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Original Article

Clinical observation of a secondary ablation in the treatment of blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation

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Abstract: Objective: To evaluate the therapeutic effect of secondary ablation in the treatment of blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation. Methods: Forty patients with blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation were selected as the observation group, and forty patients without blank-period tachycardia-bradycardia syndrome were randomly selected as the control group at the same time. By a twelve-channel real-time holter monitor, the preoperative and postoperative heart rate variability (HRV) indicators in the two groups were analyzed and compared, and the postoperative recovery of patients in the observation group after a second ablation were observed. Finally, twelve-channel real-time holter monitor was used to evaluate the recovery of sinus node function in the two groups, two weeks and three months after the surgery. Results: From 2,000 cases of atrial fibrillation catheter ablation, there were 40 patients with blank-period tachycardia-bradycardia syndrome (the incidence rate was 2.0%). There were no statistical differences in baseline data between the two groups (P>0.05). In the control group, HRV indicators (SDANN, rMSSD, PNN50, HF, VLF) decreased significantly (P<0.05), while SDNN and LF increased markedly after surgery (all P<0.05). After the first ablation in the observation group, HRV indicators showed no significant differences compared with those before the surgery (all P>0.05), but after the second ablation, HRV indicators were significantly reduced (all P<0.05). The results of the follow-up with a twelve-channel real-time holter monitor showed that the maximum RR interval (MRRI) and MRRI>2 s (NP>2 s) were significantly lower than those before surgery (both P<0.05), while the minimal heart rate (MIHR), maximum heart rate (MAHR) and mean heart rate (MEHR) were significantly higher than those before surgery (all P<0.05). Conclusion: The incidence rate of blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation is 2%. In addition, a second ablation can effectively reduce the occurrence of cardiac arrhythmia in patients with blank-period tachycardia-bradycardia syndrome within 3 months after the surgery, which contributes to the recovery of the function of the sinus node and helps achieve a good therapeutic purpose.

Keywords: Atrial fibrillation, atrial fibrillation ablation, blank-period tachycardia-bradycardia syndrome, heart rate variability

Introduction

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, which is characterized by irregular heartbeat frequency and high heart rate up to 100-160 beats/min. Too fast of a heart rate will cause the atrium lose its normal and effective systolic function, leading to the occurrence of disease [1]. With the overall aging of the general population, the widespread existence and increase in predisposing factors in the environment, as well as the improvement of various detection methods, the incidence of AF is increasing, and the age of the population of patients with AF is also gradually becoming younger [2]. Currently, drug therapy is the first choice for the treatment of paroxysmal AF in clinical practice. After the failure of drug therapy, cardiac radiofrequency catheter ablation, as a relatively mature and invasive treatment method, is widely used in the follow-up treatment of paroxysmal AF [3]. Although the therapeutic effect of radiofrequency ablation is significantly better than that

of antiarrhythmic drugs, patients still have a certain probability of AF recurrence after surgery [4].

At present, three months after the surgery is considered to be the blank period, during which the occurrence of rapid atrial arrhythmia accompanied by a long interval is called tachycardia-bradycardia syndrome. The treatment of the blank-period tachycardia-bradycardia syndrome is closely related to the prognosis. Therefore, this study retrospectively analyzed the clinical data of some patients with AF who underwent radiofrequency ablation in Lvliang People's Hospital, focused on the comparison and analysis of some relevant indicators before and after surgery, and conducted follow-up to track the prognosis of patients, aiming to analyze the blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation and observe the therapeutic effect of a subsequent secondary ablation.

Materials and methods

Research subjects

A case-control method was used in this study, and 40 patients with blank-period tachycardia-bradycardia syndrome after paroxysmal atrial fibrillation ablation in Lvliang People's Hospital from July 2007 to June 2018 were collected as the observation group. In addition, 40 patients who underwent paroxysmal atrial fibrillation ablation at the same time without blank-period tachycardia-bradycardia syndrome were randomly selected as the control group. A secondary atrial fibrillation ablation was performed on patients in the observation group after they were diagnosed with blank-period tachycardia-bradycardia syndrome. This study was approved by the Ethics Committee of Lvliang People's Hospital.

Inclusion criteria: Patients aged from 30 to 65 years old; patients with paroxysmal AF who were not well treated or could not tolerate two or more antiarrhythmic drugs; patients who met the indications of radiofrequency ablation (twelve-channel real-time holter monitor showed >3 s sinus arrest at the moment of termination of AF, and ultrasound cardiogram showed that the left cardiac function was normal, anteroposterior diameter of left atrium was <45 mm, and the left ventricular ejection fraction (LVEF) was >50%); patients who had normal thyroid function; patients who were excluded from having atrial thrombus by transesophageal ultrasound; patients who stopped taking antiarrhythmic drugs for at least 5 drug half-lives before surgery.

Exclusion criteria: Patients with long-term or permanent AF, markedly hypertrophic and enlarged left atrium, or decreased heart function; patients who had severe heart disease with or without heart failure; patients with diseases or abnormalities that could impede catheter operation such as thrombus or tumors; patients with contraindications to anticoagulant drugs.

Preoperative preparation

Some routine laboratory tests were performed before surgery, mainly including standard 12-lead electrocardiogram (ECG) and twelve-channel real-time holter monitor, transthoracic echocardiography and chest X-ray examination. Warfarin was discontinued 3 days before radiofrequency ablation and patients were switch to low-molecular-weight heparin (100 U/kg), which was discontinued 12 hours before surgery. It was necessary to make sure that the antiarrhythmic drugs had been discontinued for at least 5 drug half-lives. Transesophageal echocardiography was performed within 24-36 hours before surgery to exclude left atrial thrombus, and the anatomical structures of the left atrium and pulmonary vein were clarified by computed tomography.

Electrophysiological examination and radiofrequency ablation method

All surgical operations were performed under local anesthesia. The CARTO three-dimensional mapping system was used to monitor the cold saline perfusion, and the 10-pole catheter was placed into the coronary sinus through the puncture of the left jugular vein or the left femoral vein. After successful puncture of the atrial septum through the right femoral vein, two SL1 SWARTZ sheath tubes were placed in the left atrium for feeding the LASSO electrode and cold saline perfusion catheter. Bilateral venography and routine electrophysiological examination were used to confirm the origin point before electrode ablation. According to the patient's condition, 80-100 U/kg of hepa-

rin was injected intravenously as the first dose, and then 1,000 U was added per hour to keep the blood coagulation time at 250-300 s. The CARTO mapping system was used to establish the three-dimensional models of the left atrium and pulmonary veins. The ablation catheter was perfused with ordinary cold saline to keep its upper limit temperature <43°C, and the ablation power was controlled at about 30-35 W. During the operation, point by point ablation was performed bilaterally around the pulmonary veins to make sure they were completely isolated, and the discharge at each point was required to be more than 30 s. Pulmonary vein potential was then measured by the mapping catheter. If the potential could be detected, ablation was supplemented until the pulmonary vein potential disappeared completely or could not be transmitted to make sure the pulmonary vein was fully separated. For patients with cavotricuspid isthmus-dependent atrial flutter or tachycardia before or during surgery, additional linear ablation was required at the tricuspid valve, mitral valve and left atrial tops until bi-directional block appeared.

Postoperative management

The patients continued to receive subcutaneous injection of low-molecular-weight heparin calcium (100 U/kg) after surgery (Shenzhen Saibaoer Biopharmaceutical Co., Ltd. H2005-2319, China). On the day after surgery, warfarin (Shanghai Xudong Haipu Pharmaceutical Co., Ltd. H31020112, China) was administered orally for at least 3 months, and the international standard ratio (INR) was monitored to keep it at 2.0-3.0. Transthoracic echocardiography test and administration of proton pump inhibitor omeprazole (Changchun Haiyue Pharmaceutical Co., Ltd. H20054900, China) were used to exclude and prevent postoperative pericardial tamponade and atrial esophageal fistula. Cordarone was administered one week after surgery.

Postoperative observation and follow-up

The patients underwent a 24-hour twelve-channel real-time holter monitor examination at 1 week and 3 months after surgery to regularly observe the sinus node function and to record some indicators that could reflect the function of the sinus node, such as the maximun RR interval (MRRI), the number of times that the interval >2 s (NP>2 s), maximum heart rate (MAHR), minimal heart rate (MIHR) and mean heart rate (MEHR), as well as preoperative and postoperative HRV indicators. If, within 3 months after the surgery, if the patient had obvious palpitations, dizziness and other symptoms, they were required to go through the outpatient follow-up and have an ECG or holter examination. In addition, at 3, 6 and 12 months after surgery, regular outpatient or telephone follow-up was required to track the prognosis of patients, so as to evaluate the therapeutic effect of the surgery and determine whether the patients had complications.

HRV indicators

The genius twelve-channel real-time holter monitor system (Beijing Jinco Medical Equipment Co., Ltd., China) was used to monitor the HRV indicators before and 2 days after surgery, including standard deviation of RR intervals (SDNN), standard deviation of the average normal RR intervals for all 5-minute segments (SDANN), the square root of the mean of the squared differences between adjacent normal RR intervals (rMSSD), percent of the number of time that the difference between adjacent normal RR intervals is greater than 50 ms in the total number of NN intervals (PNN50), low frequency (LF), high frequency (HF) and very low frequency (VLF) [5].

Definition of postoperative blank-period tachycardia-bradycardia syndrome

It is known that 3 months after radiofrequency ablation for AF a blank period can occur; during which patients can have many occurrences of apparent atrial arrhythmia or may complain of a strong feeling of recurrence of AF, and then an ECG confirmation of, atrial flutter or atrial tachycardia, etc. with a duration of >30 s is performed. At the same time, there were different degrees of sinus arrest for more than 3 s after the termination of the attack, with or without long intermittent sinus bradycardia, sinus arrest, etc., and then it was defined as a blank-period tachycardia-bradycardia syndrome [6].

Statistical analysis

SPSS 20.0 statistical software was used to analyze the related data. The measurement

Table 1. Baseline data analysis

Variable	Observation group (n=40)	Control group (n=65)	χ^2/t	P
Age (year)	59.8±3.6	61.6±2.6	0.407	0.689
Gender (male)	22 (55.0%)	24 (60.0%)	0.025	0.821
Course of disease (month)	61.9±3.6	60.6±3.3	0.264	0.794
Hypertension (n)	17 (42.5%)	16 (40.0%)	0.052	0.820
Diabetes (n)	12 (30.0%)	9 (22.5%)	0.581	0.446
Coronary heart disease (n)	6 (15.0%)	8 (20.0%)	0.346	0.556
Left atrial inner diameter (mm)	41.90±1.52	41.50±1.11	0.212	0.834
Left ventricular ejection fraction (%)	57.10±1.34	55.40±1.50	0.844	0.409

Table 2. Comparison of HRV indicators before and one week after the first radiofrequency ablation in the observation group

Variable	Before-treatment	Post-treatment	t	P
SDNN (ms)	146.3±28.11	154.1±6.08	0.769	0.451
SDANN (ms)	167.8±16.57	176.5±24.14	0.612	0.869
rMSSD (ms)	126.7±24.32	116.5±22.78	0.798	0.426
PNN50 (ms)	27.6±0.73	26.7±1.04	1.424	0.137
LF (ms^2)	784.3±137.31	749.9±90.46	0.758	0.484
HF (ms^2)	1279±256.01	1203±146.18	0.642	0.529
VLF (ms^2)	2002±264.41	1965±221.66	0.628	0.592

Note: SDNN: standard deviation of RR intervals; SDANN: standard deviation of the mean of all 5 minutes segments of normal RR intervals; rMSSD: root mean square successive difference between adjacent normal RR intervals; PNN50: percent of difference between adjacent normal RR intervals that was longer than or equal to 50 ms; LF: low frequency; HF: high frequency; VLF: very low frequency.

Table 3. Comparison of HRV indicators before and one week after the first radiofrequency ablation in the control group

Variable	Before-treatment	Post-treatment	t	P
SDNN (ms)	150.2±27.36	166.4±34.26	2.746	0.007
SDANN (ms)	176.2±35.72	166.5±24.14	2.982	0.006
rMSSD (ms)	86.6±14.00	86.5±22.78	2.151	0.043
PNN50 (ms)	25.3±2.70	19.7±1.04	2.373	0.019
LF (ms^2)	732.3±140.50	749.9±90.46	2.825	0.005
HF (ms^2)	1210±240.17	1203±146.18	2.753	0.006
VLF (ms^2)	1972±3201.22	1965±221.65	2.805	0.005

Note: SDNN: standard deviation of RR intervals; SDANN: standard deviation of the mean of all 5 minutes segments of normal RR intervals; rMSSD: root mean square successive difference between adjacent normal RR intervals; PNN50: percent of difference between adjacent normal RR intervals that was longer than or equal to 50 ms; LF: low frequency; HF: high frequency; VLF: very low frequency.

data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) or median, and analyzed by two independent samples t test or repeated measures analysis of variance, and Dunnett method was adopted for post hoc comparison. The enumeration data were evaluated by the chi-square test. P<0.05 was considered as statistically significant.

Results

General information

A total of 80 patients were included in the study, including 46 males and 34 females with an average age of 60.7± 6.3 years old. Some patients had complications such as hypertension (33 cases, 41.25%), diabetes (21 cases, 26.25%) and coronary heart disease (13 cases, 16.25%). The baseline data of patients in the two groups such as age, gender, course of disease, complications, inner diameter of the left atrium and left ventricular ejection fraction showed no statistical significance (all P>0.05), as shown in **Table 1**.

Comparison of HRV indicators before and after the first radiofrequency ablation

There were no statistically significant differences in HRV indicators before the first radiofrequency ablation between the observation group and the control group (P>0.05), as shown in **Table 2**. In the observation group, there were no statistically significant differences in HRV indicators before and one week after the first ablation. In the control group, the HRV indicators (SDANN, rMSSD, PNN50, HF, VLF) were significantly lower than those before surgery, and more significantly lower than those in the observation group, while SDNN and LF were significantly higher than those before surgery (both P<0.05). See **Tables 2** and **3** for details.

Table 4. Comparison of HRV indicators before and after a second radiofrequency ablation in the observation group

Variable	Before-treatment (n=40)	One week after the second ablation (n=40)	t	P
SDNN (ms)	146.3±28.11	96.5±13.65	2.784	0.006
SDANN (ms)	167.8±16.57	93.2±22.61	2.802	0.005
rMSSD (ms)	126.7±24.32	85.2±12.67	2.543	0.014
PNN50 (ms)	27.6±0.73	19.6±0.81	2.954	0.004
LF (ms^2)	784.3±137.31	428.0±123.02	2.725	0.008
HF (ms^2)	1279±256.01	578.6±134.20	2.105	0.039
VLF (ms^2)	2002±264.40	905.5±329.95	2.468	0.018

Note: SDNN: standard deviation of RR intervals; SDANN: standard deviation of the mean of all 5 minutes segments of normal RR intervals; rMSSD: root mean square successive difference between adjacent normal RR intervals; PNN50: percent of difference between adjacent normal RR intervals that was longer than or equal to 50 ms; LF: low frequency; HF: high frequency; VLF: very low frequency.

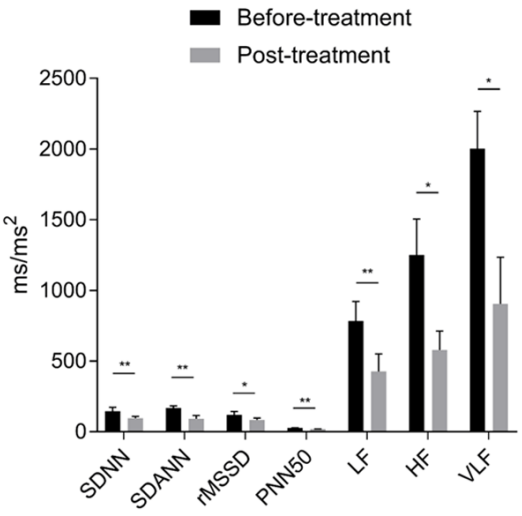

Figure 1. Comparison of HRV indicators before and after a second radiofrequency ablation in the observation group. Compared with preoperative level, *P<0.05, and **P<0.01. SDNN: standard deviation of RR intervals; SDANN: standard deviation of the mean of all 5 minutes segments of normal RR intervals; rMSSD: root mean square successive difference between adjacent normal RR intervals; PNN50: percent of difference between adjacent normal RR intervals that was longer than or equal to 50 ms; LF: low frequency; HF: high frequency; VLF: very low frequency.

Comparison of HRV indicators before and one week after the second radiofrequency ablation in the observation group

After the second ablation, the recurrence of AF in the observation group was significantly lower than that before the surgery, and HRV indicators were also significantly lower than those after the first ablation (all P<0.05), as shown in **Table 4** and **Figure 1**.

Changes of twelve-channel real-time holter monitor in both groups before and after radiofrequency ablation

Twelve-channel real-time holter monitor results showed that the MRRI and NP>2 s at one week and three months after the surgery in the control group were significantly lower, and the MIHR, MAHR and MEHR were significantly higher than those before surgery (all P<0.05), as shown in **Table 5**. In the observation group, there were no significant changes at one week after the first ablation compared with the preoperative results, while the indicators of the twelve-channel real-time holter monitor results at one week and three months after the second ablation were significantly improved compared with the preoperative results (all P<0.05), as shown in **Table 6**.

Discussion

AF is the most common type of arrhythmia. With the changes of the external environment, increase in existing pathogenic factors, the incidence trend is becoming younger, and the incidence rate is also increasing. As an increasingly mature treatment method, paroxysmal atrial fibrillation catheter radiofrequency ablation has been widely used in clinical treatment of AF in recent years [7]. The period of three months after ablation is considered as the blank period, during which some patients still have AF, atrial tachycardia, and long intervals after termination, which is defined as the blank-period tachycardia-bradycardia syndrome [8].

In the past 10 years, the incidence rate of blank-period tachycardia-bradycardia syndrome in Lvliang People's Hospital was about 2%. The data of these patients and those without blank-period syndrome during the same period were analyzed and showed that the HRV indicators, twelve-channel real-time holter monitor and other indicators were sig-

Table 5. Comparison of preoperative and postoperative twelve-channel real-time holter monitor results in the control group

Variable	Before-treatment (n=40)	One week after the surgery (n=40)	Three months after the surgery (n=40)	F	P
MRRI (s)	5.420±0.467	2.170±0.9195*	1.720±0.6110*	34.341	<0.001
NP>2 s (time)	112.8±23.543	32.40±11.157*	2.950±0.8062*	19.983	0.003
MIHR (beats/min)	36.00±5.9309	43.10±8.005*	53.80±9.555*	59.846	<0.001
MAHR (beats/min)	87.50±3.243	105.3±2.418*	128.8±2.909*	12.594	0.008
MEHR (beats/min)	55.70±10.461	65.50±15.641*	74.00±11.832*	23.499	0.002

Note: Compared with preoperative level, *P<0.05. MRRI: maximum RR interval; NP>2 s: the number of times that the interval >2 s; MIHR: minimal heart rate; MAHR: maximum heart rate; MEHR: mean heart rate.

Table 6. Comparison of preoperative and postoperative twelve-channel real-time holter monitor results in the observation group

Variable	Before the ablation (n=40)	One week after the first ablation (n=40)	One week after the second ablation (n=40)	Three months after the second ablation (n=40)	F	P
MRRI (s)	5.4±1.165	5.3±0.87	1.6±0.76*	2.2±1.15*	39.423	<0.001
NP>2 s (time)	119.5±25.77	116.9±22.83	46.5±12.83*	3.5±0.27*	43.669	<0.001
MIHR (beats/min)	32.4±7.85	31.9±8.44	36.3±6.61*	54.9±8.15*	32.652	<0.001
MAHR (beats/min)	86.2±12.31	83.9±11.13	107.2±12.83*	128.3±11.57*	85.614	<0.001
MEHR (beats/min)	56.5±11.27	53.7±11.62	65.6±10.78*	73.3±10.43*	31.701	<0.001

Note: Compared with preoperative level, *P<0.05. MRRI: maximum RR interval; NP>2 s: the number of times that the interval >2 s; MIHR: minimal heart rate; MAHR: maximum heart rate; MEHR: mean heart rate.

nificantly improved in patients who received effective ablation treatment. Studies have shown that the autonomic nervous system of the heart can affect and participate in the initiation and maintenance of AF, and HRV is an indicator that can effectively reflect autonomic nervous function at present [9]. Among HRV indicators, the ratio of LF to HF is mainly used to reflect the change of sympathetic and vagus nerve balance, and SDNN, rMSSD and SDANN are mainly related to the changes of sympathetic and vagus nerve tension [10]. After ablation, the values of these indicators were significantly lower than those before surgery, indicating a change in the autonomic nervous system of the heart, which is associated with AF. Further studies have found that rapid atrial stimulation can lead to the reconstruction of the autonomic nervous system of the heart, which is manifested by increased activity of atrial sympathetic nerves and heterogeneity of the sympathetic nerves, thus triggering AF [11].

Currently, there are mainly two kinds of antiarrhythmia drugs for the treatment of AF [12]. The first kind of drug is used to convert AF and restore sinus rhythm, including quinidine, propafenone and amiodarone, mainly acting on the atria to prolong atrial refractory period and slow down intra-atrial conduction [13]. The second kind of drugs are those that can slow down the ventricular rate and act on the atrioventricular node in order to prolong the refractory period and increase the conduction [14]. Therefore, the main purpose of using drugs is to relieve the condition, reduce and prevent the occurrence of AF. However, when drug therapy is ineffective or the efficacy is not obvious, catheter ablation is used for the treatment of AF. The main therapeutic mechanism of catheter ablation is to destroy the left atrial ganglion and atrial muscle tissue around the pulmonary vein orifices by radiofrequency energy, and electrically isolate the pulmonary vein to eliminate the electrical potentials of pulmonary vein and atrium, so as to inhibit or eliminate the initiation of AF and to destroy the regulation of autonomic nerves on the heart [15, 16]. Therefore, complete isolation of pulmonary veins during ablation is crucial to the denervation of vagus nerve. Ablation of pulmonary veins may cause vagus nerve in-

jury, and the injured vagus nerve may promote or optimize the efficacy of pulmonary vein related AF ablation [17].

The recurrence of AF after radiofrequency catheter ablation may be related to the incomplete isolation of pulmonary veins during the operation to some extent, manifesting by no significant differences in the HRV indicators of patients with blank-period tachycardia-bradycardia syndrome before and after the surgery, which may be due to the incomplete isolation of the pulmonary vein and cardiac sympathetic nerves that continue to trigger AF. This speculation needs to be confirmed by further relevant experiments. Secondary ablation can effectively make up for the deficiency of the first ablation, and further completely separate the pulmonary veins to achieve the purpose of inducing the ablation of AF [18, 19]. Therefore, after a second ablation, all HRV indicators of patients have been significantly improved, and the twelve-channel real-time holter monitor results also indicate that the sinus node function has returned to normal. However, some studies have also shown that the early recurrence of AF after ablation may be related to the fact that radiofrequency ablation destroys the efferent autonomic nerve innervation, resulting in local surplus of neurotransmitters, which are released and then activate AF again [20, 21]. In this regard, some patients may have recurrent clinical symptoms of AF within a few days after the surgery, but after a period of time, the symptoms of AF disappear, and there is no recurrence of AF at a later follow-up [22]. As a result, the recurrence rate of AF is relatively high in the short term after ablation. For patients with early recurrence of AF arrhythmia, a three-month blank period is necessary for better observation and determination of the condition.

The results of this study showed that patients with a blank-period tachycardia-bradycardia syndrome after the first catheter ablation could be effectively treated by a second ablation, and the recovery of sinus node function can be determined by HRV indicators and the twelve-channel real-time holter monitor. At present, the incidence of blank-period tachycardia-bradycardia syndrome is relatively low. Therefore, we need further research and analysis to understand the prognosis of these patients, so that they can be better treated and cured.

Disclosure of conflict of interest

None.

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