The Safety and Efficacy of Pulsed Field Ablation for Patients with Persistent Atrial Fibrillation Comorbid with HFpEF: a prospective, multicenter cohort study

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Study plan

Project name	The Safety and Efficacy of Pulsed Field Ablation for Patients with Persistent Atrial Fibrillation Comorbid with HFpEF: a prospective, multicenter cohort study		
Project source	Jiangsu Provincial Research Hospital: YJXYY202204-YSB59		
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Study Protocol Summary

Study number	2025-K119-01
Study name	The Safety and Efficacy of Pulsed Field Ablation for Patients with Persistent Atrial Fibrillation Comorbid with HFpEF: a prospective, multicenter cohort study
Study purpose	To evaluate the difference between pulsed field ablation and medical therapy in patients with persistent atrial fibrillation and HFpEF
Study design	Prospective, multicenter cohort study
Study equipment	Medtronic Pulse Select Pulsed Field Ablation
Sample size	158
Entry criteria	**Inclusion criteria** (1) Age 18-80 years; (2) Patients with persistent atrial fibrillation; (3) According to the 2021 European Society of Cardiology (ESC) guidelines for heart failure, heart failure with preserved ejection fraction (HFpEF) is defined as patients with preserved or slightly reduced left ventricular ejection fraction (LVEF) but with diastolic dysfunction. The diagnostic criteria for HFpEF include: symptoms and signs of heart failure; LVEF ⩾ 50%; and objective evidence of cardiac structural and functional abnormalities consistent with left ventricular diastolic dysfunction or increased left ventricular filling pressure. These can be verified by imaging examinations such as echocardiography and biomarkers such as B-type natriuretic peptide or NT-proBNP. The thresholds for B-type natriuretic peptide or NT-proBNP are: BNP⩾35 pg/mL or NT-proBNP ⩾125 pg/mL for patients with sinus rhythm; BNP⩾105 pg/mL or NT-proBNP ⩾365 pg/mL for patients with atrial fibrillation. (4) Agree to participate in this study and sign the informed consent form. Have clinical compliance to complete the postoperative follow-up required by the protocol. **Exclusion criteria** (1) Patients with persistent atrial fibrillation lasting for more than 3 years, (2) Patients who had used class I or class III antiarrhythmic drugs, but the use

	of the above drugs for less than 7 days to convert atrial fibrillation was allowed; (3) Previous left atrial ablation or surgery (including left atrial appendage occlusion); (4) Left atrial diameter > 50 mm; (5) Previous pulmonary vein stenting; (6) Previous pulmonary vein stenosis; (7) Presence of any heart valve prosthesis; (8) Any cardiac surgery, myocardial infarction, percutaneous coronary intervention (PCI)/percutaneous transluminal coronary angioplasty (PTCA) or coronary artery stenting within three months before signing the informed consent; (9) Unstable angina or severe coronary artery stenosis; (10) Primary pulmonary hypertension; (11) Rheumatic heart disease; (12) Thrombocytosis, thrombocytopenia; (13) Any disease that prohibits long-term anticoagulation; (14) Active systemic infection; (15) Atrial fibrillation caused by reversible causes, such as hyperthyroidism; (16) Women known to be pregnant or breastfeeding; (17) Life expectancy of less than one year; (18) Patients with intracardiac thrombus; (19) Patients with known drug or alcohol addiction; (20) Patients who are unwilling or unable to fully comply with the study protocol and complete follow-up; (21) Patients with malignant tumors; (22) Participating in other clinical trials that may interfere with the results.
End point	**Primary endpoint:** Change in quality of life at 12 months as measured by the Atrial Fibrillation Quality of Life Survey (AFEQT). Improvement in quality of life from baseline to 12 months after pulsed field ablation procedure or AAD as measured by the Atrial Fibrillation Quality of

	Life Survey (AFEQT), with values ranging from 20 - 140 (higher scores mean worse outcomes). **Secondary End Points** (1) The rate of atrial fibrillation-free recurrence during clinical follow-up within 12 months after surgery, that is, the success rate of pulsed field therapy for AF (including atrial tachycardia (AT) lasting more than 30 seconds, atrial flutter (AFL), and AF endpoint events; (2) Complications and adverse events during the pulsed field ablation surgery and during the postoperative follow-up, including readmission, cardiovascular events, cardiovascular death, all-cause death, and also including serious adverse events related to the surgery. (3) Rehospitalization due to heart failure or recurrence of atrial fibrillation 3 months after surgery; (4) The incidence of AT/AF/AFL events 3 months later.; (5) Improvement of cardiac function 6 and 12 months after surgery, including echocardiogram E/e', proBNP, etc.
Statistical analysis	OPC was analyzed based on previous clinical research data and used for comparison and evaluation of the main evaluation indicators. According to the current literature on the treatment of drug-refractory atrial fibrillation, the main evaluation indicator comparison target value was 80%. 1. Completion status and demographic analysis Summarize the number of enrollments and completions of each center, and list the list of dropouts. Make a detailed list of the size of different data sets in each group, the distribution of cases in each center, the comparison of the total dropout rate, and the reasons for non-completion. Describe, analyze and evaluate the patient's demographic characteristics (age, gender, etc.), relevant medical history, treatment history, etc. 2. Safety evaluation List the number and frequency of all adverse events, as well as the incidence of adverse events and serious adverse events. Make a cross-tabulation description of the changes in laboratory indicators before and after. The exact probability

	method was used to compare the two groups of adverse events.

Flow chart

Name	Screening period	Treatment period		Follow-up period			
Visit point	V1	V2	V3	V4	V5	V6	V7
Visit time	-14d ~ 0d	0 d （Operation）	1-7 d（Before discharge）	1m ± 7d	3m ± 7d	6m ± 7d	12m ± 7d
Informed consent	X						
General information	X						
Vital signs	X		X	X	X	X	X
Medical history	X						
Inclusion criteria	X						
Laboratory examination	X		X	X	X		X
Standard electrocardiogram	X		X	X	X	X	X
Holter					X	X	X
AFEQT scale	X			X	X	X	X
Echocardiogram	X		X	X		X	X
Medication status	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

Note: m=month; d=day; h=hour.

(1) **V1 Screening period**: If the patient has undergone relevant examinations before signing the informed consent form and within 14 days before surgery, these data can be collected as data for this clinical trial. Patients do not need to undergo relevant examinations, such as laboratory tests, electrocardiograms, etc.

(2) **General information**: date of birth, gender, height, weight.

(3) **Vital signs**: body temperature, blood pressure, heart rate/pulse.

(4) **Medical history**: including hypertension, diabetes, coronary heart disease, stroke, allergies, surgical history, etc.

5) Pregnancy test: urine/blood pregnancy test (only for premenopausal women, only before surgery).

(6) Laboratory examination (V6 only measures NT-proBNP, and all other visits involving laboratory examinations (such as V1, V3 and V4) must complete all the following examination items):

Routine blood test: red blood cells (RBC), white blood cells (WBC), hemoglobin (Hgb), platelets (PLT); Blood biochemistry: alanine aminotransferase/alanine aminotransferase (ALT), aspartate aminotransferase/aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), blood urea nitrogen/urea (BUN/CREA), creatinine (Cr), uric acid (UA); ESR; Electrolytes: potassium ion (K); Coagulation function: prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen (FIB); C β-reactive protein; D-dimer; NT-proBNP; myocardial enzyme spectrum and high-sensitive cardiac troponin T: lactate dehydrogenase (LDH), creatine kinase isoenzyme (CK-MB), and high-sensitive cardiac troponin I (hs-cTnI);

(7) Long-term Holter: Use a single-lead 7-day long-term Holter for monitoring.

(8) Medication status: Record the medication used during the study period (from the signing of the informed consent to the end of the follow-up). Routine fluid preparation (normal saline, glucose solution), intraoperative anesthetics, and intraoperative anticoagulants do not need to be recorded. Medication used for corrective treatment of adverse events also needs to be recorded.

(9) Adverse events: Record clinically significant adverse events of the subject from the signing of the informed consent to the end of the follow-up. Events in which the health status of the subject does not deteriorate seriously due to planned hospitalization for existing diseases or follow-up required by the protocol are not recorded as serious adverse events.

1. Background

Atrial fibrillation (AF) is one of the most common arrhythmias in clinical practice. It is a supraventricular tachyarrhythmia characterized by rapid and disordered atrial electrical activity, with a high disability and mortality rate[1]. There are more than 7 million patients with atrial fibrillation in my country. The incidence of atrial fibrillation has increased 20 times compared with ten years ago, and the incidence of atrial fibrillation-related stroke has increased nearly 13 times. Atrial fibrillation not only significantly reduces the patient's cardiac output, leading to heart failure[2]； It will also increase the risk of left atrial mural thrombus formation, leading to peripheral arterial embolism, especially stroke. Atrial fibrillation (AF) is currently the most common arrhythmia in patients with heart failure (HF) [1-2]. Studies have shown that atrial fibrillation is more common in patients with ejection fraction preserving heart failure (HFpEF). During the course of HFpEF, atrial dysfunction caused by atrial fibrillation may cause functional mitral regurgitation, further affecting ventricular systolic and diastolic function and accelerating the progression of heart failure. Patients with atrial fibrillation and heart failure have severe symptoms, poor prognosis, and increased hospitalization rates. Studies have reported that the annual incidence of atrial fibrillation in patients with heart failure is about 57%, and the annual incidence of heart failure in patients with atrial fibrillation is about 37%[3].

The goal of treating atrial fibrillation combined with heart failure is to alleviate patient symptoms and improve survival rate. The treatment strategies for atrial fibrillation mainly include standardized anticoagulation therapy and catheter ablation. Catheter ablation includes catheter ablation under high-power X-ray guidance, radiofrequency ablation guided by a three-dimensional mapping system, radiofrequency ablation guided by intracardiac ultrasound, high-power short-term radiofrequency ablation, cryoballoon ablation, pulsed field ablation, left atrial appendage occlusion, and "one-stop treatment for atrial fibrillation". Studies have reported that for patients with heart failure and atrial fibrillation, compared with drug treatment, radiofrequency catheter ablation significantly reduces all-cause mortality and heart failure hospitalization rate, and significantly improves cardiac function classification[4].

Currently, there are two energy sources available for catheter ablation of persistent atrial fibrillation: radiofrequency and cryotherapy. However, both are temperature-dependent. The damage effect depends on the distribution of the temperature field in the target tissue, which is the cause of the therapeutic effect and the additional damage[5,6]. Currently, the complication rate of radiofrequency or cryocatheter ablation is approximately 2.9% to 10%, of which the incidence of potentially fatal complications is 0.7% to 0.9%. The perioperative mortality rate is 0.05% to 0.55%, and the most common cause is cardiac tamponade[7,8]. Secondly, under the premise of safety, traditional energy also has certain deficiencies in the transmural properties of myocardial injury.

Pulsed field ablation (PFA) is an emerging ablative energy. The basis for the damage effect of ablation is the voltage difference between the inside and outside of the membrane formed by the high-voltage electric field. This is electric field-dependent, does not generate heat locally, and has strong penetration ability. Under the action of high-voltage electric fields, the damage threshold of different tissues is different. The damage is selective to a certain extent, and it is safer for fragile adjacent tissues such as blood vessels, esophagus, and nerves[9,10]. Currently, other energy forms used for ablation are not selective for this tissue type. In the global key study, the incidence of unsafe events for the product submitted this time was 0.7%, and no complications such as left atrial-esophageal fistula, pulmonary vein stenosis, myocardial infarction, phrenic nerve palsy, and

coronary spasm occurred. The extremely low incidence of unsafe events demonstrates the excellent safety of the product. Compared with existing technologies, the efficiency of PFA energy may also be improved. PFA delivery is completed in a few milliseconds, which may reduce isolation time and the entire operation time. By reducing the total operation time, the anesthesia time and the time the patient and doctor are exposed to radiation are reduced, which greatly improves the efficiency of the operation[11,12]. The PulseSelect™ pulsed field ablation system is a ring electrode with a central support. Compared with a point-shaped radiofrequency catheter, it isolates the pulmonary veins by ablating a whole circle of 9 electrodes at the same time, further improving the efficiency of the operation. Due to the uniqueness and safety of its energy, it can significantly reduce postoperative complications and hospitalization time, shorten the patient's recovery period, and reduce the need for secondary treatment, thereby effectively reducing the patient's medical costs and economic burden[13]. The results of the Pulsed AF study also showed that at 6 and 12 months after surgery, the overall quality of life of patients (AFEQT and EQ-5D) increased by 5 points and 0.03 points respectively compared with the baseline level, and the results were statistically significant14. It can be seen that PFA reduces the overall medical resource investment by reducing the re-ablation rate and cardiovascular events.

In summary, patients with persistent atrial fibrillation and HFpEF have a poor prognosis and lack effective treatment. This study is dedicated to treating patients with persistent atrial fibrillation and HFpEF with pulsed field catheter ablation, and will follow up for 12 months to evaluate the effectiveness and safety of pulsed field catheter ablation for these patients. It is hoped that this study will bring new hope to patients with atrial fibrillation and HFpEF.

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2 Research objectives and content

2.1 Research objectives

This study aims to evaluate the mid- and long-term clinical efficacy and safety of pulsed field ablation in the treatment of patients with persistent atrial fibrillation and HFpEF by recording and analyzing the differences between the effects of pulsed field ablation and drug therapy in patients with persistent atrial fibrillation and HFpEF. At the same time, the risk factors affecting the outcome of atrial fibrillation ablation, postoperative recurrence, and improvement of cardiac function were analyzed to better guide the application of pulsed field catheter ablation in persistent atrial fibrillation and HFpEF, and also to provide some theoretical basis and clinical evidence for the treatment strategy of patients with atrial fibrillation and HFpEF.

2.2 Research content

This study is a prospective, multicenter cohort study.

(1) To observe the perioperative safety of pulsed field catheter ablation for patients with persistent atrial fibrillation and HFpEF;

(2) To observe the improvement of cardiac function, the treatment effect and recurrence rate of atrial fibrillation in the pulsed field ablation group compared with the drug treatment group 1 month, 3 months, 6 months and 12 months after surgery;

(3) To study the treatment strategy during the pulsed field ablation procedure, such as the correlation between ablation time, ablation site and the recurrence of atrial fibrillation and cardiac function after surgery, so as to guide better cryoablation strategies.

3. Study population

This study selected patients with persistent AF and HFpEF and divided them into a drug group (treated with class I or class III antiarrhythmic drugs) and a surgical group (Medtronic Pulse Select pulsed field ablation).

3.1 Sample size estimation

After literature search, the literature mainly reported that the scale used for Qol endpoints was AFEQT, and some used the MLHFQ scale. Therefore, the scoring results of the AFEQT scale are summarized as follows.

1. CABANA study

a) The CABANA study compared the effects of medication and catheter ablation on quality of life, and conducted long-term (60 months) AFEQT and MAFSI scales. The population accounted for 946 (42.9%) paroxysmal atrial fibrillation, 1042 (47.3%) persistent atrial fibrillation and 215 (9.8%) long-term persistent atrial fibrillation. The proportion of heart function Class II/III was 776 (35.5%), and the proportion of ejection fraction ≤35% was 69 (4.5%).

b) The AFEQT scores for catheter ablation and medical therapy at 3 months were 79.8 (18.6) vs. 76.5 (20.4), and 12 months were 86.4 (16.5) vs. 80.9 (18.5). If the sample calculation is based on the above reference.

i. Based on the AFEQT score at 3 months, the two groups had 550 samples respectively.

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.80042	550	550	1100	79.8	76.5	3.3	18.6	20.4	0.05

ii. Based on the AFEQT score at 12 months, the two groups had 161 samples respectively

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.80142	161	161	322	86.4	80.9	5.5	16.5	18.5	0.05

2. CABANA sub-study heart failure cohort

a) Paroxysmal atrial fibrillation (AF) accounted for 31.6%, persistent AF accounted for 55.3%, and long-term persistent AF accounted for 13.1%. 79% of patients had a left ventricular ejection fraction (EF) ≥ 50%, 11.7% had an EF between 40% and 49%, and 9.3% had an EF < 40%.

b) The scores for catheter ablation and medical therapy at 12 months were 80.6 (19.8) and 75.0

(19.6). If the sample calculation is based on the above reference, 196 patients are needed in each group.

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.80154	196	196	392	80.6	75	5.6	19.8	19.6	0.05

3. CAPLA study

a) The CAPLA study compared the effects of PVI and PVI+PWI ablation strategies on quality of life. The average EF values of the two groups were 51.9 (12.1) vs. 52.6 (12.1), and the proportion of congestive heart failure was 71 (43.3%) vs. 70 (41.7%).

b) Long-term follow-up results showed that the AFEQT scores of PVI and PVI+PWI after catheter ablation were 88.9 (14.8) vs. 88.9 (14.8).

4. KiCS-Af study

a) The KiCS-AF study examined the effects of catheter ablation and drug therapy on heart failure with reduced ejection fraction and preserved ejection fraction, including patients with paroxysmal and persistent atrial fibrillation, with 83.4% of patients having LVEF >35%.

b) The baseline AFEQT in the catheter ablation and drug therapy groups was 71.3 (61.8–82.4) vs. 76.3 (63.0–87.0). The study classified the improvement in AFEQT scores into grades and performed a count analysis. According to the clinical significance of AFEQT improvement >5 points, the change gradient of 5 points, 10 points and 15 points was graded and the difference in the rates between the two groups was compared. There was no mean result.

5. RAFT-AF study

a) The RAFT-AF study evaluated the effects of catheter ablation and medication in patients with atrial fibrillation and heart failure. The proportion of patients with ejection fraction > 45% was 41% .

b) The AFEQT evaluation score was the difference between the baseline and follow-up nodes. The results of rate control versus catheter ablation rhythm control were 16.1±1.6 versus 23.4±1.5. Based on this sample size, only 3 cases in each group were required.

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.98614	3	3	6	16.1	23.4	-7.3	1.6	1.5	0.05

6. RCT STALL HFpEF

a) This is the first RCT on HFpEF, but the sample size is only 31 patients.

b) According to the AFEQT score results at six months, the results of the catheter ablation group and the drug therapy group were 75.2±19.9 and 57.3±23.5, respectively. The sample size was calculated to be 25 cases in each group.

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.81226	25	25	50	75.2	57.3	17.9	19.9	23.5	0.05

In view of the heterogeneity of the above study population and results, it is recommended that:

1、 The AFEQT value of the endpoint of the pulse catheter ablation group be selected from the

CABANA heart failure cohort at 12 months, which is 80.6 (19.8). Referring to the KiCS-AF cohort study, which divided the AFEQT improvement value into three levels of 5, 10 and 15, we set the AFEQT value of the drug treatment group to 75.6/70.6/65.6.

2、 Set the AFEQT of the drug group to 75.6, α=0.05, β=0.2, and 248 patients are required in each group.

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.80138	248	248	496	80.6	75.6	5	19.8	19.8	0.05

3、 Set the AFEQT of the drug group to 70.6, α=0.05, β=0.2, and 63 cases are needed in each group. Considering a dropout rate of 20%, 79 cases are needed in each group.

Numeric Results for an Unequal-Variance T-Test

δ = μ1 - μ2
Hypotheses: H0: δ = 0 vs. H1: δ ≠ 0

Target Power	Actual Power	N1	N2	N	μ1	μ2	δ	σ1	σ2	Alpha
0.8	0.80306	63	63	126	80.6	70.6	10	19.8	19.8	0.05

3.2 Subject screening

Whether the selected patients meet the inclusion criteria requires the following assessments:

(1) General information: age, gender, place of origin, contact information, etc.

(2) Physical examination: height, weight; heart rate, blood pressure, etc.

(3) Past medical history: hypertension, diabetes, coronary heart disease, cardiomyopathy, COPD, stroke, etc.; previous surgical history, including pacemaker implantation, thyroid disease history, etc.; previous medication history;

(4) Electrocardiogram (including Holter);

(5) Transthoracic echocardiogram (LVEF, LVEDD, LAD, e/e', etc.);

(6) Transesophageal echocardiogram, MRI or CT examination of the left atrium and pulmonary veins;

(7) Laboratory tests: routine blood tests, routine urine tests, routine stool tests, liver function tests, kidney function tests, electrolytes, blood sugar, blood lipids, myocardial markers, coagulation function tests, BNP or NT-proBNP, thyroid function tests, etc.

(8) Informed consent was signed for the subjects who met the above requirements and agreed to participate in the study.

In this study, no examination items were included beyond those required for routine diagnosis and treatment.

3.3 Inclusion Criteria

(1) Age 18-80 years;

(2) Patients with persistent atrial fibrillation;

(3) According to the 2021 European Society of Cardiology (ESC) guidelines for heart failure, heart failure with preserved ejection fraction (HFpEF) is defined as patients with preserved or slightly reduced left ventricular ejection fraction (LVEF) but with diastolic dysfunction. The diagnostic criteria for HFpEF include: symptoms and signs of heart failure; LVEF≥50%; and objective evidence of cardiac structural and functional abnormalities consistent with left ventricular diastolic dysfunction or increased left ventricular filling pressure. These can be verified by imaging examinations such as echocardiography and biomarkers such as B-type natriuretic peptide or NT-proBNP. The thresholds for B-type natriuretic peptide or NT-proBNP are: BNP≥35 pg/mL or NT-proBNP ≥125 pg/mL for patients with sinus rhythm; BNP≥105 pg/mL or NT-proBNP ≥365 pg/mL for patients with atrial fibrillation.

(4) Agree to participate in this study and sign the informed consent form. Have clinical compliance to complete the postoperative follow-up required by the protocol.

3.4 Exclusion criteria

(1) Patients with persistent atrial fibrillation lasting for more than 3 years,

(2) Patients who had used class I or class III antiarrhythmic drugs, but the use of the above drugs for less than 7 days to convert atrial fibrillation was allowed;

(3) Previous left atrial ablation or surgery (including left atrial appendage occlusion);

(4) Left atrial diameter > 50 mm;

(5) Previous pulmonary vein stenting;

(6) Previous pulmonary vein stenosis;

(7) Presence of any heart valve prosthesis;

(8) Any cardiac surgery, myocardial infarction, percutaneous coronary intervention (PCI)/percutaneous transluminal coronary angioplasty (PTCA) or coronary artery stenting within three months before signing the informed consent;

(9) Unstable angina or severe coronary artery stenosis;

(10) Primary pulmonary hypertension;

(11) Rheumatic heart disease;

(12) Thrombocytosis, thrombocytopenia;

(13) Any disease that prohibits long-term anticoagulation;

(14) Active systemic infection;

(15) Atrial fibrillation caused by reversible causes, such as hyperthyroidism;

(16) Women known to be pregnant or breastfeeding;

(17) Life expectancy of less than one year;

(18) Patients with intracardiac thrombus;

(19) Patients with known drug or alcohol addiction;

(20) Patients who are unwilling or unable to fully comply with the study protocol and complete follow-up;

(21) Patients with malignant tumors;

(22) Participating in other clinical trials that may interfere with the results

3.5 Exit Criteria

The criteria for subject withdrawal include, but are not limited to:

(1) The subject requests withdrawal;

(2) The researcher determines that the subject is not suitable to continue participating in the study;

The subject has the right to withdraw at any stage of the clinical trial without any financial responsibility, and has the right to withdraw at any stage of the trial without being discriminated against or retaliated against, and their medical treatment and rights are not affected. The withdrawal of the subject from the clinical trial should be recorded in the relevant research materials.

3.6 Elimination criteria

The criteria for subject exclusion include, but are not limited to: misdiagnosis; no examination or observation records;

The reasons for exclusion should be stated, and no statistical analysis of efficacy will be performed; if the patient receives treatment and has at least one safety record, he or she may participate in the safety analysis depending on the situation.

3.7 Criteria and procedures for stopping the trial/trial treatment

The criteria for stopping the study/trial treatment include, but are not limited to:

(1) The subject withdraws from the trial;

(2) Unexpected serious adverse events of the device occur, causing serious danger to the subjects participating in the study;

(3) The medical device regulatory authority or ethics committee requires the trial to be stopped;

(4) Other circumstances that require the trial/trial treatment to be stopped;

Procedures for Discontinuation of Study/Study Treatment:

(1) Subjects withdraw from the study: Regardless of the reason, the records of cases withdrawing from the study should be retained, and the last evaluation and examination results should be carried forward as the final results, and the full data set analysis should be conducted on their efficacy and safety. The study conclusions and reasons for the withdrawal of all cases should be recorded;

(2) Ethics Committee requires the study to be stopped: For ethical and scientific reasons, the ethics committee requires the study to be stopped. After the researcher learns of the situation, the researcher should stop the study in a timely manner and keep the communication records or written documents of the study cessation;

(3) Regulatory agency requires the study to be stopped: If the medical device supervision and management department requires the study to be stopped, the person in charge of the study should notify each research unit in writing in a timely manner after learning of the situation;

(4) Other situations where the study/research treatment must be stopped: The situation where the subject stops the study/research treatment due to illness or other reasons should be recorded in detail; the cessation of the entire study should be reported to each research unit in writing in a timely manner; other situations where the study/treatment must be stopped should also be recorded in detail.

4. Study plan

4.1 Treatment of patients in the drug group：

Patients who enter the drug group after screening can receive electrical cardioversion or drug cardioversion for drug treatment. If the patient undergoes electrical cardioversion, preoperative examinations must be completed before surgery to exclude surgical contraindications.

The blank period starts from the day 0 when the patient receives Class I or Class III antiarrhythmic drugs, and the blank period of the drug group is from Day 0 to the next 90 days. During the blank period, patients can undergo electrical cardioversion to recover to sinus rhythm (if patients have recurrent atrial fibrillation during the blank period, they can choose to undergo electrical cardioversion again without the limit of countless times). Titration and adjustment of antiarrhythmic drugs are allowed during the blank period. In principle, no drug adjustments will be made after the blank period. Increasing the dose of the original Class I or Class III drugs or replacing antiarrhythmic drugs due to intolerance or drug side effects is considered the end point. Adding Class II or Class IV antiarrhythmic drugs for other reasons is allowed.

4.2 Treatment of patients in the surgical group:：

4.2.1 Preoperative preparation:

(1) Class II and IV antiarrhythmic drugs, diuretics, digitalis drugs, etc. are allowed before surgery. The purpose is to control ventricular rate and improve heart failure treatment. The researcher can decide whether to continue taking the above-mentioned drugs;

(2) Anticoagulants, including warfarin and new oral anticoagulants, should not be discontinued before surgery. For warfarin, INR should be routinely tested before surgery;

(3) Complete preoperative examinations to exclude surgical contraindications (such as left atrial thrombus, abnormal coagulation function, severe thrombocytopenia, liver dysfunction, acute renal dysfunction, acute heart failure, etc.).

4.2.2 Intraoperative operation:

(1) General anesthesia;

(2) Heparin anticoagulation and maintaining ACT at 250-350 seconds;

(3) Single atrial septal puncture via femoral vein;

(4) Conventional PulseSelect PFA ring catheter preparation: flush the guidewire cavity, then insert the guidewire into the catheter through the guidewire Luer interface, retract the ring electrode into the introducer, slowly push the catheter slide control button forward to make the ring electrode linear, and at the same time push the introducer to retract the ring electrode. PulseSelect PFA ring catheter is inserted into the sheath.

(5) Pulmonary vein orifice-vestibular step ablation: advance the catheter along the adjustable curved sheath until the guidewire enters the left atrium. Before fully deploying the ring tip, ensure that the guidewire is advanced into the orifice of one of the left pulmonary veins for at least 5 cm. Continue to advance the catheter along the guidewire until the fourth electrode on the ring spiral begins to leave the sheath, and the catheter tip forms a ring in the LA. It is recommended to perform at least 8 ablations for each pulmonary vein, at least 4 ablations for the ostium and at least 4 ablations for the vestibule, with 4 pulse sequences in each ablation.

(6) Use the PulseSelect PFA catheter to determine bidirectional block. Use the PulseSelect catheter for pacing bidirectional block determination according to the standard electrophysiological procedure.

(7) Cardioversion after PVI ablation for persistent atrial fibrillation;

(8) Perform matrix mapping under sinus rhythm after cardioversion. If the voltage of the posterior wall of the left atrium is low, pulse ablation can be performed. If there is a trigger focus in the superior vena cava, pulse field ablation of the superior vena cava can be performed;

(9) Record the intraoperative medication situation;

(10) Record the rhythm changes during the operation, whether cardioversion was performed, and the rhythm changes after cardioversion;

(11) Record the intraoperative and postoperative complications and adverse event monitoring, including surgery-related death, atrial esophageal fistula, acute coronary syndrome, vascular events at the puncture site (requiring surgical intervention), severe hematoma, pericardial tamponade or pericardial effusion requiring puncture drainage, thromboembolic events, stroke/transient ischemic attack, pulmonary edema, pulmonary vein stenosis, etc.

4.3 Clinical follow-up

(1) V1 screening period (-14 ~ 0 days)

If the patient has undergone relevant examinations before signing the informed consent form and within 14 days before surgery, these data can be collected as data for this clinical trial, and the patient does not need to undergo relevant examinations again. The following process should be completed:

- Sign the informed consent form;
- General information: date of birth, gender, height, weight;
- Vital signs: including blood pressure, heart rate/pulse, body temperature;
- Medical history: including hypertension, diabetes, coronary heart disease, stroke, allergies, surgical history, etc.;
- Inclusion criteria assessment;
- Laboratory tests;
- Standard electrocardiogram;
- AFEQT atrial fibrillation patient quality of life score sheet;
- Cardiac ultrasound;
- Medication status;
- Adverse events & serious adverse events;

(2) V2 Surgery (Day 0)

The following information should be collected/completed on the day of surgery:

- Medication status
- Adverse events & serious adverse events

(3) V3 Postoperatively (1-7 days, before discharge)

The following information needs to be collected/completed:

- Vital signs
- Laboratory tests
- Standard electrocardiogram
- AFEQT quality of life score for patients with atrial fibrillation
- Cardiac ultrasound

- Medication status
- Adverse events & serious adverse events

Post-discharge patient management recommendations:

Class I or Class III antiarrhythmic drugs can be used to maintain sinus rhythm within the 3-month window period after ablation or antiarrhythmic drugs.

Anticoagulants: Oral anticoagulation should be continued for at least 2 months after catheter ablation. After 2 months, anticoagulation can be selected based on the patient's CHA2DS2-VASc-60 score (see Appendix 14.3), rather than the effect of rhythm control (I, C). Male patients with a CHA2DS2-VASc-60 score of 1 or female patients with a CHA2DS2-VASc-60 score of 2 should consider discontinuing OAC 3 months after ablation, provided that there is no recurrence of atrial fibrillation under strict monitoring. Male patients with a CHA2DS2-VASc-60 score of 2 or female patients with a CHA2DS2-VASc-60 score of 3 without a history of stroke/TIA or systemic embolism should consider discontinuing OAC 3 months after ablation, provided that there is no recurrence of atrial fibrillation under strict monitoring. Male patients with CHA2DS2-VASc-60 score ≥3 or female patients with ≥4, or patients with a history of stroke/TIA or systemic embolism, should consider long-term use of OAC after catheter ablation, regardless of whether it is successful or not.

Postoperative anticoagulation therapy monitoring plan

1. NOAC should be the first choice for NOAC/OAC treatment. NOAC has good efficacy and safety, and routine monitoring of coagulation function is not required during use. For patients who have received anticoagulation therapy with NOAC, liver and kidney function should be reviewed regularly and anticoagulation therapy should be adjusted in time.

2. Warfarin

After starting warfarin, INR should be tested once a day. After INR stabilizes, INR should be tested at least once a month to keep INR stable at 2.0~3.0 and TTR≥70%.

(4) V4 1 month after surgery

During the follow-up visit 1m±7d after surgery, the following information should be collected/completed:

- Vital signs
- Laboratory tests
- Standard electrocardiogram
- AFEQT quality of life score for patients with atrial fibrillation
- Cardiac ultrasound

- Medication status
- Adverse events & serious adverse events

(5) V6 3 months after surgery

The following information should be collected/completed during the 3m±7d follow-up after surgery:

- Vital signs
- Laboratory tests
- Standard electrocardiogram
- AFEQT quality of life score for patients with atrial fibrillation
- Cardiac ultrasound
- Medication status
- Adverse events & serious adverse events

(6) V7 6 months after surgery

The following information should be collected/completed at the 6m±15d follow-up after surgery:

- Vital signs
- Standard electrocardiogram
- Holter
- AFEQT quality of life score for patients with atrial fibrillation
- Cardiac ultrasound
- Medication status
- Adverse events & serious adverse events

(7) V8 12 months post-surgery

The following information should be collected/completed at the 12m±15d follow-up after surgery:

- Vital signs
- Laboratory tests
- Standard electrocardiogram
- Holter
- AFEQT quality of life score for patients with atrial fibrillation
- Cardiac ultrasound

- Medication status
- Adverse events & serious adverse events

Note: Medication status: Record the medication status during the study period (from signing the informed consent to the end of follow-up). Routine solution preparation (normal saline, glucose solution), intraoperative anesthetics, and intraoperative anticoagulants do not need to be recorded. Drugs used for corrective treatment of adverse events also need to be recorded.

Adverse events: Record clinically significant adverse events of the subjects from signing the informed consent to the end of follow-up. Events in which the health status of the subjects does not deteriorate seriously due to planned hospitalization for existing diseases or follow-up required by the protocol are not recorded as serious adverse events.

5. End point

5.1. Primary endpoint:

Change in quality of life at 12 months as measured by the Atrial Fibrillation Quality of Life Survey (AFEQT). Improvement in quality of life from baseline to 12 months after pulsed field ablation procedure or AAD as measured by the Atrial Fibrillation Quality of Life Survey (AFEQT), with values ranging from 20 - 140 (higher scores mean worse outcomes).

5.2 Secondary endpoint：

(1) The rate of atrial fibrillation-free recurrence during clinical follow-up within 12 months after surgery, that is, the success rate of pulsed field therapy for AF (including atrial tachycardia (AT) lasting more than 30 seconds, atrial flutter (AFL), and AF endpoint events;

(2) Complications and adverse events during the pulsed field ablation surgery and during the postoperative follow-up, including readmission, cardiovascular events, cardiovascular death, all-cause death, and also including serious adverse events related to the surgery.

(3) Rehospitalization due to heart failure or recurrence of atrial fibrillation 3 months after surgery;

(4) The incidence of AT/AF/AFL events 3 months later.;

(5) Improvement of cardiac function 6 and 12 months after surgery, including echocardiogram E/e', proBNP, etc.

6. Methods and timing for evaluating, recording and analyzing safety parameters

(1) Record the occurrence of death, stroke or transient ischemic attack of the subjects during the study;

(2) Surgical operation-related parameters (operation time, left atrial operation time, number of ablation discharges, X-ray exposure time and X-ray radiation, etc.) and intraoperative complications: Observe and record the occurrence of surgery-related adverse events from the beginning to the end of the surgery. All adverse events should be tracked and followed up until they return to normal or baseline, or are sufficient to explain the abnormality. If the subject's participation in this trial ends, it should be tracked until the last follow-up;

(3) Clinically significant vital signs and related examinations:

Vital signs: Vital signs should be checked during the screening period, 1, 2, 3, 6 and 12 months of outpatient follow-up, and observed and recorded;

Laboratory examination: blood routine, blood biochemistry, coagulation function, electrolytes, coagulation function, NT-proBNP, D-dimer, myocardial enzyme spectrum and high-sensitivity cardiac troponin I are performed during the follow-up period. When clinically significant abnormal laboratory test results are found, they should be re-examined and followed up until they return to normal or have no clinical significance or baseline status; relevant laboratory tests need to be completed before the patient is discharged;

Standard electrocardiogram: 12-lead surface electrocardiogram is performed during the screening period, 1, 3, 6 and 12 months of follow-up;

Holter is used for follow-up at 3, 6 and 12 months after surgery.

Echocardiogram: The investigator may choose to perform transthoracic echocardiogram or/and transesophageal echocardiogram according to the patient's condition;

AFEQT Atrial Fibrillation Patient Quality of Life Scale: The patient's quality of life is scored during the screening period and 1, 3, 6 and 12 months after surgery;

(4) The occurrence of other adverse events and serious adverse events: Observe and record them throughout the trial. Serious adverse events should be tracked until the problem is resolved or the investigator determines that it has become "chronic" or "stable" or "sufficient to explain this abnormality". Reports of these adverse events should be recorded.

7. Safety evaluation

Safety refers to the absence of pulmonary vein stenosis, cardiac tamponade, phrenic nerve injury, esophageal injury, and femoral artery and vein injury, thrombosis/air embolism, myocardial infarction, stroke, TIA, asymptomatic cerebral infarction, coronary artery spasm, vagal reflex with severe bradycardia and other surgical complications during the perioperative period.

8. Time of participation in the study (each participation time and total time)

The time of participation in the study is the time when patients with persistent atrial fibrillation and HFpEF are planned to receive drug treatment or pulsed field ablation surgery, that is, the time of enrollment. The follow-up time is 1 month, 3 months, 6 months, and 12 months after enrollment. The total time is 12 months after the start of treatment.。

9. Data management and statistical analysis plan, data confidentiality plan

(1) The research data are managed and stored in the cardiology laboratory by full-time scientific research personnel.

(2) Data statistics and analysis

1. Statistical processing: SPSS22.0 statistical software was used for statistical analysis.

2. Normally distributed quantitative data, such as troponin, liver and kidney function, blood lipids, height, weight, EF, e/e', proBNP, etc.

3. Non-normally distributed quantitative data, such as age, are described as median ± interquartile range.

4. A t-test is planned for the results of molecular experimental data;

5. The composition ratio is used for statistical description of qualitative data, and the chi-square test is used for statistical inference. Cardiac function (NYHA classification) is tested using the K-W rank sum test;

6. $P < 0.05$ is considered significant.

10. Confidentiality Plan

The results of this project may be published in medical journals, but we will keep the patient's information confidential in accordance with the law. Unless required by relevant laws, the patient's personal information will not be disclosed. If necessary, government management departments and hospital ethics committees and their relevant personnel may review the patient's information in accordance with regulations.

11、Risk/Benefit Assessment

11.1 Personal Benefits: This study provides reasonable treatment strategies for patients' diseases according to the guidelines for the treatment of atrial fibrillation, which may help patients improve the symptoms and prognosis of atrial fibrillation.

Social Benefits: This study may delay the progression of atrial fibrillation, delay the related complications caused by atrial fibrillation, and may improve the quality of life. We hope that the

information obtained from your participation in this study will benefit you or patients with the same condition as you in the future.

11.2 Risks

Participating in this study will not exceed the risks of conventional treatment. All risks are within the range of the risks of the original treatment methods, and this study does not increase any unnecessary risks.

11.3 Risks and Protection of Special Populations

None

12 Ethical issues in the study

12.1 Ethical approval

The project was approved by the Ethics Committee of the Affiliated Hospital of Nantong University.

12.2 Informed consent

Each participant was informed of the personal and social significance of the project before enrollment, and was informed of the possible risks and measures to reduce the risks. The patient was enrolled only after obtaining the patient's consent.

13 Annual Plan

2025.05-2025.11: Collect patients who meet the inclusion criteria and conduct drug treatment and pulsed field ablation treatment. Complete some follow-up.

2025.12-2026.05: Continue to enroll cases and follow up on patients who have been enrolled. Organize some data. And make effective improvements.

2026.05-2027.05: Basically complete all follow-up data, analyze data, do statistics, summarize and complete the writing of the paper, and submit it for publication.

14 Evaluation indicators

This study participates in clinical registration research. The research results will be published in the form of papers, and it is expected to publish one core or SCI paper.

15 Preliminary research foundation and working conditions

Our hospital has several national-level center titles, including the Cardiogenic Stroke Prevention and Treatment Base, Heart Failure Center, and Atrial Fibrillation Center. In 2018, we were awarded the first batch of national-level Atrial Fibrillation Centers and Heart Failure Centers, and were awarded the title of Cardiogenic Stroke Prevention and Treatment Base Construction Unit. In 2018, the Nantong Heart Failure Alliance and Cardiogenic Stroke Prevention and Treatment Alliance were established in Nantong. In 2019, it became the Jiangsu Province Atrial Fibrillation Center Alliance Demonstration Center. In 2020, it became the National Standardized Atrial Fibrillation Center Demonstration Center and the National Cardiogenic Stroke Prevention and Treatment Base. In 2024, the Arrhythmia Diagnosis and Treatment Center was established.

Our hospital is at the leading level in China in the prevention and treatment of cardiogenic stroke and the standardized management of atrial fibrillation. In addition, the pacemaking and electrophysiological interventions in our cardiology department have maintained a growth rate of about 20% to 30% in the past three years. The number of radiofrequency ablation operations has exceeded 500 per year in recent years, and the number of pacemaker implants ranks among the top five in the province. Thousands of left atrial appendage occlusion operations have been completed. The technical difficulty and number of operations are at the leading level in the country and Jiangsu Province. We are one of the few pacing and electrophysiology teams in the province that can independently perform one-stop operations for atrial fibrillation radiofrequency ablation + pulsed field ablation + pulsed field ablation, left atrial appendage occlusion, and atrial fibrillation.

16. Other issues that need to be explained

16.1 Cooperation on the project

Jiangsu Provincial Research Hospital: YJXYY202204-YSB59

16.2 Results publication form and signature arrangement

Publish 1 core journal or SCI paper.

16.3 Other issues that need to be explained

None

The applicant promises and signs:

I guarantee the authenticity of the application content. I will perform the duties of the project leader, strictly abide by the relevant national regulations on clinical research, ensure the time of research work, carry out the work conscientiously, submit relevant materials on time, and submit relevant reports in the research process in accordance with the requirements of the ethics committee approval. If the filling is false and violates the regulations, I will bear full responsibility.

Signature of the project leader:

Date： 2025.4.25