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Original Article

Predictive value of CTRP3 for the disease recurrence of atrial fibrillation patients after radiofrequency ablation

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Abstract: Objective: To explore the expression of plasma CTRP3 in patients with non-valvular paroxysmal atrial fibrillation after radiofrequency ablation and its predictive value for disease recurrence. Methods: In this retrospective study, the patients in the Heart Center of Beijing Chaoyang Hospital from June 2016 to November 2017 were collected. According to the guidelines for diagnosis and treatment of atrial fibrillation 2016, patients diagnosed with paroxysmal atrial fibrillation were selected as the study subjects. All patients with successful radiofrequency ablation of atrial fibrillation were followed up by telephone or outpatient service at 1, 3, 6 and 12 months after radiofrequency ablation, respectively. Recurrence of atrial fibrillation was defined as a duration of rapid atrial arrhythmia ≥30 seconds confirmed by electrocardiogram or 24-hour ambulatory electrocardiogram 3 months after radiofrequency ablation. According to the follow-up results, the patients were divided into a recurrent group and non-recurrent group. The level of CTRP3 was detected by enzyme-linked immunosorbent assay (ELISA). Results: Analysis of clinical baseline data showed significant differences between the recurrent group and the non-recurrent group in age, systolic blood pressure, diastolic blood pressure, EGFR, thyroid stimulating hormone level, platelet count, high-sensitivity C-reactive protein, NT proBNP, left atrial anterior posterior diameter, left atrial upper and lower diameter and CTRP3 ($P < 0.05$). The univariate logistic regression showed that older age (or = 1.08, $P < 0.001$), increased diastolic blood pressure (OR = 1.051, P = 0.002), cardiac dysfunction (OR = 2.594, P = 0.01), high-sensitivity C-reactive protein (OR = 1.134, P = 0.008) and NT proBNP (OR = 1.000, P = 0.005), increased anterior posterior diameter of left atrium (OR = 1.158, $P < 0.001$), increased upper and lower diameter of left atrium (OR = 1.133, $P < 0.001$), thrombocytopenia (OR = -0.008, $P < 0.027$) and CTRP3 (OR = 1.007, P = 0.006) were the risk factors for the recurrence of atrial fibrillation after radiofrequency ablation. Moreover, the multivariate logistic regression analysis demonstrated that CTRP3 (or = 1.032, P = 0.005) was an independent predictor of recurrence. Conclusion: The plasma concentration of CTRP3 increased significantly in patients with recurrent atrial fibrillation after radiofrequency ablation. Moreover, CTRP3 was a predictor of recurrence after radiofrequency ablation in patients with atrial fibrillation.

Keywords: Atrial fibrillation, atrial fibrosis, catheter ablation, recurrence, CTRP3

Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias. Currently, 33 million people suffer from AF, which is expected to be tripled in the next 40 years. Atrial fibrillation increases the risk of stroke, myocardial infarction, heart failure, dementia and chronic kidney disease (CKD) [1]. The incidence of atrial fibrillation increases rapidly with age, and most patients are over 65 years old. The increase in the prevalence of atrial fibrillation will put an economic burden on patients, families, and society. Some research showed that epicardial adipose tissue (EAT) had an effect on the occurrence and development of AF. EAT plays a role through the secretion of adipokines, and its mechanism involves inflammation, atrial structural remodeling, and fibrosis.

Adipose tissue plays a role by secreting adipokines. Studies have found that some adipokines had effect on occurrence of AF [4-6]. Classical adipokines had an effect on the occurrence and development of AF [7, 8]. In addition, some researchers have found that EAT may

directly participate in AF [9, 10] through inflammatory factors. In the rabbit heart failure model, the level of adiponectin in atrium and peripheral adipose tissue increased, while tumor necrosis factor decreased and the incidence of atrial fibrillation decreased [11]. Adiponectin has also been reported to be related to human atrial structural remodeling. One study showed that adiponectin was associated with atrial septal thickness and left atrial volume [12]. Shimano et al. [13] suggested that adiponectin had an effect on the occurrence and maintenance of AF.

Complement C1q/tumor necrosis factor associated protein (CTRP) is a superfamily of adipokines. It is structurally similar to adiponectin. Studies have shown that CTRP3 can inhibit myocardial fibrosis, and has a protective effect on myocardial infarction and diabetic myocardial injury [14, 15]. The aim of this study was to assess whether plasma CTRP3 is a risk factor for the recurrence of AF and to further explore the possible mechanism of adipokines involved in the occurrence and development of AF. This will provide new targets for treatment and prediction of recurrence.

Data and methods

Clinical data

In this retrospective study, 216 patients diagnosed with paroxysmal atrial fibrillation treated in the Beijing Chaoyang Hospital from June 2016 to November 2017 were selected as the research objects. The study was approved by the Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (Approval No. 20160502).

Inclusion and exclusion criteria

Inclusion criteria: ① Patients with non-valvular paroxysmal atrial fibrillation who underwent radiofrequency ablation in our hospital; The diagnosis of atrial fibrillation refers to the definition of atrial fibrillation in Current Understanding and Treatment Suggestions 2015: the diagnostic standard of paroxysmal atrial fibrillation is that 12 lead body surface ECG indicates atrial fibrillation. The onset time is less than 7 days. Atrial fibrillation can occur repeatedly at different frequencies; ② Patients with preoperative antiarrhythmic drug withdrawal for at least five half-lives; ③ Patients who were excluded from left atrial thrombosis by complete transesophageal ultrasound before operation; ④ Patients who voluntarily accepted relevant examinations before and after operation and follow-up.

Exclusion criteria: ① Patients with organic heart disease complicated with dilated cardiomyopathy, hypertrophic cardiomyopathy, rheumatic heart disease and severe valve disease; ② Patients combined with thrombosis, tumor or other abnormalities or diseases that hinder catheter operation; ③ Patients with atrial fibrillation secondary to thyroid disease, disordered electrolytes, or other reversible non cardiac factors; ④ Patients with transesophageal echocardiography showing left atrial thrombosis; ⑤ Patients with contraindications to anticoagulant therapy; ⑥ Patients who cannot cooperate to complete relevant examinations before and after operation and follow-up; and ⑦ Pregnant or lactating women.

Intervention

All patients received radiofrequency ablation. The patient lay flat on the catheter bed and underwent ECG monitoring to monitor the heart rhythm. Routine disinfection, towel laying, local anesthesia and medium and deep sedation were performed on the patients. The right femoral vein was punctured and the short sheath of 8F vein was insert. Intravenous heparin administration was used to maintain the activated clotting time (ACT) between 250-300 s during the operation. The ten-pole coronary sinus electrode was sent to the coronary sinus through the left femoral vein, and the ablation electrode (lasso electrode, BioSense Webster, USA) was placed into the left atrium through the femoral vein. The three circumference anatomical images of left atrial activation sequence were reconstructed under the mapping of Carto three-dimensional mapping system, bilateral circumferential pulmonary vein ablation was performed, and bilateral pulmonary veins were mapped with annular mapping catheter respectively. If pulmonary vein potential had still been mapped, radiofrequency ablation could be supplemented until isolation. If a typical atrial flutter had been induced by atrial programmed stimulation after pulmonary vein isolation, additional ablation of the right atrial isthmus to

bidirectional block should be performed. If there was a trigger focus from outside the pulmonary vein during the operation, the trigger focus shall be removed by relevant isolation at the same time (such as segmental electrical isolation of vena cava). The end point of catheter ablation was the electrical isolation state of bilateral pulmonary veins and the bidirectional block of relevant linear ablation.

All patients with successful radiofrequency ablation of atrial fibrillation were followed up. Outpatient visits and 12 lead ECG or 24-hour ambulatory ECG were arranged at the 1st, 3rd, 6th, 12th month and every half a year after operation. If the patient couldn't go to the clinic, the ECG and ambulatory ECG results were recorded through telephone follow-up. The end point of follow-up was recurrence of atrial fibrillation. Recurrence of atrial fibrillation was defined as the onset duration of tachyarrhythmia ≥ 30 seconds confirmed by ECG or 24-hour ambulatory ECG 3 months after radiofrequency ablation. According to the follow-up results, they were divided into a recurrence group and non-recurrence group.

Observation index

Cardiac ultrasound: After admission, the patients were examined by color Doppler ultrasound (Philips EPIQ 7C) by professional physician to measure the end diastolic diameter of left ventricle, end systolic diameter of left ventricle, anterior posterior diameter of left atrium, upper and lower diameter of left atrium, left ventricular ejection fraction, ventricular septal thickness and other indexes. According to the American Society of Echocardiography (ASE) guidelines, the modified Simpson method was used to measure the left ventricular ejection fraction.

Plasma CTRP3 detection: Enzyme linked immunosorbent assay (ELISA) was used. The ELISA kit of CTRP3 was purchased from Jianglai Biology, Shanghai Future Industry Co., Ltd. All patients underwent intravenous blood collection of 5 ml under fasting state. All samples were allowed to stand at room temperature for 1 hour. After the blood samples were fully solidified, they were separated for 15 minutes by desktop high-speed centrifuge at the speed of 3000 r/min. The upper plasma was separated, numbered uniformly, sub-packed in EP tube, stored in -80°C refrigerator, and ELISA detection of serum CTRP3 was carried out in batches.

Statistical analysis

IBM spss23 software package was used to process the data. The measured data that met the normality and homogeneity of variance were expressed as mean ± standard deviation (X±s), and analyzed using t-test. The measured data that did not conform to the normal distribution were expressed by the median (P_{25}, P_{75}), and the Kruskal Wallis test was used for inter-group comparison. The counted data were expressed in frequency and independent sample t-test or rank sum test was used to compare the difference of circulating CTRP3 expression between the recurrent group and non-recurrent group in patients with paroxysmal atrial fibrillation after radiofrequency ablation. Taking the recurrence of atrial fibrillation after radiofrequency ablation as the dependent variable, various clinical data were included, and the risk factors of the recurrence of atrial fibrillation after radiofrequency ablation were analyzed by univariate logistic regression. After adjusting the related variables, multivariate logistic regression was used to analyze whether plasma CTRP3 concentration was an independent factor for the recurrence of atrial fibrillation after radiofrequency ablation. $\alpha = 0.05$ was the test level, and the difference was statistically significant when $P < 0.05$ (2-sided).

Results

Clinical characteristics

Totally 216 patients were enrolled in this study, including 45 patients with recurrence (recurrence group) and 171 patients without recurrence (non-recurrence group). There was no significant difference in the gender ratio, body mass index, history of coronary heart disease, renal insufficiency, hyperthyroidism, sleep apnea, hypertension, diabetes, hyperlipidemia, carotid stenosis, or smoking history and drinking history (all $P > 0.05$). There were significant differences between the two groups in age, systolic blood pressure, diastolic blood pressure and history of cardiac insufficiency (all $P < 0.05$) (**Table 1**).

Table 1. Clinical characteristics of two groups

		Recurrence Group (n = 45)	Non-recurrence group (n = 171)	*P Value*
Gender	Male	25 (55.6%)	98 (57.3%)	0.833
	Female	20 (44.4%)	73 (42.7%)	0.817
Age		71.1±8.3	64.3±10.4	0.000
BMI (kg/m^2)		28.8±4.3	25.9±3.1	0.880
Systolic pressure (mmHg)		137.5 (120.0-147.5)	130.0 (119.0-138.0)	0.044
Diastolic pressure (mmHg)		81.5±13.2	75.7±9.9	0.001
Coronary heart disease		19 (43.2%)	75 (44.4%)	0.887
Cardiac insufficiency		33 (73.3%)	88 (51.5%)	0.008
Renal insufficiency		5 (11.4%)	9 (5.3%)	0.148
Hyperthyroidism		1 (2.2%)	4 (2.3%)	0.963
Sleep apnea		2 (4.4%)	2 (1.2%)	0.148
Hypertension		33 (73.3%)	104 (60.8%)	0.122
Diabetes		12 (26.7%)	45 (26.3%)	0.962
Hyperlipidemia		37 (84.1%)	129 (75.9%)	0.247
Smoking		14 (31.8%)	63 (37.3%)	0.504
Drinking		6 (13.6%)	33 (19.5%)	0.371

Table 2. Comparison of laboratory indices between the two groups ($\bar{x}$±s)

	Recurrence Group (n = 45)	Non-recurrence group (n = 171)	*P Value*
Total cholesterol (mmol/L)	3.9±0.9	4.1±0.9	0.232
Triglyceride (mmol/L)	1.1 (0.8-1.8)	1.3 (1.0-1.7)	0.510
High density lipoprotein (mmol/L)	1.1 (0.9-1.3)	1.0 (0.9-1.2)	0.776
Low density lipoprotein (mmol/L)	2.2±0.8	2.4±0.8	0.356
Aspartate aminotransferase (U/L)	20.5 (16.8-24.3)	20.0 (16.0-23.0)	0.305
Alanine aminotransferase (U/L)	18.0 (13.0-25.0)	18.0 (13.0-27.0)	0.944
eGFR (ml/min1.73m^2)	80.3 (65.9-101.3)	91.1 (79.5-96.6)	0.005
Creatinine (umol/L)	75.9 (61.3-84.3)	71.4 (59.7-78.2)	0.053
Uric acid (umol/L)	412.5 (336.5-461.3)	351.0 (316.0-416.0)	0.130
Fasting blood glucose (mmol/L)	5.1 (4.1-5.9)	5.0 (4.4-5.7)	0.257
Glycosylated hemoglobin (%)	5.9 (5.5-6.6)	5.9 (5.6-6.5)	0.427
TSH (μIU/ml)	2.4 (1.2-4.5)	1.9 (1.2-3.0)	0.027
White blood cell (10^9/L)	6.5 (5.2-6.9)	6.3 (5.1-7.2)	0.708
Hemoglobin (g/L)	132.2±15.5	137.9±21.5	0.099
Platelet (10^9/L)	185.0 (141.3-215.0)	206.0 (177.5-245.5)	0.049
High sensitivity C-reactive protein (mg/dl)	1.6 (0.7-5.6)	1.2 (0.7-3.0)	0.037
NT-proBNP (pg/ml)	524.5 (137.3-1399.8)	158.0 (78.7-350.8)	0.000002
Troponin I (ng/ml)	0.5 (0.0-2.9)	0.8 (0.0-4.1)	0.331
CTRP3 (ng/ml)	54.5 (27.2-146.5)	25.9 (14.5-67.6)	0.00002

Comparison the laboratory index between the two groups

As shown in **Table 2**, there was no significant difference in total cholesterol, triglycerides, high density lipoprotein, low density lipoprotein, aspartate aminotransferase, alanine aminotransferase, creatinine, uric acid, fasting blood glucose, glycosylated hemoglobin, leukocyte count, hemoglobin and troponin I peak between recurrence group and non-recurrence group (all $P > 0.05$); however, there were significant differ-

Table 3. Comparison of Cardiac ultrasound indices between the two groups ($\bar{x}$±s)

	Recurrence group (n = 45)	Non-recurrence group (n = 171)	*P Value*
Left atrial anteroposterior diameter (mm)	41.9±4.9	38.9±4.4	0.00001
Superior and inferior diameter of left atrium (mm)	55.9±5.0	52.3±5.5	0.00003
Ejection fraction	65.0 (61.0-67.0)	67.0 (63.5-69.0)	0.106
Left ventricular end diastolic diameter (mm)	47.0 (45.5-52.0)	48.0 (45.5-50.0)	0.567
Left ventricular end systolic diameter (mm)	30.0 (26.8-34.0)	30.7 (27.5-33.0)	0.825

Note: Compared with the recurrence group, significant difference as P < 0.05.

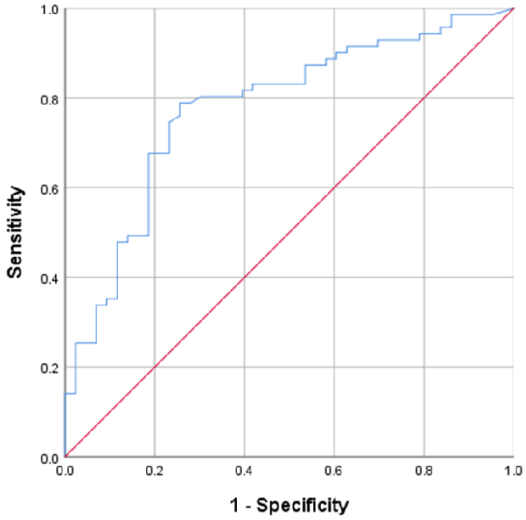

Figure 1. ROC curve analysis of CTRP3 predicting recurrence of atrial fibrillation after radiofrequency ablation.

ences between the two groups in EGFR, TSH, platelet count, high-sensitivity C-reactive protein, NT pro-BNP and ctrp3 (all P < 0.05).

Comparison of cardiac ultrasound index between the two groups

There was no significant difference in left ventricular ejection fraction and left ventricular end diastolic diameter between recurrent group and non-recurrence group (P > 0.05, but there was significant difference in left atrial anterior posterior diameter and left atrial upper and lower diameter (all P < 0.05) (**Table 3** and **Figure 2**).

Univariate and multivariate logistic regression analysis

We assessed the recurrence of AF after radiofrequency ablation in selected patients, the data included plasma CTRP3 levels, age, BMI, systolic blood pressure, diastolic blood pressure, coronary heart disease, heart failure, renal insufficiency, hyperthyroidism, sleep apnea, hypertension, diabetes, total cholesterol, triglyceride, high-density lipoprotein, low density lipoprotein, and glutamic pyruvic transaminase. Univariate and multivariate logistic regression analysis were performed. As shown in the **Tables 4** and **5**, older age, increased diastolic blood pressure, cardiac insufficiency, increased high-sensitivity C-reactive protein, NT proBNP, CTRP3, left atrial anterior posterior diameter, left atrial upper and lower diameter, and decreased platelet count were risk factors for recurrence of atrial fibrillation after radiofrequency ablation. Moreover, the multivariate logistic regression analysis demonstrated that CTRP3 level was an independent related factor for the recurrence of atrial fibrillation after radiofrequency ablation (P = 0.005).

ROC curve analysis of CTRP3 predicting recurrence of atrial fibrillation after radiofrequency ablation

ROC curve analysis showed that the AUC of CTRP3 in predicting the recurrence of atrial fibrillation after radiofrequency ablation was 0.778 [(95% CI, 0.690-0.866), P = 0.005] (**Figure 1**).

Discussion

In order to explore the predictive effect of CTRP3 on the recurrence of atrial fibrillation after radiofrequency ablation, we took the recurrence of atrial fibrillation after radiofrequency ablation as the dependent variable and various variables including the plasma CTRP3 concentration, and conducted univariate logistic regression analysis [16]. Results showed

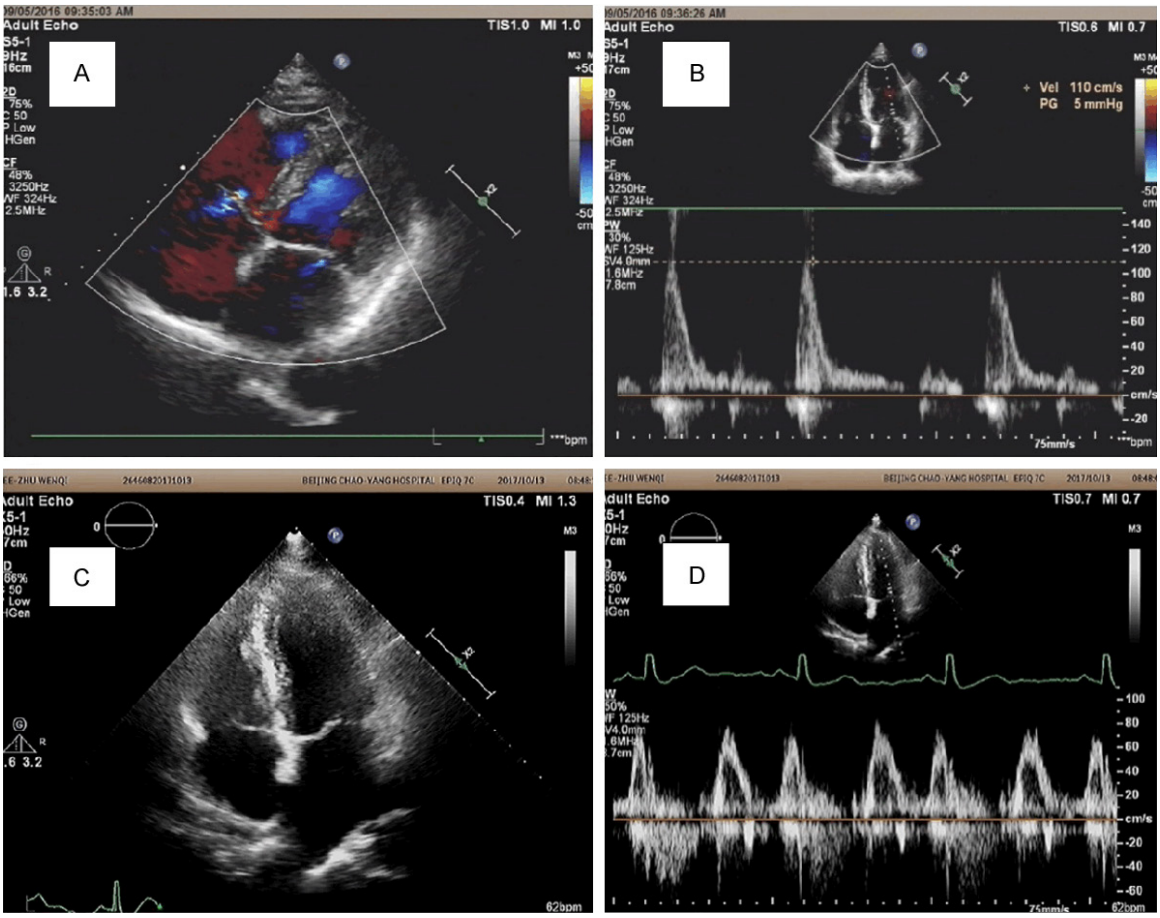

Figure 2. Cardiac ultrasound images of two groups. A, B: Cardiac ultrasound images of recurrence patient; C, D: Cardiac ultrasound images of non-recurrence patient.

that plasma CTRP3 was a risk factor for the recurrence of atrial fibrillation after radiofrequency ablation, which agrees with some other research [17-20]. Moreover, Romero et al. found that there was no significant correlation between CTRP3 and coronary heart disease [21], the reason being that the population of this study was coronary heart disease patients taking hypoglycemic drugs, in which the hypoglycemic drugs influenced the concentration of CTRP3.

CTRP3 is abundantly expressed in adipose tissues and heart tissues. Relevant clinical and basic studies have found that CTRP3 can regulate endocrine, glucose and lipid metabolism, immune, and inflammatory reactions [22, 23]. In recent years, the effect of CTRP3 on myocardial fibrosis has attracted extensive attention. Studies have shown that CTRP3 inhibits TGF by activating AMP activated protein kinase (AMPK)-β 1 induced Smad3 nuclear translocation and binding with P300 to inhibit the phenotypic transformation of myofibroblasts [24], thereby reducing the production of connective tissue growth factor, type I and type III collagen, and further inhibiting myocardial fibrosis [25]. Relevant studies have also found that the expression of CTRP3 is inhibited in the stage of myocardial remodeling after myocardial infarction. Supplementing exogenous CTRP 3 can reduce the myocardial infarction area, inhibit myocardial fibrosis and myocardial remodeling, and increase the survival rate of myocardial infarction mice [26-28]. This suggests that CTRP3 may play a significant role as a new therapeutic target in inhibiting myocardial fibrosis, reducing cardiac remodeling and improving cardiac function. CTRP3 can also inhibit the proliferation of vascular smooth muscle cells and myocardial fibrosis, so as to improve ventricular remodeling. Structural re-

Table 4. Univariate logistic regression analysis

	β	SE	OR (95% CI)		*P*
Age (years old)	0.077	1.08	1.038	1.123	< 0.001
BMI (kg/m^2)	-0.007	0.993	0.911	1.083	0.880
systolic pressure (mmHg)	0.018	1.018	0.999	1.037	0.063
Diastolic pressure (mmHg)	0.050	1.051	1.018	1.085	0.002
Coronary heart disease	-0.049	0.953	0.488	1.860	0.887
Cardiac insufficiency	0.953	2.594	1.255	5.358	0.010
Renal insufficiency	0.830	2.293	0.728	7.227	0.156
Hyperthyroidism	-0.052	0.949	0.103	8.705	0.963
Sleep apnea	1.369	3.93	0.538	28.704	0.177
Hypertension	0.572	1.772	0.855	3.671	0.124
Diabetes	0.018	1.018	0.484	2.141	0.962
CTRP3 (ng/ml)	0.007	1.007	0.996	1.108	0.006
eGFR (ml/min1.73m^2)	-0.011	0.989	0.985	0.993	0.079
TSH (μIU/ml)	0.172	1.188	1.016	1.388	0.310
Platelet (10^9/L)	-0.008	0.993	0.986	0.999	0.027
High sensitivity C-reactive protein (mg/dl)	0.126	1.134	1.034	1.244	0.008
NT-proBNP (pg/ml)	0.000	1.000	1.000	1.001	0.005
Troponin I (ng/ml)	-0.088	0.916	0.820	1.023	0.120
Left atrial anteroposterior diameter (mm)	0.147	1.158	1.069	1.255	< 0.001
Superior and inferior diameter of left atrium (mm)	0.125	1.133	1.060	1.212	< 0.001
Ejection fraction	-0.019	0.982	0.944	1.021	0.360
Left ventricular end diastolic diameter (mm)	0.008	1.008	0.929	1.094	0.850
Left ventricular end systolic diameter (mm)	0.013	1.013	0.948	1.084	0.695

Table 5. Multivariate logistic regression analysis

	B	SE	OR (95% CI)	P
CTRP3 (ng/ml)	0.032	0.011	1.032 (1.010-1.056)	0.005
Diastolic pressure (mmHg)	0.072	0.088	0.098 (0.954-1.023)	0.489
Cardiac insufficiency	1.102	0.982	1.23 (0.9378-1.515)	0.079
Platelet (10^9/L)	0.554	0.119	1.048 (0.488-2.249)	0.905
High sensitivity C-reactive protein (mg/dl)	0.092	0.674	1.005 (0.999-1.010)	0.096
NT-proBNP (pg/ml)	0.078	0.227	1.004 (0.971-1.037)	0.823
Left atrial anteroposterior diameter (mm)	0.076	0.682	1.000 (0.988-1.011)	0.944
Superior and inferior diameter of left atrium (mm)	0.167	0.228	1.002 (0.998-1.006)	0.387

modeling caused by atrial fibrosis is an important factor affecting the occurrence and recurrence of atrial fibrillation. The plasma CTRP3 concentration in patients with persistent atrial fibrillation is lower than that in patients with paroxysmal atrial fibrillation [29].

Furthermore, CTRP3 is also an effective anti-inflammatory mediator, that is negatively correlated with pro-inflammatory cytokines, interleukin-6 and C-reactive protein [30]. Studies have proven that inflammation is involved in the occurrence and development of atrial fibrillation. Our study found the correlation between CTRP3 and high-sensitivity CRP, but its specific mechanism needs further exploration. CTRP3 promotes the osteogenic differentiation of vascular smooth muscle cells induced by phosphate [31], resulting in the increase of vascular calcium ions, which will accelerate arteriosclerosis and aging [32, 33].

Undeniably, this study has some limitations. First, this study is a single center study with small sample size and non-continuous observation. There might be a certain degree of

selection bias in the selection of patients. Second, we failed to collect epicardial adipose tissue to detect the expression of CTRP3. The expression of plasma CTRP3 cannot fully represent the expression of CTRP3 in tissues. Third, this study is a retrospective analysis, which did not explain the causal relationship between CTRP3 and atrial fibrillation. The exact mechanism of CTRP3 in atrial fibrillation needs further animal research and molecular cell biology study.

Conclusion

The plasma concentration of CTRP3 increased significantly in patients with recurrent atrial fibrillation after radiofrequency ablation. Moreover, CTRP3 is a predictor of disease recurrence for patients with atrial fibrillation after radiofrequency ablation.

Disclosure of conflict of interest

None.

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