Initial experience with ablation of the innervation surrounding sinus and atrioventricular nodes to treat paroxysmal bradyarrhythmia

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Abstract

Background: The symptomatic bradyarrhythmia is Class I indication for pacing therapy which is not a radical cure. The present study aimed to assess the feasibility and to present the initial results of the restricted ablation of the parasympathetic innervation surrounding sinus and atrioventricular (AV) nodes for treating patients with bradyarrhythmia.

Methods: A total of 13 patients with cardiogenic syncope were included from May 2008 to June 2015. Under the guidance of fluoroscopy and /or three-dimensional geometry by 64-slice spiral computed tomography, atrial activation sequence in sinus rhythm was mapped. Chamber geometry was reconstructed manually or automatically using the Niobe II magnetic navigation system integrated with the CARTO-remote magnetic technology (RMT) system. Cardioneuroablation was targeted at the high-amplitude fractionated electrograms surrounding the regions of His bundle and the site with the earliest activation in sinus rhythm. Areas surrounding the sinus node, AV node, and the phrenic nerve were avoided.

Results: Thirteen patients completed the studies. Ablation was successfully performed in 12 patients and failed in one. The high-frequency potential was recorded in atrial electrograms surrounding the sinus or AV nodes in all the patients and disappeared in 15 s after radiofrequency applications. The vagal reaction was observed before the improvement of the sinus and AV node function. No complications occurred during the procedures. Patients were followed up for a mean of 13.0 ± 5.9 months. During the follow up ten patients remained free of symptoms, and two patients had a permanent cardiac pacemaker implanted due to spontaneous recurrence of syncope. The heart rate of post-ablation was higher than pre-ablation (69.0 ± 11.0 *vs*. 49.0 ± 10.0 beats/min, $t = 4.56$, $P = 0.008$). The sinus node recovery time, Wenckebach block point, and atrium-His bundle interval were significantly shorter after ablation (1386.0 ± 165.0 *vs*. 921.0 ± 64.0 ms, $t = 7.45$, $P = 0.002$; 590.0 ± 96.0 *vs*. 464.0 ± 39.0 ms, $t = 2.38$, $P = 0.023$; 106.0 ± 5.0 *vs*. 90.0 ± 12.0 ms, $t = 9.80$, $P = 0.013$ before and after ablation procedure, respectively).

Conclusions: Ablation of sinoatrial and AV nodal peripheral fibrillar myocardium electrical activity might provide a new treatment to ameliorate paroxysmal sinus node dysfunction, high degree AV block, and vagal-mediated syncope.

Keywords: Electrophysiology; Radiofrequency ablation; Sinus node dysfunction; Atrioventricular block; Syncope

Introduction

Symptomatic bradyarrhythmia is Class I indication for pacing therapy which is not a radical cure. Patients experiencing refractory bradyarrhythmia episodes have a poor quality of life and high risk of bradyarrhythmia-related physical injuries. Although pacing therapy is effective in treating severe symptomatic bradyarrhythmia, complications after pacemaker implantation are commonly seen, such as pacemaker bag infection, dislocation of the pacemaker lead, pacemaker syndrome, premature exhaustion of pacemaker batteries and pacemaker-related cardiac perforation, and so on.

It has been recently reported that ablation of the cardiac autonomic parasympathetic innervations by spectral mapping for the treatment of patients with sinus node dysfunction and atrioventricular (AV) block caused by increased vagal tone action could help to exempt the implantation of a pacemaker.[1-10] The above-mentioned approach was performed by on-line spectral analysis with special instruments. However, non-selective ablation of cardiac ganglia may affect the regulation of the autonomic nervous system on myocardial nutrition and the function of coronary arteriovenous flow. Therefore, we suggested a restricted ablation of the parasympathetic innervation surrounding sinus and AV nodes, so that cardiac ganglia would not be damaged.

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In this study, we reported a method and results of restricted ablation of the parasympathetic innervation surrounding sinus and atrioventricular nodes (AVNs) for the treatment of patients with functional bradyarrhythmia.

Methods

Ethical approval

The retrospective study was approved by the Institutional Ethics Committee of the Beijing Anzhen Hospital (No. 015026X). All patients provided written informed consent.

Patients enrollment

A total of 13 patients (nine women, four men, mean age of 36.0 ± 9.0 years) with cardiogenic syncope and apparently normal heart (left ventricular ejection fraction = $65.3\% \pm 4.0\%$) were included in the study from May 2008 to June 2015 [Table 1]. All patients had: (1) neurally mediated reflex syncope with spontaneous and recurrent episodes (mean 4.5 ± 2.0 syncope/patient) refractory to medical treatment; (2) recurrent palpitations, fatigue, chest tightness, dizziness, fainting, and other symptoms; (3) no structural cardiopathy; (4) electrocardiogram (ECG) or Holter monitoring done, showing high degree of AV block [Figure 1] or sinus dysfunction; (5) functional bradycardia confirmed by normal response to atropine test.[11] Patients with coronary artery disease, myocarditis, myocardiopathy, or valvular heart disease were excluded.

Study protocol

The patients underwent electrophysiological (EP) study and catheter ablation. Surface and intra-cardiac ECGs were digitally recorded and stored (PruckaCardioLab EP System, GE Healthcare, Waukesha, WI, USA). Non-fluoroscopic three-dimensional mapping was performed in each case either using the Carto (Biosense-Webster, Diamond Bar, CA, USA) or the Niobe II magnetic navigation system (Stereotaxis Inc., StLouis, MO, USA) integrated with CARTO-remote magnetic technology (RMT) system (Biosense Webster, Inc. 33 Technology Drive Irvine, CA, USA)[12] at the operator's discretion.

The conventional EP leads were placed properly, and multiple electrode catheter was advanced into the heart and placed at the right atrium and ventricle, at the His bundle and within the coronary sinus. A routine EP study was carried out under local anesthesia. Sinus node recovery time (SNRT), Wenckebach block point (WP), AV conduction time, atrium-His bundle (AH), and His bundle-ventricle (HV) interval and their changes were recorded before and after ablation. Bipolar electrograms were recorded with a bandpass filter at 30 to 500 Hz using a 4-mm-tip mapping/ablation catheter (NaviStar, Biosense Webster, Diamond Bar, CA, USA).

Ablation of the parasympathetic innervation

Ablation target location

An electroanatomic shell of the right atrium was created, and the atrial activation sequence was recorded during sinus rhythm in all patients [Figure 2]. Pace mapping was performed around the sinus node. The location of each pacing site was tagged on the electroanatomic map. The electroanatomic map confirming precise anatomy and catheter location was merged with a pre-procedural computed tomographic (CT) angiogram of the right atrium. Detailed activation mapping during sinus rhythm was performed in the right atrium and AVN region to

Table 1: Clinical information and ablation results on the patients.

Case	Gender	Age (years)	DOS	Complaint	Diagnosis	Immediate reflection post-ablation	Outcome	Follow-up (months)	Symptom
1	M	28	6 months	Palpitation/dizziness	High AVB, junctional rhythm	WP reduced	Successful	20	Disappeared
2	F	38	2 years	Dyspnea/palpitation	Junctional rhythm	WP reduced	Successful	20	Relapsed
3	M	41	3 months	Dizziness/amaurosis	SSS	HR initially fast then slowed down	Successful	19	Disappeared
4	M	36	6 months	Palpitation/dizziness	Sinus bradycardia	HR initially fast then slowed	Successful	19	Disappeared
5	M	47	1month	Fatigue/dizziness	Junctional rhythm	SNRT reduced	Failed	17	Pacemaker
6	F	44	5 months	Palpitation	Junctional rhythm	WP reduced	Successful	14	Disappeared
7	M	39	1 month	Palpitation/dizziness	Junctional rhythm	WP reduced	Successful	12	Disappeared
8	M	37	1 year	Palpitation/syncope	High AVB	WP reduced	Successful	11	Relapsed
9	M	51	24 years	Palpitation/syncope	SSS	HR initially fast then slowed, SNRT reduced	Successful	11	Disappeared
10	M	38	6 months	Dizziness/amaurosis	SSS	HR initially slowed then fast, SNRT reduced	Successful	11	Disappeared
11	F	14	6 months	Palpitation/dizziness	High AVB, junctional rhythm	HR initially slowed then fast, WP reduced, SNRT reduced	Successful	9	Disappeared
12	M	30	3 months	Palpitation/syncope	High AVB	AH initially longer then shorten, WP reduced	Successful	9	Disappeared
13	F	29	2 years	Palpitation/dizziness	SSS	HR initially slowed then fast, SNRT reduced	Successful	9	Disappeared

DOS: Duration of symptoms; M: Male; F: Female; AVB: Atrioventricular block; SSS: Sick sinus syndrome; WP: Wenckebach block point; HR: Heart rate; SNRT: Sinus node recovery time; AH: Atrium to bundle of his time.

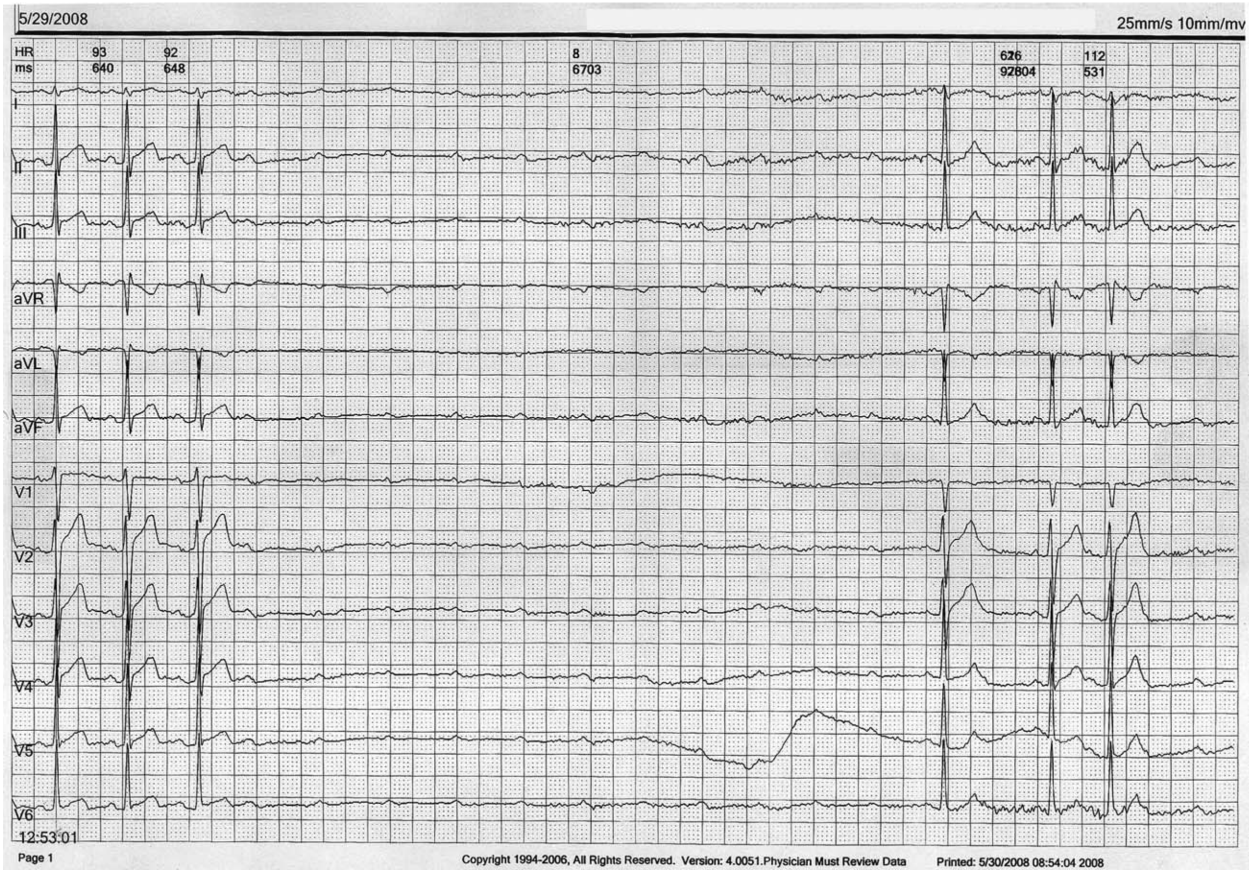

Figure 1: 12-lead ECG of paroxysmal high degree atrioventricular block, from a 30-year-old male patient. The patient had recurrent syncope after starvation, with positive results from the tilt test, and electrophysiological study of the heart did not show any abnormality. ECG: Electrocardiogram.

locate the potential neural-interface tissue as an ablation target.

Ablation procedure

Radiofrequency (RF) applications were applied to the site that exhibited the fibrillar myocardium potential bipolar activity (contains high-frequency spike[13]) during sinus rhythm with a target temperature of 50°C and starting power of 20 W, which was gradually titrated to a maximum power of 45 W. Significant fibrillar myocardium electrical potential was regarded as a valid ablation target. If potential disappearance occurred in the first 10 s, RF delivery typically was continued for an additional 10 s. If potential disappearance did not occur in the first 10 to 15 s of RF delivery, RF delivery was terminated and the catheter was repositioned. RF ablation was first performed with a 4-mm, standard, non-irrigated catheter. An irrigated catheter was used only if inadequate power delivery occurred with a standard 4-mm-tip catheter. The maximum power delivery was 30 W with the irrigated ablation catheter. The temperature-controlled ablation mode: the temperature was set to 60°C, power was set to 45 W, and the discharge time was 30 to 60 s. Fibrillar pattern potential disappearance was regarded as a valid discharge. 100 to 500 Hz frequency bandpass filter was used, and high-frequency spike potentials around the sinus node and AVN inside the right atrium were recorded. Restricted ablation for 10 to 15 s was carried out in part of the patients, followed by the disappearance of high-frequency potential. During the ablation procedure, vagus effects such as sinus bradycardia, slow junctional ectopic beat, and AH interval prolongation may take place, which was not serious.

The procedures were aimed at achieving the following: (1) Elimination or attenuation of the fibrillar myocardium electrical activity surrounding the sinus and AV node regions; (2) Persistent increase in the sinus rate (increased by 20%) and/or SNRT shortening by 20%; (3) Persistent reduction in the WP (<500 ms) and/or persistent shortening in the AH interval (≥ 20 ms) [Figure 3].

Post-ablation medication

Oral anti-coagulant (warfarin) to maintain the prothrombin time between two and three international normalized ratios was prescribed for a 1-month post-ablation followed by aspirin (100 mg/day for 5 months).

Follow-up

The follow-up consisted of clinical evaluation (at discharge, ≥1 month and every 3 months), ECG (at discharge, ≥1 month and every month), Holter (every month and in case of symptoms). The patients and clinic physicians were

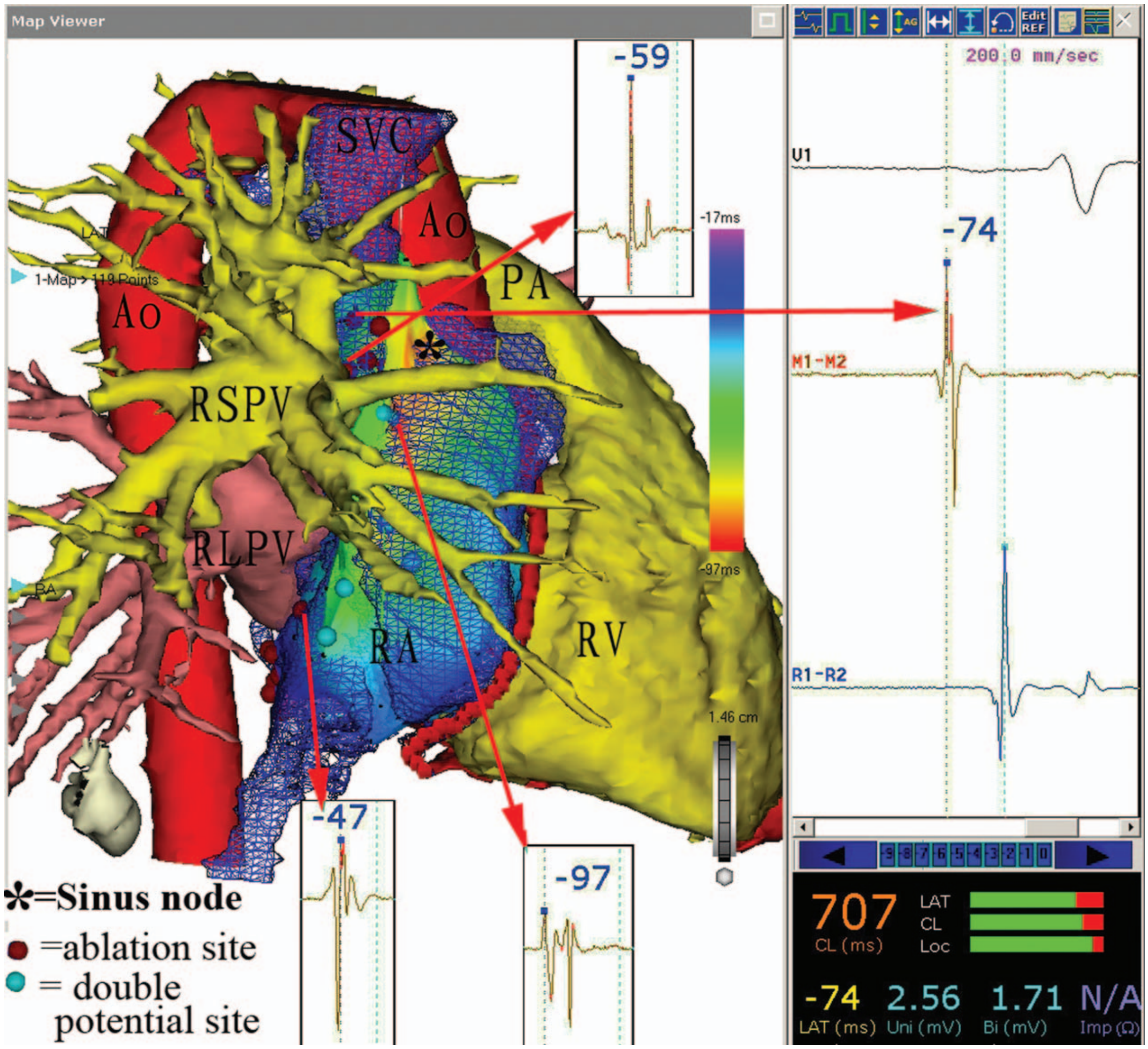

Figure 2: The sequence of the right atrium activation, combined with spiral CT three-dimensional imaging of the heart, showing the double potentials of the earliest stimulatory site and the high-frequency potential of the fibrillar myocardium ablation targets. The arrows show high-frequency potential. AO: Aorta; CT: Computer tomography; PA: Pulmonary artery; RA: Right atrium; RLPV: Right lower pulmonary vein; RSPV: Right upper pulmonary vein; RV: Right ventricle; SVC: Superior vena cava.

regularly contacted by phone. The primary endpoint was the spontaneous recurrence of syncope. Relapsing brady-arrhythmias by Holter was considered to be a secondary endpoint.

Statistical analysis

The data with normal distribution were presented as mean ± standard deviation, and an independent sample t-test was used to assess the difference between the two groups. Other continuous data with abnormal distribution were shown as median (Q1, Q3). Categorical data were presented as percentages (cases/absolute numbers). Correlations between continuous variables were quantified using the Spearman correlation coefficient (ρ). The differences between groups were analyzed by the Fisher exact tests for the categorical data and by the Mann-Whitney U test for the continuous data. A P value <0.05 was considered statistically significant. Statistical analyses were done by IBM SPSS statistics 22.0 (IBM SPSS Inc., Chicago, IL, USA).

Results

Ablation procedure feature

A total of 13 ablations were performed in 13 patients (one for each). Immediate success was achieved in 12 cases, and one procedure (case 5) failed with persistent high degree AV block. The heart rate of post-ablation was higher than pre-ablation (69.0 ± 11.0 *vs.* 49.0 ± 10.0 beats/min, $t = 4.56$, $P = 0.008$). The SNRT, WP, and AH interval were significantly shorter after ablation (1386.0 ± 165.0 *vs.* 921.0 ± 64.0 ms, $t = 7.45$, $P = 0.002$; 590.0 ± 96.0 *vs.* 464.0 ± 39.0 ms, $t = 2.38$, $P = 0.023$; 106.0 ± 5.0 *vs.* 90.0 ± 12.0 ms, $t = 9.80$, $P = 0.013$ before and after ablation procedure, respectively) [Table 2]. There were no major complications. One male patient (case 3) had an

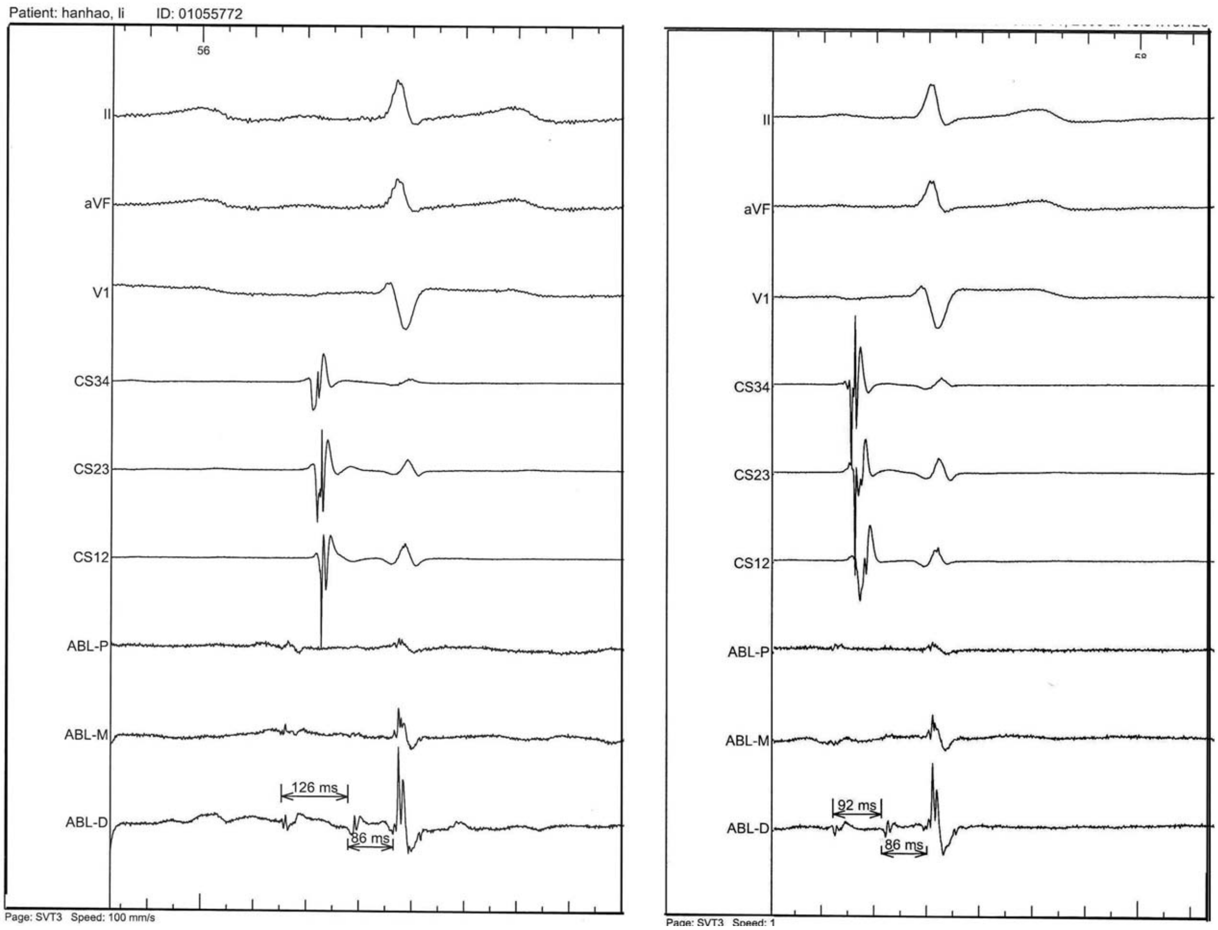

Figure 3: AH interval was shortened by ≥20 ms at the same site after ablation. AH: Atrial his; CSD: Coronary distal; CSM: Coronary sinus medium; CSP: Coronary sinus proximal.

Table 2: EPS data in patients pre- and post-ablation.

Parameters	*n*	Post-ablation	Pre-ablation	*t*	*P*
HR (beats/min)	9	69.0 ± 11.0	49.0 ± 10.0	4.56	0.008
SNRT (ms)	5	921.0 ± 64.0	1386.0 ± 165.0	7.45	0.002
WP (ms)	7	464.0 ± 39.0	590.0 ± 96.0	2.38	0.023
AH interval (ms)	6	90.0 ± 12.0	106.0 ± 5.0	9.80	0.013
HV interval (ms)	6	46.0 ± 20.0	45.0 ± 22.0	2.50	0.936

Values are presented as mean ± standard deviation. EPS: Electrophysiological study; HR: Heart rate; SNRT: Sinus node recovery time; WP: Wenckebach block point; AH: Atrial his; HV: His ventricular.

ablation target in the superior vena cava. His heart rate was markedly raised during ablation, with an increase of blood pressure, chest tightness, shortness of breath, but no ST-T change. These symptoms disappeared 1 h after the ablation. Sinus heart rate was fast initially in case 13 during ablation but was slowed down 10 min later.

Follow-up

In a mean follow-up of 13.0 ± 5.9 months (7.0–20.4 months), syncope was not observed in ten patients. Spontaneous recurrence of syncope occurred in two patients (case 2 and case 8) due to bradyarrhythmias relapse verified by Holter and thus permanent cardiac pacemaker was implanted. The patients were discharged after 2 days.

Discussion

Our data suggest that ablation of the fibrillar myocardium around the sinus and AVN may be an effective treatment of vagus-mediated slow arrhythmias. It has been shown that in the atrial electrogram of all the patients, high-frequency spike potentials disappeared within 10 to 15 s of RF releasing. Transient bradyarrhythmia may be observed during ablation [Figure 4], followed by sinus and AVN functional improvement. After ablation, HR increased

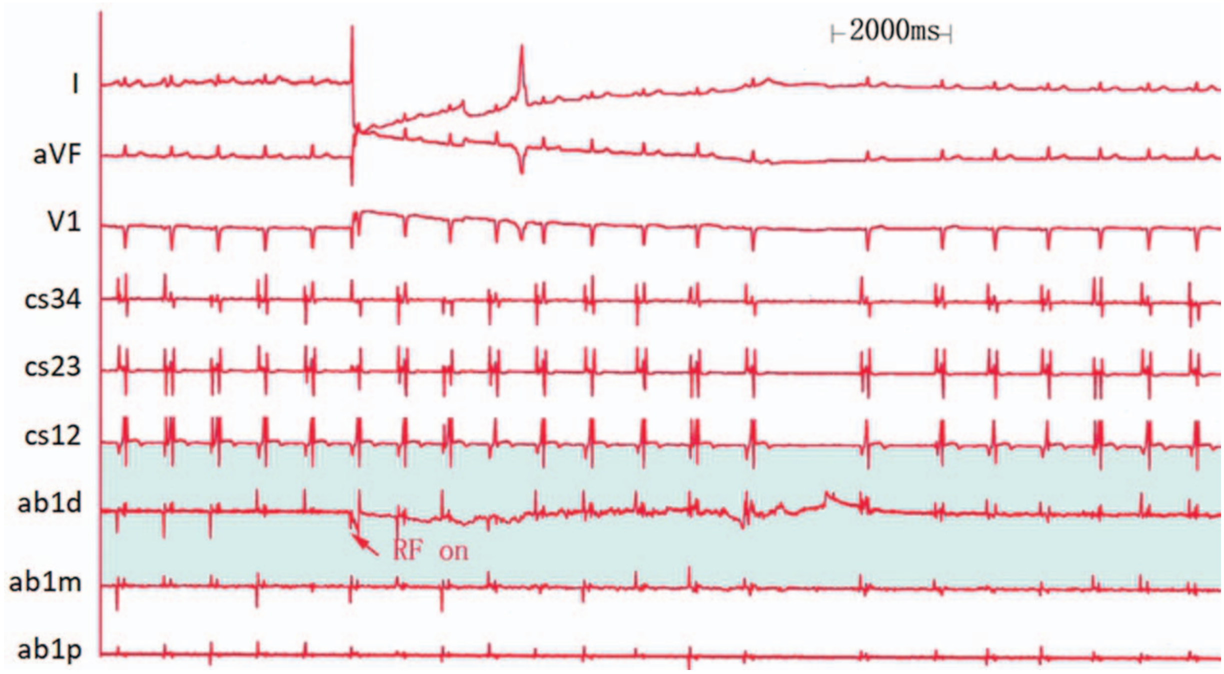

Figure 4: Bradyarrhythmia induced during cardioneuroablation. AblP, AblM, and AblD are proximal, medium, and distal electrograms of the ablation catheters. The arrow shows the begin of ablation. AblD: Ablation distance; AblM: Ablation medium; AblP: Ablation proximal; RF: Radiofrequency.

rapidly, SNRT, WP, AH intervals were all shortened, while the HV interval remained unchanged. Those features prompted that ablation therapy was effective in parasympathetic tone modification. There was a complete or partial reduction in the number of bradyarrhythmic attack events during the follow-up, and the short-term treatment effectiveness was considered satisfactory. Areas surrounding the sinus node, AVN, and the phrenic nerve were avoided during the procedure so that the complications such as injuries to these areas did not occur.

The use of spectral mapping ablation of three atrial ganglia was reported in Pachon *et al*.[2,3] It was found that normal myocardial-electrogram energy converges in the 40 Hz region, while the main frequency band of nervous fibrillar myocardium tissue was found to be greater than 100 Hz by the use of fast Fourier transform (FFT) analysis of the spectrum of an atrial electrical diagram. With the nervous fibrillar myocardium electrical activity tissue as the target point in combination with the anatomical position, 20 cases were successfully ablated under general anesthesia. By drawing on the experience of Pachon *et al*[3] as a reference, we developed a restricted catheter ablation for the treatment of vagus-mediated bradyarrhythmias, with the following modifications:

1. Localization and ablation targets: In the study, spiral CT imaging combined with three-dimensional electroanatomical mapping was used in some patients, achieving more degree of precision for electrical activity. X-ray imaging (used as the sole localizing tool) may cause large areas of damage and affect other neuronal functionalities of the heart, such as the nutritional role of myocardium, negative dromotropic/chronotropic properties and negative inotropic effects.
2. Identification of fibrillar myocardium electrical activity: FFT analysis involves a large number of calculations and needs to augment a dedicated pre-amplifier instrument. The length of the data obtained from the FFT analysis influences the spectrum resolution, that is, a low-frequency resolution is gained if the data is shorter than one cardiac cycle, and confounding factors may be added if the data is longer than one cardiac cycle, thus increasing the difficulty of the procedure. In our study we employed a simplified form for the mapping of the fibrillar myocardium by using a digital filtering spectrometer, allowing real-time recordings display changes of the components in the intra-cardiac electrogram. The cut-off frequency was set at 100 Hz so that the myocardial tissue potential signals were significantly attenuated while highlighting the high-frequency components of nervous fibrillar myocardium electrical activity.
3. Anesthesia: general anesthesia may affect the autonomic nervous system tone function, and to hinder the evaluation of the effects of ablation due to the difficulty in observing patients', subjective and objective responses during the procedure. In our study, local anesthesia was used to avoid such interruptions, thus preventing disturbances to the observation of ablation reactions.
4. It has been shown that nerve sprouting occurs at both infarcted and non-infarcted areas.[14] These heterogeneous neuronal changes may result in arrhythmias.[15] We could not be sure whether this phenomenon had occurred in those relapsed patients in our data.

The present study had some limitations. First, the procedure of case 5 was failed although vagal irritation reaction occurred during ablation. The symptoms were persistent and did not conform to the variation of vagal tension. It may be caused by occult organic lesions, suggesting that nerve ablation is not suitable for the treatment of organic bradycardia. The recurrence after ablation in cases 2 and 8 may be related to insufficient ablation depth, too small ablation range and too short ablation time. It is necessary to explore more appropriate ablation range and energy. Second, the innervation of the sinus and of the AV node are very extensive and comes from all directions. As such, it is very important to extend the ablation even to the left atrium to get an extensive, sustained, and prolonged denervation.[16] A very important amount of innervation of the sinus node, for example, comes from ganglia located in the antrum of the right superior pulmonary vein. The success of the treatment of this place depends on the left atrium ablation. Therefore, a restricted ablation must be considered to be a limitation of the study. It will be necessary to further follow-up to see if the results are sustained. Third, currently, the identification of fibrillar myocardium electrical activity is mainly based on electrical stimulation and vagal reflex during the ablation as mediate evidence.[1,16] However, the high-frequency potentials of the heart may also originate from the potentials of the conduction system or the fragmented atrial potentials. It is not fully understood how to distinguish between these two conditions. Further researches are needed.

In conclusion, bradyarrhythmia evoked by increased pathological vagus tone is commonly seen in the clinic. Most of those patients were young adults, with normal cardiac structure and function, but have severe symptoms. Drug therapy is disappointing with many serious side effects. The pacing is considered to be a non-radical cure and is not easily accepted by patients because of the need to replace it several times during a patient's lifetime. The main implication of this study is that restricted ablation of sinoatrial and AV nodal peripheral fibrillar myocardium electrical activity may provide a new treatment to ameliorate paroxysmal sinus node dysfunction, high degree AV block, and vagal-mediated syncope.

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Conflicts of interest

None.

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