

The cardiac ultrasound was performed for each patient. As shown in **Table 2**, there were no significant differences in the left atrium diastolic diameter (LA), left ventricular diastolic diameter (LV) and left ventricular ejection fraction (EF) between the two groups (all *P* > 0.05).

AF group had higher hypersensitive C-reactive protein (CRP) and B-type natriuretic peptide precursor (BNP) levels

The blood test index of the two groups was compared. Both groups had similar levels of serum potassium (K), urea nitrogen (BUN), creatine (Cre), uric acid (UA), serum albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), troponin (TnT), thrombolytic dimer (D-Dimer), white blood cell count (WBC), hemoglobin (Hb), platelet count (PLT), and thyroid stimulating hormone (TSH) (all *P* > 0.05, **Tables 3** and **4**). However, the levels of CRP and BNP in AF group were significantly higher than those in the SR group (both *P* < 0.05).

CRP, BNP, and AF duration were identified as the influencing factors for AF recurrence

The factors with significant between-group difference were further used as independent variables for multi-factor logistic regression model to analyze the risk factors for AF recurrence following cryoballoon catheter ablation. CRP, BNP, and AF duration (in years) were identified as the influencing factors for AF recurrence (all *P* < 0.05, **Table 5**).

Discussion

Cryoballoon catheter ablation is a new method of AF ablation with a higher success rate and a lower post-operational complication rate compared with the conventional radiofrequency catheter ablation [10]. Although AF commonly occurs within 1 to 3 months after surgery, most patients can recover without any intervention [11, 12]. In this study, we therefore recorded AF that recurred since 3 months after cryoballoon catheter ablation, and divided these patients into AF recurrence group and sinus rhythm maintenance group accordingly. We compared the general patient characteristics, cardiac ultrasound index, and blood test index between the tow groups by student's t test, and identified CRP, BNP and AF duration as independent risk factors for AF recurrence via multivariate logistic regression analysis.

Recent studies have shown that inflammatory factors such as CRP play an important role in the development and progression of AF [13, 14]. High levels of CRP in blood circulation are directly involved in the inflammatory response of local tissues. CRP can bind with the corresponding ligand on the cardiomyocyte membrane to activate the complement cascade, causing direct damage to myocardial cells; Moreover, the occurrence of AF is closely asso-

Table 3. Comparisons of blood test data between AF recurrence (AF) and sinus rhythm maintenance group (SR)

Group	Case number	K (mmol/L)	BUN (mmol/L)	Cre (umol/L)	UA (mmol/L)	Alb (g/L)	ALT (U/L)	AST (U/L)	CRP (mgl/L)
AF	17	4.32±0.33	5.04±1.07	69.59±12.59	319.18±75.45	44.86±4.01	24.84±12.21	22.27±8.62	10.20±17.66
SR	81	4.22±0.32	5.28±1.45	72.12±14.41	316.06±72.23	43.04±5.79	19.84±11.62	20.22±11.55	3.85±6.01
t		1.11	-0.66	-0.67	0.16	1.23	1.6	0.69	3.16
P		0.273	0.508	0.501	0.466	0.222	0.114	0.490	0.014

Table 4. Comparisons of blood test data between AF recurrence (AF) and sinus rhythm maintenance group (SR) (Cont.)

Group	Case number	LDL-C (mmol/L)	HDL-C (mmol/L)	TnT (mmol/L)	BNP (ng/mL)	D-Dimer (ug/L)	WBC (10^9/L)	Hb (g/L)	PLT (10^9/L)	TSH (mmol/L)
AF	17	3.63±0.90	1.32±0.27	0.01±0.01	422.29±81.12	0.46±0.47	6.74±2.10	142.47±17.95	253.24±57.13	2.27±1.99
SR	81	3.01±0.68	1.22±0.28	0.01±0.01	228.73±31.47	0.37±0.25	6.68±1.58	140.19±14.17	217.62±50.34	3.36±8.22
t		3.23	1.38	0.35	2.55	1.12	0.13	0.58	2.59	-0.55
p		0.168	0.170	0.723	0.014	0.262	0.903	0.574	0.109	0.329

Table 5. Logistic regression analysis for influencing factors of AF recurrence

Influencing factors	β	SE	Wald	OR (95% CI)	P
Coronary heart disease	-1.470	1.172	1.572	0.230 (1.14±12.09)	0.210
CRP	0.089	0.041	4.631	1.093 (2.37±10.35)	0.031
BNP	1.311	0.603	4.721	1.002 (43.73±353.39)	0.030
AF duration	0.317	0.083	14.52	1.374 (5.31±9.84)	0.011

ciated with the increased apoptosis and interstitial fibrosis [15]. CRP is also directly involved in the removal of apoptotic cells, which decreases the total number of atrial cells and aggravates the interstitial fibrosis [16]. Letsas *et al*. followed up 72 AF patients who underwent AF ablation for 12.5±5.7 months, and found that postoperative recurrence of AF was associated with serum CRP level [17]. Consistently, our study also identified serum CRP level as a factor influencing the recurrence of AF after cryoballoon catheter ablation.

BNP is a neurohormone synthesized by cardiomyocytes when the tension and pressure of the heart is increased. BNP has marked diuretic and natriuretic effects; It can also dilate blood vessels and inhibit the renin-angiotensin-aldosterone system; The level of BNP can directly reflect the tension of the myocardium [18]. Studies have found that high BNP content can aggravate the atrial structural and electrical remodeling, and thus is not beneficial for the maintenance of sinus rhythm during recovery from paroxysmal AF [19]. Mabuchi et al. have suggested BNP level as a biochemical marker of AF recurrence in patients with mild congestive heart failure [20], which is consistent with our finding.

A long duration of AF causes aggravated electrical and structural reconstruction of atrial cells, leading to fibrosis of atrial muscles. Consequently, different parts of the atrial muscles have inconsistent effective refractory periods, which makes it difficult to maintain the sinus rhythm [21, 22]. Irfan *et al.* have suggested an association between the duration of AF and AF recurrence after cryoballoon catheter ablation [23].

Our study has suggested that CRP and BNP level as well as the duration of AF are independent risk factors for postoperative AF recurrence in paroxysmal AF patients who undergo cryoballoon catheter ablation. The clinicians need to taken into consideration these factors when deciding whether cryoballoon catheter ablation is the appropriate surgical method for AF patients. It is worth noting that the current single-center study is largely limited by the relatively small sample size and short follow-up time (mean: 11.2 months). Further multi-center studies with longer follow-up time shall be performed to validate our findings.

Disclosure of conflict of interest

None.

Address correspondence to: Hongliang Cong, Department of Cardiology, Tianjin Chest Hospital, 261 South Taierzhuang Road, Jinnan District, Tianjin 300200, China. Tel: +86-22-88185032; Fax: +86-22-88185032; E-mail: hongliangcong@163.com

References

[1] Berkman NL, Lamb LE. The wolff-parkinson-white electrocardiogram. N Engl J Med 1968; 278: 492-494.

[2] Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, Seward JB, Tsang TS. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation 2006; 114: 119-125.

[3] Bhatia S, Sugrue A, Asirvatham S. Atrial fibrillation: beyond rate control. Mayo Clin Proc 2018; 93: 373-380.

[4] January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation 2014; 130: 2071-2104.

[5] Graves KG, Jacobs V, May HT, Cutler MJ, Day JD, Bunch TJ. Atrial fibrillation ablation and its impact on stroke. Curr Treat Options Cardiovasc Med 2018; 20: 2.

[6] Liang JJ, Muser D, Santangeli P. Approaches to catheter ablation of nonparoxysmal atrial fibrillation. Curr Treat Options Cardiovasc Med. 2018:20:39.

[7] Aryana A, Bowers MR, O'Neill PG. Outcomes of cryoballoon ablation of atrial fibrillation: a comprehensive review. J Atr Fibrillation 2015; 8: 1231.

[8] Luik A, Radzewitz A, Kieser M, Walter M, Bramlage P, Hörmann P, Schmidt K, Horn N, Brinkmeier-Theofanopoulou M, Kunzmann K, Riexinger T, Schymik G, Merkel M, Schmitt C. Cryoballoon versus open irrigated radiofrequency ablation in patients with paroxysmal atrial fibrillation. Circulation 2015; 132: 1311-1319.

[9] Packer DL, Kowal RC, Wheelan KR, Irwin JM, Champagne J, Guerra PG, Dubuc M, Reddy V, Nelson L, Holcomb RG, Lehmann JW, Ruskin JN; STOP AF Cryoablation Investigators. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American arctic front (STOP AF) pivotal trial. J Am Coll Cardiol 2013; 61: 1713-1723.

[10] Andrade JG, Dubuc M, Guerra PG, Macle L, Mondésert B, Rivard L, Roy D, Talajic M, Thibault B, Khairy P. The biophysics and biomechanics of cryoballoon ablation. Pacing Clin Electrophysiol 2012; 35: 1162-1168.

[11] Bertaglia E, Stabile G, Senatore G, Zoppo F, Turco P, Amellone C, De Simone A, Fazzari M, Pascotto P. Predictive value of early atrial tachyarrhythmias recurrence after circumferential anatomical pulmonary vein ablation. Pacing Clin Electrophysiol 2005; 28: 366-371.

[12] Vasamreddy CR, Lickfett L, Jayam VK, Nasir K, Bradley DJ, Eldadah Z, Dickfeld T, Berger R, Calkins H. Predictors of recurrence following catheter ablation of atrial fibrillation using an irrigated-tip ablation catheter. J Cardiovasc Electrophysiol 2004; 15: 692-697.

[13] Phillips KP. Role of inflammation in initiation and perpetuation of atrial fibrillation: a systematic review of the published data. J Atr Fibrillation 2013; 6: 935.

[14] Galea R, Cardillo MT, Caroli A, Marini MG, Sonnino C, Narducci ML, Biasucci LM. Inflammation and C-reactive protein in atrial fibrillation: cause or effect? Tex Heart Inst J 2014; 41: 461-8.

[15] Fordjour PA, Wang Y, Shi Y, Agyemang K, Akinyi M, Zhang Q, Fan G. Possible mechanisms of C-reactive protein mediated acute myocardial infarction. Eur J Pharmacol 2015; 760: 72-80.

[16] Alegret JM, Aragonès G, Elosua R, Beltrán-Debón R, Hernández-Aguilera A, Romero-Menor C, Camps J, Joven J. The relevance of the association between inflammation and atrial fibrillation. Eur J Clin Invest 2013; 43: 324-331.

[17] Letsas KP, Weber R, Bürkle G, Mihas CC, Minners J, Kalusche D, Arentz T. Pre-ablative predictors of atrial fibrillation recurrence following pulmonary vein isolation: the potential role of inflammation. Europace 2009; 11: 158-163.

[18] Wong PC, Guo J, Zhang A. The renal and cardiovascular effects of natriuretic peptides. Adv Physiol Educ 2017; 41: 179-185.

[19] Tsuchida K, Tanabe K. Influence of paroxysmal atrial fibrilation attack on brain natriuretic peptide secretion. J Cardiol 2004; 44: 1-11.

[20] Mabuchi N, Tsutamoto T, Maeda K, Kinoshita M. Plasma cardiac natriuretic peptides as biochemical markers of recurrence of atrial fibrillation in patients with mild congestive heart failure. Jpn Circ J 2000; 64: 765-71.

[21] Iravanian S, Dudley SC Jr. The renin-angiotensin-aldosterone system (RAAS) and cardiac arrhythmias. Heart Rhythm 2008; 5: S12-17.

[22] Takigawa M, Takahashi A, Kuwahara T, Okubo K, Takahashi Y, Watari Y, Takagi K, Fujino T, Kimura S, Hikita H, Tomita M, Hirao K, Isobe M. Long-term follow-up after catheter ablation of paroxysmal atrial fibrillation: the incidence of recurrence and progression of atrial fibrillation. Circ Arrhythm Electrophysiol 2014; 7: 267-273.

[23] Irfan G, de Asmundis C, Mugnai G, Poelaert J, Verborgh C, Umbrain V, Beckers S, Hacioglu E, Hunuk B, Velagic V, Stroker E, Brugada P, Chierchia GB. One-year follow-up after second-generation cryoballoon ablation for atrial fibrillation in a large cohort of patients: a single-centre experience. Europace 2016; 18: 987-993.