Prospective Randomized Controlled Clinical Study of Physiological Ventricular Rhythm Resetting in Patients with Atrial Fibrillation and Heart Failure: Rationale and Design

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Abstract

Background

Atrial fibrillation (AF) and heart failure (HF) frequently co-exist. HF may present in 20-30% of AF patients. Both AF and HF facilitate the occurrence and aggravate the prognosis of each other, which significantly affects the quality of life and increases mortality. This paper describes the rationale and the design of the trial 'Prospective randomized controlled clinical study of physiological ventricular rhythm resetting in patients with atrial fibrillation and heart failure' and the need to improve the treatment of the patients with AF and HF.

Methods

This study is a registry-based, prospective, randomized, parallel, single-center trial. The primary aim is to determine whether the physiological ventricular rhythm resetting (atrioventricular node ablation with physiological LBBP) can improve clinical outcomes (all-cause mortality or rehospitalization for HF) compared with medical rate control. A total of 110 patients will be enrolled in the trial and followed up for 1 year.

Summary

The cardioversion of AF is a major treatment for AF patients with HF. However, the recurrence rate of atrial fibrillation ablation is high and part of these patients are not suitable for ablation, which raised the difficulty to treat such patients. Some observational studies found that AVNA with physiological pacing could improve the prognosis of these patients. Thus, results from this trial may influence future treatment strategies and guidelines specific to AF patients with HF.

Background And Rationale

Atrial fibrillation (AF) and heart failure (HF) frequently co-exist. HF may present in 20-30% of AF patients [1]. Both AF and HF facilitate the occurrence and aggravate the prognosis of each other, which significantly affects the quality of life and increases mortality. The management of AF patients with HF is extremely challenging.

Rate-control and rhythm-control of AF are central to the treatment of these patients [1]. The optimal heart rate in patients with AF remains unclear. Compared with strict rate-control (rest heart rate $\leq$ 80bpm, moderate activity heart rate $\leq$ 110bpm), recent studies found that lenient rate-control (rest heart rate $\leq$ 110bpm) showed no significant difference in composite clinical endpoints, NYHA class and hospitalization [2-5]. Rhythm control includes two ways, drugs and catheter ablation. A meta-analysis found that rhythm control by drugs had no advantage over rate control. Rhythm control by catheter

ablation could reduce all-cause mortality and rehospitalization for HF, improve quality of life, and increase LVEF by 6.8% compared with medical therapy [6]. However, due to the high recurrence rate and surgical cost of AF ablation, whether catheter ablation for these patients remains a difficult decision [6–8].

Atrioventricular node ablation (AVNA) and pacing therapy (Ablation and Pacing Therapy, APT) have proved to improve the quality of life and increase LVEF as catheter ablation [9]. However, APT needs long-term right ventricular apical pacing (RVAP), which may further aggravate HF by leading to ventricular electromechanical dyssynchrony [10]. Hence, APT was only served as the last strategy for patients who are unresponsive or intolerant to intensive rate and rhythm control therapy [1]. According to recent studies, patients with AF and HF can benefit from physiological APT strategy [AVNA with His bundle pacing (HBP) or left bundle branch pacing (LBBP)] even the heart rate controlled very well [11, 12]. This suggests that irregular ventricular rhythm may be an important reversible factor in patients with AF and HF.

Here, we describe a new concept of physiological ventricular rhythm resetting (AVNA with physiological pacing) and designed a prospective, randomized clinical trial to determine whether the physiological LBBP ventricular rhythm resetting (AVNA with LBBP) can improve clinical outcomes (all-cause mortality or rehospitalization for HF) compared with medical rate-control treatment.

Methods

The physiological ventricular rhythm resetting is a registry-based, prospective, randomized, parallel, single-center trial. The primary aim is to determine whether the irregular ventricular rhythm is an important reversible factor for patients with AF and HF and whether physiological ventricular resetting reduces the composite clinical endpoints, including the rate of all-cause mortality and rehospitalization for HF. The second aims are to determine whether physiological ventricular resetting improves cardiac function, ventricular remodeling, and the quality of life. The study was approved by Ethics Review Boards in China. No. of the ethic committee: 2021-SRFA-417. Clinical Trials Registration number: ChiCTR2100047640.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Study Population And Follow Up

Inclusion and exclusion criteria in **Table I**. The study concerned with patients enrolled in the first affiliated hospital of Nanjing Medical University from July 2021 to June 2023. 110 eligible patients are expected to be included in the trial with a 1:1 allocation to receive treatment with either physiological ventricular resetting group or medical rate control group (**Figure I**) with 1 year follow-up. A computer-generated list of random treatment allocations will be used to randomize enrolled subjects. If a subject is randomized to the physiological ventricular resetting group, the procedure should implement within 30 days.

All subjects should undergo a detailed evaluation before the randomization, including baseline echocardiography (TTE), 24h-Holter electrographic monitoring, pro-B-type natriuretic peptide (pro-BNP), NYHA class, 6-minute walk test (6MWT), and the six-item specific symptom scale score (SSS). All subjects will be followed up at 1 week, 1, 3, 6, and 12 months after discharge. If a subject experienced increased edema, decreased urine, or chest tightness during follow-up, pro-BNP and TTE tests should be evaluated as early as possible. Adverse events will be recorded and handled promptly.

Procedure

All patients will receive standard treatment for AF and HF. β -blocker is the first choice for rate control (digoxin can be used when β -blocker is contraindications or not effective), aiming to make heart rate below 110 beats per minute. Any changes in the medication regimen should be written and documented.

The patients of the physiological ventricular resetting group will undergo extra AVNA and LBBP. Before the procedure, patients need to sign the consent form.

LBBP: The procedure is performed under local anesthesia. The 7-Fr guiding catheter (Model C315-S10; Medtronic Inc) and the pacing electrodes (models 3830, Medtronic Inc) were advanced into the right ventricular transvenous by left subclavian or axillary vein puncture. Move the catheter towards the apex of the heart by 1.5-2.0cm after mapping His bundle potential. Then the pacing lead was perpendicularly screwed through the interventricular septum (IVS) to the LV septal sub-endocardium of the LBB region. The paced QRS morphology and duration, pacing impedance were assessed and recorded frequently via unipolar pacing. Intra-catheter angiography was performed at the left anterior oblique position of 40° to assess the position of the electrodes and the presence of perforation. The pacing QRS and the peak time of the left ventricle were measured after high-voltage and low-voltage single-pole pacing. A pacing threshold below 1.5V@0.5ms is acceptable. During the procedure, if the left interventricular septal surface is penetrated during the screwing of the electrode, the electrode should be withdrawn, replaced, and re-implanted. All pacemakers use the VVI model and determine if defibrillation function is required according to the guidelines. The lower rate of pacemaker sets according to the mean heart rate of 24h-Holter, to ensure the heart rate is at the same level before and after the procedure. The lower rate of the pacemaker will be set according to the doctor's request and the patient's condition after the trial.

AVNA: We will perform AVN ablation after successful LBBP at the same procedure time. AVNA was performed using the quadripolar 7-Fr 4-mm tip ablation catheter. An 8.0Fr venous sheath is inserted through the right femoral vein. The key point is to record his potential after sent the ablation catheter into the right atrium. The methods for AVNA are described as follows: (i) The compact AV node was ablated from the atrial side marked by HIS potential. (ii) The ablation catheter was positioned at least 10mm away from the LBBP electrode tip. (iii) The ablation power was set at 30-50W and temperature at 43°C for a duration of 60-120s. The criteria of successful ablations are as follows: 1) persistent complete atrioventricular block; 2) the left bundle capture threshold and QRS morphology remain unchanged after ablation.

Clinical Endpoints

The primary endpoints are all-cause mortality and rehospitalization for HF. All-cause mortality is defined as the percentage of deaths for any cause. Rehospitalization for HF is defined as requiring hospitalization due to worsening symptoms of HF or AF.

The secondary endpoints are the changes in cardiac structure and function. Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular ejection fraction (LVEF) will be analyzed by TTE. Pro-BNP will also be examined to evaluate cardiac function. The functional status of general health-related quality of life will be measured by changes in the classification of NYHA, the distance of 6MWT, and the scores of the SSS scale (Table II).

Safety

Safety endpoints will be collected at visit or telephone interviews at 1, 3, 6, and 12 months post the procedure. Both the intraoperative and long-term adverse events will be well documented. Adverse events define as pneumothorax, hemopneumothorax, hematoma, pericardial effusion, an episode of acute HF, deteriorating quality of life, rehospitalization for HF and sudden death. Among them, a prolonged hospitalization, disability, impair work capacity or endanger life or death are defined as severe adverse events. The trials will be suspended if more than one subject experience severe adverse events or over half of the subjects experience adverse events. Request the evaluation of relevant experts before deciding whether to continue the trial.

Statistics Methods

The study will be considered a success if the primary endpoint is met. The expected rate of success is estimated to be an increased LVEF of 7.4% (SD=11.7), based on the data from historical trials^[6, 11]. Given a one-side test significance level of 2.5%, a total of 88 randomized subjects will provide 90% power to demonstrate superiority after adjusting for attrition. Consider the rate of loss to follow up maybe 20%, 110 subjects will be required.

Continuous variables will be expressed as mean $\pm$ standard deviation and categorical variables will be expressed as percentages. Paired comparisons were made using a Student's t-test for continuous variables. The Chi-squared or Fisher's test will be used for categorical data. Cox Proportional Risk regression model will be used to assess the risk ratio (HR) for different treatment regimens. P-value $\leq$ 0.05 was considered significant. Data management and analysis will be applied with SPSS v20.0 (IBM Corp).

Results

The study began enrolling patients in July 2021. As of November 2021, our center has randomized six patients. The majority were women (83.33%) and the mean age was 65(SD 9.3) years.

Discussion

Although the treatment for AF and HF has made great progress, it is still extremely difficult to deal with, which seriously affects the quality of life and increases mortality. In current guidelines, APT is only used as the ultimate option for patients who are unresponsive or intolerant to intensive rate and rhythm control therapy ^[1]. We analyzed the advantages, and disadvantages of different forms of APT ^[9–11, 13–16] (**Table III**). Studies found that regular RVAP can improve immediate hemodynamics compared with irregular RVAP of the same heart rate ^[9]. Nevertheless, the long-term clinical efficacy of AVNA with RVAP did not decrease rehospitalization for HF and mortality. The reason could be the mode of pacing, because RVAP may lead to ventricular mechanical dyssynchrony, and the long-term and high percentage of RVAP could induce cardiomyopathy ^[10]. To overcome the problem, biventricular pacing began to be used in APT. APAF-CRT study compared the efficacy of AVNA with biventricular pacing therapy and medical therapy. The results showed that AVNA with biventricular pacing therapy was superior to medical therapy in reducing the incidence of HF, shortening hospitalization, improving the quality of life, and reducing all-cause mortality ^[13, 14]. This study proved the efficacy of biventricular pacing but we should not ignore its disadvantages, including high incidence of nonresponse, high operative difficulty, and high cost ^[15–17]. With the emerge of physiological pacing, Wu found that patients with AF and HF could benefit from a new type of APT, AVNA with HBP or LBBP ^[11]. They proved that AVNA with HBP or LBBP could both improve cardiac function even in the patients with strict rate-control.

Based on the studies above, we speculate that irregular ventricular rhythm is an important reversible factor in patients with AF and HF. Both regular ventricular rhythm and physiological pacing are indispensable for the treatment of the disease.

We propose a new concept of physiological ventricular rhythm resetting. It is a theoretical innovation and is different from the rhythm-control or rate-control strategies for AF. Physiological ventricular rhythm resetting is a combination of both and is expected to become a major treatment strategy for patients with AF and HF. However, there are no large-scale randomized controlled trials to prove the safety and efficacy of this treatment.

Compared with HBP, LBBP has a higher success rate, and the pacing lead is more stable and secure, which can benefit more patients. Hence, we choose LBBP as the physiological pacing strategy. Based on this, we design a prospective, randomized clinical trial to determine whether the physiological ventricular rhythm resetting (AVNA with LBBP) can improve clinical outcomes (all-cause mortality or rehospitalization for HF) compared with medical rate control. The results may eventually improve the existing APT guideline evidence level.

Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

All authors intellectually contributed to the study protocol development including study design, trial intervention, inclusion and exclusion criteria of patients, measurement of variable and endpoints, and statistical analysis.

Ethics approval

The study was approved by Ethics Review Boards in China. No. of the ethic committee: 2021-SRFA-417. Clinical Trials Registration number: ChiCTR2100047640.

Consent to participate

Informed consent must be obtained from all individual participants included in the study.

Consent to publish

The authors affirm that human research participants provided informed consent for publication.

Data Availability Statements

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1 Inclusion and exclusion criteria

Inclusion criteria
1. Unsuitable or rejected for AF catheter ablation and failure in rhythm control
2. Persistent AF (resting heart rate ≤110bpm) combined with HF (LVEF < 50%) after optimal drug treatment for at least 3 months
3. Narrow QRS wave on ECG (≤120ms)
4. Age≥18 years and the expectancy life over 1 year
5. Agree to participate in the clinical trial and sign a written informed consent
Exclusion criteria
1. History of an acute coronary syndrome, cerebrovascular accident, and gastrointestinal bleeding within the last 3 months
2. Other serious heart diseases requiring surgical treatment
3. Any contraindications to ventricular rhythm resetting therapy
4. Pregnant or preparing to become pregnant or mentally ill

Table 2 Six-item Specific Symptom Scale score

	Score
Palpitations	0-10
Effort dyspnoea	0-10
Rest dyspnoea	0-10
Effort intolerance	0-10
Easy fatigue	0-10
Chest discomfort	0-10

Table 3 Advantages and disadvantages of different forms of APT

	Physiological pacing mode	Technical difficulty	Symptoms improvement	Rehospitalization Rate	mortality
AVNA+RVAP	N	+	↑	–	–
AVNA+BIVP	Partly	+++	↑	â	â
AVNA+HBP	Y	++	↑	NA	NA
AVNA+LBBP	Y	+	↑	NA	NA

APT: ablation and pacing therapy; AVNA: atrioventricular node ablation; RVAP: right ventricular apical pacing; BIVP: biventricular pacing; HBP: his bundle pacing; LBBP: left bundle branch pacing; N: not; Y: yes; +: relatively difficult; ++: difficult; +++: very difficult; ↑: symptom improvement; â: positive outcome; –: neutral outcome; NA: not available

Figures

Figure 1

Flowchart of the physiological ventricular rhythm resetting trial