Clinical Efficacy Study of Bachmann Bundle Pacing in Improving New-Onset Atrial Fibrillation in Patients with Cardiac Insufficiency

Study Protocol

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1 Study Overview/Background/Rationale

Chronic heart failure (HF) is one of the most common cardiovascular diseases with a poor prognosis at present and in the future. For specific types of HF patients, cardiac resynchronization therapy (CRT) or implantable cardioverter-defibrillator (ICD) can effectively improve cardiac function and prevent sudden cardiac death. Atrial fibrillation (AF) is the most common arrhythmia comorbid with HF, and the two conditions often coexist, interact synergistically, and cause each other. According to the Framingham Heart Study, more than half of patients with new-onset HF have comorbid AF, and more than one-third of patients with new-onset AF suffer from HF. The risk of death is significantly higher when the two conditions coexist. Epidemiological data show that the cumulative incidence of AF after pacemaker implantation is as high as 30-40%, which is significantly higher than that in the general population without pacemaker implantation. Different pacing modes and sites may have different impacts on the incidence of post-operative AF.

Traditional atrial pacing involves placing the atrial electrode in the right atrial appendage (RAA). Due to its anatomical characteristics, the RAA offers reliability and stability for electrode lead implantation, making it a commonly used pacing site in clinical practice. However, RAA pacing prolongs interatrial conduction, leads to asynchronous atrial contraction and hemodynamic changes, and is prone to inducing AF, which is a non-

physiological pacing method. Studies have indicated that the incidence of new-onset AF in patients with sinus bradycardia receiving RAA pacing is as high as 30-40%. How to prevent new-onset AF in chronic HF patients undergoing CRT or ICD therapy has long been a major clinical challenge. The Bachmann bundle is currently recognized as the most physiological pacing site within the atria. Implanting a pacing electrode in the Bachmann bundle region not only ensures stable pacing parameters but also results in a narrower P wave compared with the intrinsic sinus rhythm and traditional RAA pacing, achieving synchronous activation of the left and right atria. A study by Bailin et al. demonstrated that Bachmann bundle pacing can reduce the relative risk of paroxysmal AF progressing to persistent AF. Another retrospective study comparing the effects of traditional atrial pacing (including RAA pacing and right interatrial septal pacing) and Bachmann bundle pacing on AF/atrial tachycardia (AT) showed that patients receiving Bachmann bundle pacing had a significantly lower AF/AT burden than those receiving traditional atrial pacing ($P<0.001$). During long-term follow-up, the atrial arrhythmia burden in patients with Bachmann bundle pacing was lower than that in the traditional atrial pacing group ($P<0.05$), and the risk of AF/AT recurrence and new-onset AF/AT in the Bachmann bundle pacing group was also lower than that in the traditional atrial pacing group ($P<0.01$).

Based on these findings, our research team hypothesizes that Bachmann

bundle pacing helps reduce the risk of new-onset AF and related adverse HF events in HF patients undergoing CRT/left bundle branch pacing (LBBP) or ICD therapy. However, such studies are still scarce both domestically and internationally.

Our research team has long been engaged in the field of physiological pacing, and the relevant preliminary research results provide key support for this study entitled "Clinical Efficacy of Bachmann Bundle Pacing in Improving New-Onset Atrial Fibrillation in Patients with Cardiac Insufficiency". The team has published numerous research articles focusing on physiological pacing, which corely confirmed that left bundle branch area pacing can effectively reduce the incidence of new-onset AF in patients compared with traditional right ventricular pacing. Derived from the core logic that "physiological pacing can optimize cardiac electrophysiological conduction and reduce the risk of arrhythmias", this conclusion provides direct efficacy-related evidence for the study hypothesis that "Bachmann bundle pacing (a nearly physiological atrial pacing site) can reduce the risk of new-onset AF in HF patients", verifying the application value of physiological pacing technology in the prevention of AF.

Meanwhile, the team's ongoing "Randomized Controlled Study on the Clinical Efficacy of LBBP-CRT and BiVP-CRT (LBBP-RESYNC Study)", the world's first multicenter, prospective, head-to-head comparative study

independently completed by Chinese scholars, has confirmed that LBBP-CRT can improve left ventricular function and promote left ventricular reverse remodeling more significantly than traditional BiVP-CRT, providing a novel strategy for CRT therapy in patients with end-stage HF. This study not only accumulated experience in the design of clinical studies on physiological pacing (such as randomized controlled framework, multi-dimensional efficacy evaluation), technical operation specifications and data quality control methods for the team, but also further consolidated the theoretical basis of "physiological pacing can improve the prognosis of HF patients" from the perspective of "physiological pacing optimizes cardiac structure and function". It forms a technical logical response with the exploration of the atrial-level efficacy of Bachmann bundle pacing in this study, providing a solid preliminary guarantee for the smooth implementation of the study and the reliability of the conclusions.

2 Study Objectives

Chronic HF and AF are two highly prevalent diseases in the cardiovascular field, and they often form a "vicious circle": in HF patients, decreased left ventricular function leads to left atrial structural remodeling and electrophysiological disorders, which are more likely to induce AF; in turn, AF episodes further result in the loss of atrial booster pump function and further impairment of ventricular pump function, significantly increasing the hospitalization rate, stroke incidence and all-cause mortality in HF

patients. With the continuous growth in the number of patients with chronic HF, the risk of new-onset AF is also rising. At the same time, adverse events caused by AF episodes, such as stroke and exacerbation of HF, further increase the consumption of medical resources and impose a heavy burden on the social medical system. Therefore, preventing AF in patients with chronic heart failure is an important clinical challenge that must be faced in the cardiovascular field at present and in the future.

At present, clinical treatment for preventing AF in patients with chronic heart failure still faces many difficulties. Both the limitations of drug intervention and the deficiencies of traditional pacing technology highlight the important clinical challenge of this field at present and in the future. There are three internodal tracts connecting the sinoatrial node and the atrioventricular node. The interatrial tract (Bachmann bundle) branching from the anterior internodal tract can conduct electrical impulses to the left atrium. Therefore, the Bachmann bundle is an important component of the cardiac conduction system, mainly located in the myocardial tissue at the top of the right atrium and extending to the upper part of the left atrium. It ensures the coordinated contraction of the left and right atria by rapidly conducting electrical signals generated by the sinoatrial node to the left atrium, and is a key structure for maintaining normal cardiac rhythm.

The emergence of Bachmann bundle pacing technology may become a safe, effective, low-cost and promotable pacing technology for preventing new-

onset AF without increasing the cost of pacing therapy. Therefore, exploring whether Bachmann bundle pacing technology can prevent or reduce the risk of new-onset AF in chronic HF patients undergoing CRT/LBBP or ICD therapy, thereby improving the prognosis and reducing related adverse events such as HF rehospitalization and stroke, has important clinical significance.

This study intends to explore the clinical efficacy of Bachmann bundle pacing technology in reducing new-onset AF and improving cardiac function and related adverse events in HF patients undergoing CRT or ICD therapy through a multicenter, randomized controlled study. By comparing and analyzing whether Bachmann bundle pacing is superior to traditional right atrial appendage pacing in its effects on new-onset AF and cardiac function in HF patients undergoing CRT/LBBP or ICD therapy, this study aims to explore a new atrial pacing treatment strategy for chronic HF patients and provide important evidence-based medical evidence for the improvement of clinical outcomes in HF patients undergoing CRT or ICD therapy with the new Bachmann bundle pacing technology.

3 Study Methods

3.1 Study Design

This study is designed as a multicenter, prospective, assessor-blinded, randomized controlled clinical trial. The study subjects are sinus rhythm HF patients with indications for CRT/LBBP or ICD implantation and no

previous history of AF. Patients will be randomly assigned to the Bachmann bundle pacing group or the traditional atrial pacing group before surgery, and followed up at regular intervals of 3-6 months after surgery. The primary study endpoint is the occurrence of new-onset AF during the 12-month follow-up after atrial electrode implantation. By comparing and analyzing the clinical efficacy of Bachmann bundle pacing group and traditional atrial pacing group on new-onset AF in HF patients undergoing CRT/LBBP or ICD therapy, the study aims to explore whether Bachmann bundle pacing is superior to traditional atrial pacing in its effects on cardiac function in patients with chronic cardiac insufficiency.

This study adopts an assessor-blinded design, i.e., "blinding is applied to outcome assessors and data statisticians, but not to the operating surgeons". The reason for not blinding the surgeons is that there are significant differences between Bachmann bundle pacing and traditional atrial pacing in electrode implantation sites and intraoperative localization methods (requiring identification of Bachmann bundle potentials), and surgeons need to be clearly aware of the grouping to complete the surgical operation. However, blinding the outcome assessors can minimize bias to the greatest extent. The specific blinding measures are as follows:

1. Pacemaker programmers, electrocardiogram (ECG) and Holter analysts (core outcome measure assessment)

1.1 Blinded subjects: Full-time physicians in the hospital's ECG

department (responsible for analyzing pacemaker programming parameters, 12-lead ECG P-wave parameters, and 24-hour Holter arrhythmia events).

1.2 Implementation measures:

a) During pacemaker programming, ECG and Holter recording, the device number is only associated with the patient's screening number, and the grouping information is not displayed;

b) The analysis report only describes "P-wave duration/amplitude during paced rhythm" and "type of atrial events (e.g., AF episodes)", without mentioning "Bachmann bundle pacing" or "traditional pacing";

c) If pacing-related problems requiring confirmation are found in the analysis (e.g., abnormal pacing threshold), communication with the study coordinator is only conducted through the screening number, without inquiring about grouping information.

2. Echocardiographic assessors (cardiac function measure assessment)

2.1 Blinded subjects: 3 senior echocardiography experts responsible for measuring echocardiographic related parameters.

2.2 Implementation measures:

a) During echocardiographic examination, the examining technician only records the patient's screening number and does not label the grouping information;

b) When storing echocardiographic reports and images, fields related to

"pacing mode" (e.g., description of electrode implantation site) are concealed, and only basic patient information (screening number, examination date) is retained;

c) When reviewing images, experts from the core echocardiographic laboratory only obtain de-identified images and reports without grouping information, complete the measurement of indicators independently, and enter the measurement results into a special blinded database, with no communication with the study execution team before statistical analysis.

3. Statistical analysts (data processing and result analysis)

3.1 Blinded subjects: Independent statistical team (responsible for data entry, verification and statistical analysis).

3.2 Implementation measures:

a) During the data entry stage, "group code substitution" is adopted, with the "Bachmann bundle pacing group" labeled as "Group A" and the "traditional atrial pacing group" labeled as "Group B". Statisticians only have access to the codes and do not know the actual grouping corresponding to the codes;

b) After the completion of statistical analysis, a "blinded analysis report" (presenting results with Group A/B) is issued first. After the research team confirms no data questions and completes data locking, the statistical center will unblind the data and generate the final analysis report corresponding to the actual grouping.

4. Adverse event assessors (safety outcome assessment)

4.1 Blinded subjects: Adverse event assessment experts designated by the hospital's clinical research ethics committee (responsible for judging whether complications are related to pacing mode).

4.2 Implementation measures:

a) In the adverse event report form, only "type of event (e.g., lead displacement, pericardial effusion)", "occurrence time" and "treatment measures" are recorded, with pacing mode information concealed;

b) When conducting assessments, experts independently judge the correlation between events and treatment based on de-identified report forms without grouping information and original medical records (with the description of pacing site in surgical records concealed), and submit the assessment results directly to the ethics committee without feedback to the study execution team.

5. Blinding maintenance and unblinding rules

5.1 Blinding maintenance:

a) All study data with de-identified grouping information (e.g., echocardiographic images, ECGs, case report forms) are labeled with a "blinded" identifier, stored in a special encrypted folder, and only authorized blinded subjects have access;

b) In project meetings held during the study, surgeons and follow-up physicians are prohibited from disclosing patient grouping information to

outcome assessors and statisticians; if an "unexpected unblinding" occurs (e.g., an assessor accidentally learns the grouping), the unblinding time, reason and involved patients must be recorded immediately. The data of these patients must be marked separately in the analysis, and sensitivity analysis must be performed if necessary.

5.2 Unblinding rules:

a) Unblinding time: Unblinding will be witnessed by the study principal investigator (PI, Professor Fan Xiaohan), independent statistician and representative of the ethics committee after all patients complete the 12-month follow-up and all data are entered and locked after verification;

b) Unblinding sequence: First, unblind the "correspondence between group codes and actual grouping", and then improve the final statistical report based on the unblinding results; if a serious adverse event occurs during the study and emergency judgment on its correlation with treatment is required, an "emergency unblinding" can be applied for, but it must be approved by the ethics committee, the reason for unblinding must be recorded, and only the relevant judging personnel are informed. The blinded state will be restored after the judgment is completed.

This study adopts a stratified block randomization design, with "type of implanted device" as the stratification factor, dividing the study subjects into the "CRT/LBBP implantation subgroup" and the "ICD implantation subgroup". The stratification is based on the differences in indications,

implantation procedures and patients' basic conditions of different devices in clinical treatment. Stratified randomization can ensure the balance of baseline characteristics between the Bachmann bundle pacing group and the traditional atrial pacing group in each subgroup, reduce the confounding effect of device type differences on the study results, and make the comparison of efficacy between groups more targeted and reliable. Setting blocks can ensure the balance of the number of patients between the experimental group and the control group. The block size is determined by the independent statistical team according to the actual situation. The specific measures of the randomization scheme are as follows:

1. Enrollment confirmation and stratification: After the patient completes the screening period assessment (meeting the inclusion/exclusion criteria and signing the informed consent form), the study coordinator selects the corresponding stratified subgroup (CRT/LBBP or ICD) in the randomization system according to the finally determined "type of implanted device".
2. Allocation execution: Using a central randomization system, after the study coordinator enters the basic patient information (e.g., initials, screening number) into the system, the system automatically generates a unique random allocation number and immediately feeds back the "allocated group" (Bachmann bundle pacing group or RAA

pacing group). This process is irreversible and fully traceable.

3. Surgical connection: The study coordinator informs the surgeon of the allocation result and performs electrode implantation according to the allocated group; if the attempt of Bachmann bundle pacing fails, it will be converted to traditional atrial pacing according to the protocol. The reason for failure (e.g., anatomical variation, inability to place the electrode) must be recorded in detail in the "surgical record form" and included in the intention-to-treat (ITT) analysis.

3.2 Study Subjects

3.2.1 Definition of Inclusion and Exclusion Criteria for All Study Populations

Inclusion Criteria

1. Aged 18 to 70 years;
2. Diagnosed with chronic cardiac insufficiency in accordance with current guidelines based on symptoms and signs, and receiving guideline-directed medical therapy (GDMT) for at least 3 months;
3. With indications for CRT/LBBP or ICD implantation and an expected atrial pacing percentage of more than 20%, including: ① Symptomatic HF patients with sinus rhythm, QRS duration >120 ms, left bundle branch block (LBBB) and LVEF ≤35%; ② Symptomatic HF patients with sinus rhythm, QRS duration ≥150 ms, non-LBBB and LVEF ≤35%; ③ Symptomatic HF patients with sinus rhythm,

QRS duration >120 ms, LBBB and LVEF of 36%-50%; ④ Symptomatic HF patients with an expected ventricular pacing percentage >20% and LVEF ≤50%; ⑤ Patients with symptomatic HF and LVEF ≤50% who require ICD implantation for primary or secondary prevention of sudden death, and have indications for atrial pacing due to sinus bradycardia or an expected atrial pacing percentage of more than 20%; ⑥ Patients with pacing-induced HF requiring upgrade therapy, in sinus rhythm and undergoing reimplantation of atrial electrodes or reimplantation after removal of the original atrial electrodes.

4. Signed the study informed consent form.

Exclusion Criteria

1. Expected survival time of less than 12 months;
2. Post mechanical tricuspid valve replacement or congenital heart disease (including dextrocardia, transposition of the great arteries, persistent left superior vena cava);
3. Previous history of AF;
4. Previous cardiac surgery or need for surgical treatment due to severe structural heart disease within 1 year;
5. Pregnancy, planned pregnancy or heart transplantation;
6. Refusal of the patient to participate.

3.2.2 Grouping of Study Subjects

This study adopts a stratified block randomization design, with "type of implanted device" as the stratification factor, dividing the study subjects into the "CRT/LBBP implantation subgroup" and the "ICD implantation subgroup". The stratification is based on the differences in indications, implantation procedures and patients' basic conditions of different devices in clinical treatment. Stratified randomization can ensure the balance of baseline characteristics between the Bachmann bundle pacing group and the traditional atrial pacing group in each subgroup, reduce the confounding effect of device type differences on the study results, and make the comparison of efficacy between groups more targeted and reliable. Setting blocks can ensure the balance of the number of patients between the experimental group and the control group. The block size is determined by the independent statistical team according to the actual situation.

3.2.3 Study Procedures and Interventions

The study is carried out in three stages, covering enrollment, follow-up and data processing, with strict quality control and blinded design throughout the process.

1. Preparatory stage

1.1 Protocol approval: Complete study registration and ethical committee review to ensure compliance with the Declaration of Helsinki and medical ethical norms.

1.2 Personnel training: Conduct special training for surgeons, follow-up personnel and data statisticians to unify surgical operation specifications, endpoint definitions (e.g., diagnostic criteria for new-onset AF) and data collection standards.

1.3 Pilot study: Conduct pre-collection and pre-analysis of data from a small number of cases, correct data collection problems, and initiate formal enrollment after confirming the feasibility of the process.

2. Patient enrollment and intervention implementation stage

2.1 Patient screening: Screen patients aged 18-70 years with a diagnosis of chronic cardiac insufficiency, indications for CRT/LBBP or ICD implantation and no history of AF in accordance with the inclusion/exclusion criteria.

2.2 Random grouping: Adopt a stratified block randomization design with "type of implanted device" (CRT/LBBP or ICD) as the stratification factor, and divide the patients into the Bachmann bundle pacing group (55 cases) and the traditional atrial pacing group (55 cases) at a 1:1 ratio. The allocation results are generated through a central randomization system.

2.3 Surgical intervention: The surgeon performs pacing electrode implantation according to the grouping. The Bachmann bundle pacing group needs to localize the Bachmann bundle region and record the intracavitary ECG, while the traditional group undergoes implantation in the right atrial appendage; if the attempt of Bachmann bundle pacing fails,

it is immediately converted to traditional atrial pacing, and the reason for failure is recorded.

2.4 Baseline data collection: Collect patient demographic information, medical history, cardiovascular medication, NYHA classification, echocardiographic parameters (atrial size, LVEDD, etc.), 24-hour Holter, NT-proBNP and pacing-related parameters (threshold, sensing, impedance).

3. Follow-up and data processing stage

3.1 Regular follow-up: Conduct follow-up at 1 week, 3 months, 6 months, 9 months and 12 months after surgery to collect information on survival status, clinical symptoms, medication status, ECG, Holter, echocardiography, pacemaker parameters and adverse events (e.g., HF rehospitalization, death); additional assessments are performed at any time when patients develop symptoms.

3.2 Data management: Collect data using standardized case report forms (CRFs) and an electronic data capture (EDC) system. Establish a special team for data desensitization, storage and quality control. The core echocardiographic laboratory adopts blinded image review to analyze cardiac function indicators.

Statistical analysis: Data are processed in accordance with the ITT principle. The primary endpoint (new-onset AF within 12 months) and secondary endpoints (e.g., surgical success rate, changes in cardiac

function) are analyzed using t-test, chi-square test, Kaplan-Meier method, etc. Subgroup analysis is performed according to the "type of implanted device" to verify the reliability of the results.

Interventions: The core of the intervention is the comparison of two atrial pacing modes, focusing on technical operation and efficacy and safety assessment.

1. Experimental group: Bachmann bundle pacing

1.1 Operation method: Intraoperatively identify the Bachmann bundle region through anatomical localization and intracavitary ECG, and implant the pacing electrode in this region to ensure characteristic ECG manifestations during pacing (e.g., positive P waves in leads I, II, III and aVF, biphasic or negative P waves in lead V1, and narrowed P wave duration compared with sinus rhythm).

1.2 Parameter monitoring: Record pacing threshold, sensing and impedance intraoperatively, and regularly program the pacemaker during post-operative follow-up to adjust parameters for maintaining stable pacing function.

1.3 Failure contingency plan: If the electrode cannot be accurately localized or the pacing parameters fail to meet the standards, immediately convert to traditional atrial pacing to ensure effective treatment for the patient.

2. Control group: Traditional atrial pacing

1.1 Operation method: Implant the pacing electrode in the right atrial appendage (RAA), a routine clinical operation that relies on the anatomical convenience of the site to ensure electrode stability.

1.2 Parameter monitoring: Same as the experimental group, monitor pacing threshold, sensing, impedance and other parameters intraoperatively and during post-operative follow-up to ensure normal pacing function.

General interventions and follow-up management

- Basic therapy: Patients in both groups continue to receive GDMT for at least 3 months, and medication adjustments are recorded during follow-up.
- Safety monitoring: Track perioperative complications (e.g., lead displacement, pericardial effusion) and adverse events within 12 months after surgery (all-cause death, HF rehospitalization, stroke) throughout the study. Experts designated by the ethics committee conduct blinded assessments of the correlation between events and pacing mode.

3.2.4 Follow-up Methods

All study subjects will be enrolled within 1 year, and various observation indicators will be followed up according to the following schedule:

Data Collection Criteria	**Screening Visit**	**Baseline**	**Month 3**	**Month 6**	**Month 9**	**1 Year**	**Unscheduled**
Inclusion/Exclusion Criteria	√						

Data Collection Criteria	Screening Visit	Baseline	Month 3	Month 6	Month 9	1 Year	Unscheduled
Patient Demographic Information, Medical History	√						
Cardiovascular Medication	√	√	√	√	√	√	√
Physical Examination (Including NYHA Classification)	√	√	√	√	√	√	√
Routine Echocardiography	√			√		√	√
24-hour Holter Examination	√		√	√	√	√	√
Posteroanterior Chest X-ray		√	√			√	√
NT-proBNP		√		√		√	√
Implantation Data (Including Implantation Time, Fluoroscopy Time)		√					
Fluoroscopic Images of Pacemaker Lead Implantation (RAO 30°, LAO 45°)		√					
12-lead ECG and EGM in Intrinsic Rhythm	√	√					
Information on Pacemaker and Electrode Lead Type		√					
12-lead ECG and EGM in Paced Rhythm		√	√	√	√	√	√
Pacemaker Pacing, Sensing, Impedance and		√	√	√	√	√	√

Data Collection Criteria	Screening Visit	Baseline	Month 3	Month 6	Month 9	1 Year	Unscheduled
Battery Life Data, Atrial/Ventricular Pacing Percentage, Atrial High-Rate Events, etc.							
Recent or New-Onset Arrhythmia Events	√	√	√	√	√	√	√
Recent Cardiovascular Surgery and Operative Events	√		√	√	√	√	√
All-Cause Death			√	√	√	√	√
Newly Diagnosed HF Requiring Diuretic or Device Therapy			√	√	√	√	√
Pacing-Related Serious Adverse Events		√	√	√	√	√	√
Study Protocol Deviation Report (if applicable)	√						

Note: The time window for each follow-up point is the preset core time point ± 30 days.

3.3 Selection and Confirmation of Study or Outcome Measures

3.3.1 Primary Study Endpoint

Occurrence of new-onset AF during the 12-month follow-up after implantation of CRT/LBBP or ICD devices.

For the primary endpoint of incidence of new-onset atrial fibrillation at 12 months post-implantation, in addition to the overall population analysis, a

pre-specified stratified subgroup analysis by type of implanted device will be performed as a confirmatory analysis of the primary efficacy.

3.3.2 Secondary Study Endpoints

1. Time to the occurrence of new-onset AF during the follow-up after implantation of CRT/LBBP or ICD devices;
2. Immediate surgical success rate of Bachmann bundle pacing and incidence of perioperative complications in the two pacing groups;
3. Changes in echocardiographic parameters such as atrial size, valvular regurgitation severity, LVEDD and LVESV assessed by echocardiography in the two groups at 12 months of follow-up compared with baseline;
4. Changes in NYHA classification, 6-minute walk distance and NT-ProBNP level in the two groups at 12 months of follow-up compared with baseline;
5. Comparison of ECG P-wave duration, P-wave amplitude, P-wave vector, interatrial block, ventricular pacing threshold, sensing and impedance between the two groups at baseline and 12 months of follow-up;
6. Surgical complications in the two groups within 12 months of follow-up;
7. HF rehospitalization events, all-cause death events or stroke events

in the two groups within 12 months of follow-up.

All secondary endpoints (including time to new-onset atrial fibrillation, surgical success rate, changes in cardiac function, incidence of adverse events, etc.) will also undergo pre-specified subgroup analysis comparing CRT/LBBP vs ICD concurrently.

3.3.3 Definition of Study Endpoints

1. Definition of new-onset AF after device implantation: AF episodes with a duration of at least 30 seconds detected by pacemaker programming or surface 12-lead ECG, confirmed as AF by manually checking atrial high-rate episodes (atrial rate ≥190 bpm) detected by the device.
2. All-cause death: Refers to death from any cause occurring during the study period, including cardiovascular death and non-cardiovascular death.
3. HF rehospitalization event: Refers to rehospitalization treatment events caused by exacerbation of HF during the study period. Patients are required to have: A. New or worsened HF symptoms; B. Objective evidence of HF exacerbation, including physical examination or laboratory indicators; C. Dose escalation of original HF treatment drugs, application of intravenous therapeutic drugs or

initiation of mechanical or surgical intervention therapy.

3.3.4 Definition of Successful Bachmann Bundle Pacing

1. Judgment of Bachmann bundle pacing by paced ECG manifestations: Positive P waves in leads I, II, III and aVF, similar to normal sinus rhythm; biphasic or negative P waves in lead V1; peaked and symmetrical P waves in inferior leads, with the amplitude of paced P waves generally greater than that of sinus P waves; compared with sinus P wave duration, the P wave duration of Bachmann bundle pacing is narrowed, and if underlying intraatrial block exists, the narrowing is usually more than 10 ms.
2. Judgment of Bachmann bundle pacing by combining intraoperative intracavitary ECG and paced surface ECG manifestations: Recording of Bachmann bundle potentials; narrowed P wave duration of Bachmann bundle pacing compared with sinus P wave duration; similar P wave morphology and electrical axis of Bachmann bundle pacing to sinus P waves; transformation of P wave morphology of Bachmann bundle pacing from non-selective to selective under high and low pacing output voltages.

3.3.5 Measurement Method of Paced QRS Complex Duration

Measurement is performed at a paper speed of 100 mm/s and an output of 2 V/0.4 ms on a multichannel recorder. The QRS complex duration is defined as the time from the pacing signal to the end of the QRS complex

in lead V1.

3.3.6 CIED Adverse Events

Including perioperative death, surgery-related cardiac tamponade, pericardial effusion, pneumothorax, hemothorax, lead displacement, ventricular septal perforation, implant system infection, etc.

3.4 Early Termination of the Study

Triggers for early termination: Combining the study design objectives and risk control priorities, the core scenarios triggering early termination include the following two categories:

1. Efficacy-related termination criteria:

1.1 Clear superiority or ineffectiveness shown by interim data analysis: The independent statistical team conducts interim data monitoring according to the preset protocol (e.g., when 50% of patients are enrolled or at 6 months of follow-up). Termination assessment can be initiated if the following conditions occur:

a) Excessive superiority: The incidence of new-onset AF within 12 months in the Bachmann bundle pacing group is significantly lower than that in the traditional group (e.g., intergroup difference ≥30% and $P<0.001$), and the trend is still maintained after continuous verification. From an ethical perspective, continuing to let the control group receive traditional pacing may deprive patients of benefits, and early termination is required to promote the optimal scheme.

b) Confirmation of ineffectiveness: Interim data show no statistically significant difference in the incidence of new-onset AF between the two groups (P>0.5), and subgroup analysis (CRT/LBBP subgroup, ICD subgroup) does not suggest the advantage of Bachmann bundle pacing. Continuing enrollment will fail to achieve the study objectives and cause resource waste.

1.2 Emergence of alternative therapies or new evidence: If high-level evidence-based evidence (e.g., multicenter RCT) is published during the study, confirming the ineffectiveness of Bachmann bundle pacing in the same population or the existence of a better alternative technology, the study needs to be terminated from the perspective of scientific rationality.

2. Safety-related termination criteria:

2.1 Clustered occurrence of serious adverse events (SAEs): If SAEs directly related to the intervention occur in the Bachmann bundle pacing group, the study must be suspended immediately and termination assessed if any of the following conditions is met:

a) Two or more SAEs of the same type occur in a single center (e.g., intraoperative cardiac tamponade, severe arrhythmia caused by lead displacement within 30 days after surgery), and are judged by adverse event assessment experts to be directly related to Bachmann bundle pacing operation.

b) The incidence of SAEs in the group is significantly higher than the preset

safety threshold (e.g., perioperative SAE incidence >10%, far exceeding the baseline reference of "traditional pacing complication incidence of about 3%-5%" in the application), or significantly higher than that in the control group (e.g., the incidence of SAEs in the Bachmann bundle group is 3 times or more that in the traditional group).

2.2 Failure of safety verification of pacing technology: Unexpected long-term safety risks of Bachmann bundle pacing are found during post-operative follow-up, such as:

a) Unstable pacing parameters: Pacing threshold continues to increase (more than 50% higher than the intraoperative baseline value) within 3 months after surgery and cannot be improved by programming, resulting in a pacing failure rate >15%.

b) Delayed complications: Occurrence of delayed pericardial effusion, cardiac structural injury (e.g., atrial septal perforation) related to electrode implantation, with an incidence exceeding the clinically acceptable range.

4 Sample Size Estimation and Statistical Analysis

4.1 Sample Size Estimation

This study is a prospective, single-blinded, randomized controlled study, with the experimental group receiving Bachmann bundle pacing and the control group receiving traditional atrial pacing. Since there are no relevant research reports on the effect of Bachmann bundle pacing on new-onset AF in patients with cardiac insufficiency at present, based on previous

research results and clinical experience, the incidences of paroxysmal AF progressing to persistent AF after traditional atrial pacing and Bachmann bundle pacing are 53% and 25%, respectively. The sample size is calculated with reference to the above trial results. With a two-sided test significance level of α=0.05 and a power of 0.9, the sample size ratio of the experimental group to the control group is set to 1:1, and considering a certain loss to follow-up rate (not exceeding 10%), the final planned enrollment number of this study is 140 cases, including 70 cases in the experimental group and 70 cases in the control group.

The specific reference is as follows: BAILIN S J, ADLER S, GIUDICI M. Prevention of chronic atrial fibrillation by pacing in the region of Bachmann's bundle: results of a multicenter randomized trial [J]. J Cardiovasc Electrophysiol, 2001, 12(8): 912-7.

4.2 Statistical Analysis Plan

The trial data of this study will be analyzed in accordance with the ITT principle. The specific analysis methods include: descriptive analysis using mean ± standard deviation or frequency and percentage according to variable types; comparison of baseline balance between groups using independent samples t-test, Wilcoxon rank-sum test (for quantitative indicators with normal or non-normal distribution), or chi-square test and Fisher's exact probability test (for qualitative indicators); for the primary endpoint indicator, analysis of covariance is used to compare the

differences in new-onset AF or atrial high-rate events between patients with different pacing modes, with block factors as covariates. Similar statistical analysis methods to baseline are used for secondary and safety indicators; further subgroup analysis is performed when necessary to evaluate the reliability of the trial results. Statistical software such as SPSS (IBM, USA), Stata (StataCorp, USA) or R language is used for statistical analysis.

Combined with the study design type of "multicenter, prospective, single-blinded, randomized controlled" and the core objective of "evaluating the preventive effect of Bachmann bundle pacing on new-onset AF in HF patients", a two-sided test is uniformly adopted with a strict test level of $\alpha=0.05$. The specific application scenarios and basis are as follows:

Primary endpoint analysis (core efficacy judgment)

For the primary endpoint of this study: "whether new-onset AF occurs during the follow-up after device implantation". Calculate the incidence of new-onset AF in the experimental group and the control group at 12 months after surgery, estimate the difference in the incidence of new-onset AF at 12 months after surgery between the two groups and its 95% confidence interval (CI), and compare the lower limit of the CI of the difference with 0 to judge whether the superiority hypothesis is established. Meanwhile, the Kaplan-Meier (KM) method is used to estimate the difference in the incidence of new-onset AF at 12 months after surgery and

its 95% CI as a sensitivity analysis.

Secondary endpoint analysis (supportive efficacy and safety judgment)

For secondary endpoints (e.g., time to first new-onset AF after device implantation, surgical success rate, changes in cardiac function indicators, incidence of complications, etc.), the test level is set to $\alpha=0.05$ synchronously without multiple test correction. The specific logic is as follows:

1. Time to first new-onset AF: The "AF-free survival curve" of the two groups is plotted by the Kaplan-Meier method, and the log-rank test is used to compare the differences between the curves, also with $\alpha=0.05$ as the boundary. If $P<0.05$, it indicates that Bachmann bundle pacing has an advantage in delaying the occurrence time of new-onset AF, which is consistent with the core study objective of "reducing the risk of AF occurrence and improving prognosis".
2. Surgery-related indicators: When comparing the immediate surgical success rate and the incidence of perioperative complications (e.g., lead displacement, pericardial effusion) between the two groups, the chi-square test or Fisher's exact probability test is used. $\alpha=0.05$ is used to judge the technical feasibility and safety of Bachmann bundle pacing. If $P<0.05$, it indicates that this technology is superior to traditional pacing in surgical effect or safety.
3. Cardiac function and electrophysiological indicators: When

analyzing echocardiographic parameters (LVEDD, LVESV, atrial size, etc.), NYHA classification improvement rate, changes in 6-minute walk distance, reduction amplitude of NT-proBNP level, and differences in ECG P-wave duration/amplitude between the two groups, the independent samples t-test (for normally distributed data) or Wilcoxon rank-sum test (for non-normally distributed data) is used. $\alpha=0.05$ is used to verify whether Bachmann bundle pacing can simultaneously improve cardiac function and atrial electrophysiological stability.

Subgroup analysis (exploratory conclusions)

When conducting subgroup analysis stratified by "type of implanted device" (CRT/LBBP subgroup, ICD subgroup), the comparison of "whether new-onset AF occurs" within each subgroup still adopts $\alpha=0.05$, but it is clearly stated that this analysis is an exploratory conclusion and not used as the sole basis for the final efficacy judgment:

1. Only when $P<0.05$ is shown in each subgroup (CRT/LBBP subgroup, ICD subgroup) and the effect direction is consistent (all indicating the superiority of Bachmann bundle pacing), it can assist in explaining the consistency of the efficacy of this technology in populations treated with different devices;
2. If heterogeneity occurs between subgroups (e.g., $P<0.05$ in one subgroup and $P>0.05$ in another), further analysis should be

conducted in combination with patients' baseline characteristics to avoid overinterpreting the exploratory results and affecting the core conclusions, which is consistent with the study design logic of "focusing on the primary endpoint and taking into account the secondary endpoints".

5 Data Management

This study is a multicenter randomized clinical study. The Uncom Medical Research Cloud Platform EDC system is used for data entry and verification. The principal investigator, Director Fan Xiaohan, has full access and management rights to all data. Data entry personnel only have the right to enter data, without the rights to delete, export or store data. If an application for data modification is required, a modification application must be submitted to Director Fan Xiaohan, and the modification can only be made after approval. All entered data is encrypted and de-identified on the platform, and the data entry quality controller is responsible for manual verification. For the future use of data, a data analysis plan must be provided and submitted to Chief Physician Fan Xiaohan, and the application for use can only be made after discussing the feasibility. All applications are traceable on the platform.

6 Confidentiality Principles

Issue of protecting subjects' right to informed consent and autonomous choice: Inadequate informed of study details may lead to

incomplete informed consent of subjects and affect autonomous decision-making.

Countermeasures: Strictly follow the Declaration of Helsinki. Before the start of the study, researchers shall comprehensively and clearly introduce the study purpose, process, potential risks and benefits to subjects or their legal representatives in writing, and give sufficient time for consideration; subjects can be enrolled only after signing the informed consent form approved by the ethics committee; if new safety information appears during the study, the informed content must be updated and re-signed, and it is clearly stated that subjects have the right to withdraw from the study at any time without reason, and this will not affect subsequent conventional treatment.

Issue of balancing study protocol compliance and subject safety: Bachmann bundle pacing is a relatively new physiological pacing technology with a certain risk of operation failure, and the study population is patients with chronic cardiac insufficiency with low physical tolerance, so it is necessary to balance technological exploration and patient safety.

Countermeasures: The study protocol is implemented only after being approved by the ethics committee to ensure no off-label treatment; an intraoperative emergency plan is formulated for the failure of Bachmann bundle pacing, and if it fails, the clinically mature traditional atrial pacing is immediately performed to ensure effective treatment for the patient; a

special follow-up management group is established to regularly evaluate the patient's condition and risks, record adverse events (e.g., exacerbation of HF, surgical complications, etc.), and take intervention measures in a timely manner to minimize safety risks.

Issue of protecting subjects' privacy and data security: The study involves sensitive information such as patients' personal health records, cardiac imaging data and follow-up data, with the risk of privacy leakage.

Countermeasures: Establish a strict data management system; all collected data are desensitized to remove personally identifiable information; the leading center and participating centers clarify the rights to data storage and use; original data are properly preserved by each study center, and desensitized data are only used for study analysis; regularly verify the data management process to ensure compliance with relevant privacy protection regulations and prevent data leakage.

Issue of ensuring study quality and result credibility: Non-standard data collection and inconsistent evaluation standards may affect the authenticity of study results, indirectly damage the scientificity of medical decision-making, and thus affect the rights and interests of future patients.

Countermeasures: Before the study, conduct training for all participating researchers to unify data collection standards, endpoint definitions and operation specifications; establish a core echocardiographic laboratory composed of three senior ultrasound experts, and adopt blinded image

review to analyze cardiac ultrasound data at baseline and follow-up to reduce assessment bias; conduct pre-collection and pre-analysis of data from a small number of preliminary cases to correct data collection problems in a timely manner; the leading center verifies the data of each center every month, requires the provision of original data for verification of questionable data, and eliminates unqualified data to ensure study quality.

7 Quality Control of the Study

Quality control: The following measures will be adopted for quality control in this study: 1) Before the official start of the study, researchers from participating centers will be organized to receive training on the study, including the study protocol, specific definitions, data collection standards, etc. All study centers must collect data in strict accordance with the trial protocol, and the collected variables shall be accurately defined in accordance with the study protocol to ensure data quality. 2) Establish a core echocardiographic laboratory (composed of three senior ultrasound experts). Cardiac ultrasound data at baseline and follow-up are analyzed by the core echocardiographic laboratory through blinded image review to extract data. 3) Each center conducts preliminary pre-collection of data from a small number of cases in the early stage, and the data are collected by the leading center for pre-analysis, so as to find and correct problems in the data collection process in a timely manner and conduct re-training. The

official data collection can only be started after the quality of the pre-collected data is confirmed to be qualified. 4) The leading center will be equipped with professional and technical personnel to collect data every month at the beginning of the study and conduct regular verification of the data collected by each study center to uniformly control the data quality. For questionable data after verification, each study center shall provide original data and objective evidence for confirmation, and the data still questionable after verification shall be eliminated. The person in charge of the data source center shall bear the impact caused by incorrect data collection.

8 Organizational Management of the Study

In this study, the principal investigator, Chief Physician Fan Xiaohan, is responsible for determining the study plan, screening patients, implanting devices, interpreting results and writing papers. Well-trained doctors and engineers will conduct device testing during follow-up and data entry. Data verification and quality control are managed and performed by a professional team from Fuwai Hospital, Chinese Academy of Medical Sciences to ensure the smooth progress of the study and the authenticity and completeness of the data.

9 Ethical Principles

This study strictly follows the Declaration of Helsinki and relevant clinical research ethical norms to protect the legitimate rights and interests and

safety of study participants. The specific requirements are as follows:

9.1 Ethical Committee Approval

Before enrolling study participants, ethical committee approval for the study protocol and informed consent form must be obtained. During the study, annual ethical review reports must be submitted on time to ensure that the study progress complies with ethical requirements. If the study protocol is revised, an ethical amendment review must be submitted in a timely manner, and the revised protocol can only be implemented after approval.

9.2 Informed Consent of Study Participants

Before study participants participate in this clinical study, researchers shall use the Ethics Committee-approved version of the *Informed Consent Form for Study Participants (ICF)* to fully inform participants or their legal representatives of all relevant information about participating in the study, including the study purpose, process, potential risks and benefits, data usage methods, etc. Written informed consent from participants or their legal representatives must be obtained. During the process, any coercion, inappropriate influence or inducement shall be avoided, and the legitimate rights of study participants shall not be infringed or waived in a disguised form. If a study participant is unable to read or write, a fair third party is allowed to act as a witness to assist in completing the ICF signing and data protection-related processes. The witness must sign and indicate the date

on the ICF and relevant authorization documents. The signed ICF shall be filed at the study center for supervision and review, and a signed and dated copy of the ICF must be provided to the study participant. During the entire study process, if important new information related to the study appears, it must be informed in writing to newly enrolled and already enrolled subjects; if the relevant information affects the subjects' willingness to continue participating in the study, all affected subjects are required to confirm their continued informed consent in writing.

9.3 Withdrawal of Subjects

Subjects have the right to voluntarily withdraw from the study at any time during the study process without giving reasons, and the withdrawal will not affect their subsequent conventional treatment rights and interests. After a subject withdraws from the study, no further study data will be collected from them, and no further study-related visits will be conducted. However, all available data collected before withdrawal will be used for statistical analysis in accordance with the study protocol, and data processing will strictly follow the confidentiality principles. If a subject chooses to withdraw, the researcher must record the reason for withdrawal in detail and file it in the study archives. After the completion of implant-related device implantation, if a subject withdraws, no new subjects will be enrolled to replace them.

10 References

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11 Participating Study Centers and Principal Investigators

Leading Study Center:

Fuwai Hospital, Chinese Academy of Medical Sciences

Principal Investigator: Fan Xiaohan

Participating Study Centers:

Zhongshan Hospital, Fudan University

Principal Investigator: Chen Xueying

Fuwai Huazhong Cardiovascular Hospital

Principal Investigator: Chen Ke

Tianjin Chest Hospital

Principal Investigator: Xu Jing