A New Operation (Left Atrial Geometric Volume Reduction, Pulmonary Vein Island Isolation and Left Appendage Base Closure) for the Treatment of Long Standing Persistent Atrial Fibrillation (AF) During Mitral Valve Surgery

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Ethical committee approval:
The study was approved by research ethical committee in Fujian Medical University Union Hospital (Protocol NO. CLW2017AF**).**
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Subject Information and Consent Form

A New Operation (Left Atrial Geometric Volume Reduction, Pulmonary Vein Island Isolation and Left Appendage Base Closure) for the Treatment of Long Standing Persistent Atrial Fibrillation During Mitral Valve Surgery

Qualified Investigator: [Insert name and contact inform
Sub-Investigator(s): [Insert name(s) and contact info
Sponsor:Fujian Medical University

Introduction

You are being invited to take part in a research study. This research will study a new operation designed for the treatment of long-standing persistent atrial fibrillation based on Left Atrial Geometric Volume Reduction, Pulmonary Vein Island Isolation and Left Appendage Base Closure. It is your choice if you want to be in this study or not. Research studies are different from regular care. Research studies are ways of finding out new information that might help other people with similar conditions or illnesses to yours. This form explains why we are doing the study, and how the treatment that is being offered to you is different from regular care. It tells you what will happen during the study. It also tells you about any inconvenience, discomfort or risk with this study. It also gives you a complete description of the treatment offered. This information will help you decide whether you wish to be part of the study.

What Is The Purpose of The Study?

The main reason for doing this study is to help answer the following research question:

- Whether this new operation will maintain stable sinus rhythm after initial surgery.

Who Can Take Part In The Study?

To take part in this study you must have the diagnosis of history of a long-standing form of atrial fibrillation as defined by the HRS/EHRA/ECAS Consensus Statement. Our preliminary clinical results of our new operation concluded that this new operation can restore 100% sinus rhythm in 20 strictly selected patients and reshape the left atrium to a physiological one. Based on this satisfactory early results,a single-arm study with consecutive subjects with long-standing persistent AF will be started in the portion .For this part of the study, subjects eligible for cardiac surgery will be enrolled. Subject of phase II is scheduled to undergo elective open cardiac surgical procedure(s) to be performed on cardiopulmonary bypass for one or more of the following: Coronary Artery Bypass Grafting, Mitral valve repair or replacement, Aortic valve repair or replacement, Tricuspid valve repair or replacement. In conjunction with these procedures patent foramen ovale (PFO) or atrial septal defect (ASD) repair are allowed. The study doctor or study staff has discussed with you the requirements for being in this study. It is important that you are completely honest with the doctor and staff about your health history. You should not take part in this study if you do not meet all requirements.

You can participate in this study if:

- Able to sign Informed Consent and Release of Medical Information forms
- Age ⩾ 18 years
- Clinical indications for mitral valve surgery for the following:

Organic mitral valve disease; or Functional non-ischemic mitral regurgitation; or

Ischemic mitral regurgitation with evidence of concomitant structural mitral valve disease.

Note: May include need for surgical management of functional tricuspid regurgitation or patent foramen ovale. May also include concomitant CABG, aortic arch or aortic valve procedure. Surgical intervention may be performed via sternotomy or minimally invasive procedure.

- Longstanding persistent AF is defined as continuous AF of greater than one year duration.
- Able to use heart rhythm monitor

You cannot participate in this study if:

- Stand alone AF without indication(s) for concomitant cardiac surgery.
- Need for emergent cardiac surgery (i.e. cardiogenic shock).
- Preoperative need for an intra-aortic balloon pump or intravenous inotropes.
- Pregnancy or desire to get pregnant for the duration of the study (concomitant surgical procedure through the thirty six (36) month follow-up period).
- Enrolled in another clinical trial that could confound the results of this study.

What Does The Study Involve?

About 120 study subjects will be taking part in this study.

Your participation in this study is expected to last until you or your physician decides that there is no clear benefit for you to continue treatment. However, your physician will ask you afterwards to visit him on regular basis to follow-up on your health status.

If you decide to take part in this study, the procedures and visits you can expect are explained in the attachment called Study Procedures - Attachment 1. This will give you information about what taking part in the study will mean to you, for example, how often you have to come to see the study doctor, how long each visit might take, when tests and procedures will be performed.

Treatment Assignment

If you have indication for elective mitral valvular surgery with concomitant longstanding

persistent AF elimination, you will then enter this study. You'll be assigned to receive our new operation. The surgery you will receive will be done by surgeon or professor eligible for participation. They are required to have expertise with traditional Cox-Maze III or IV procedure.
You will continue to receive further ICU (intensive care unit) treatment for necessary cardiopulmonary support, until the status of disease improves, your doctor will decide to let you later be discharged after a total examination. Afterwards, your doctor will ask you to visit him/her on regular basis to follow-up on your health status, that is your heart function and restoration of sinus rhythm.

Study Procedures
Examinations will be taken at different time points as described in Attachment 1. The purpose of these Examinations is to help your study doctor decide if you can take part in this study and to check your health during the study.
All blood samples collected for specified laboratory tests will be destroyed within 60 days of confirmation of the test results, unless laws, regulations, or international laboratory certification standards require a longer retention period. This confirmation will either occur immediately after initial testing, or may require that samples be held to be retested at a defined later point in time.

At every other visit, or when needed, echo exams will be completed to take a series of pictures of your heart.

Following your active participation in the study, the study doctor or one of the staff members may contact you to obtain information regarding the status of your health and quality of life. If you have moved or plan to move, please provide your new contact information to the study doctor or his/her staff.

What Are The Possible Harms and Side Effects?

If you take part in this study, there may be risks to you. The **Harms and Side Effects** mainly come from the surgery, particularly the valvular surgery.

Risks and Discomforts Associated with a common heart surgery

1) Since the heart is an essential organ, there is a certain risk or danger in any cardiac surgery. Any surgical procedure is not yet 100% safe, nor can accurate predictions be made before surgery.

2) Heart surgery is thoracic surgery via median sternotomy. Due to the long operation time and large wounds, there may be a large amount of bleeding during and after surgery.Thus, blood transfusion is needed during and after operation, and even reoperation for hemostasis.

3) This operation must require the use of cardiopulmonary bypass. As a mechanical life support device, it has additional adverse effects on the human body, including disturbance in blood pressure, electrolyes, coagulation function and body temperature, etc..

4) Various arrhythmias may occur during and after heart surgery, and doctors may need to treat them by drugs or defibrillator.Very few arrhythmias are life-threatening and even require permanent pacemaker or open-chest cardiac resuscitation.

5) Trauma of heart surgery may cause irreversible damage to the heart or multiple organs of the whole body.

6) Surgical trauma may cause perioperative heart damage, cardiac insufficiency (heart failure), requiring drugs or mechanical devices (intra-aortic balloon pump, extracorporeal membrane oxygenation, ventricular assistive device, etc.), which can also cause certain side effects while assisting the heart.

7) Surgical trauma can cause damage to organs outside the heart (including liver, kidney, lungs, brain, etc.).

8) Cerebrovascular accident, cerebral thrombosis or cerebral hemorrhage, coma, hemiplegia, aphasia, confusion, epilepsy, etc. may occur.

9) Hemodialysis treatment or peritoneal dialysis is needed to treat when kidney damage, oliguresis or anuria exist.

10) Liver function damage, and postoperative jaundice, transaminase hyperplasia or even fulminant liver damage sometimes occur.

11) When postoperative respiratory function is impaired, which cannot be detached from the ventilator, the tracheal incision is required. Pneumothorax, hemothorax, pleural effusion, and pneumonia may occur during ventilator support.

12) Very few patients are suspended due to the existence of special types of lesions or other diseases that may affect the operation or the outcome.

13) Patients with bad wound healing, non-healing of the sternum or mediastinal infection which need long-term dressing change, may need to a reoperation for sternal fixation.

14) Hemolysis may occur after surgery, and severe cases need to be treated again. Some cases may require reoperation.

15) Reoperation of valve is needed for patients with severe postoperative paravavular leakage.

16) Endocarditis may occur after the implantation of prosthesis.

17) When patients implanted mechanical valve(s), valve(s) may fail, leading to acute heart failure or sudden death. Anticoagulant drugs may be used for life, and complications associated with anticoagulation may occur.

18) When patients implanted biological valve(s),valve(s) may decay and break. These patients are required to redo a valvular operation. Study doctors are unable to expect the exact time of biological valve decay, which can only be discovered through regular follow-up or the emergence of new-onset clinical symptoms.

19) For patients with valveoplasty, the effect of valve plastic surgery may not achieve the expected effect, or the effect may decline over time, and may need to reoperate (or even multiple times) if necessary.

Risks and Discomforts Associated with our new operation

1) The new operation combined with other open heart surgery may be a time-consuming procedure by prolonging cardiopulmonary bypass duration, which is a risk factor for increasing postoperative mortality.

2) The new operation is a complex procedure required manipulating several incisions to create transection of superior vena cava and isolation of pulmonary island. Thus, reattachments of these incisions may cause some risks. Reattachment of superior vena cava may cause bleeding, stenosis and thrombosis which may need to be reoperated.The anastomoses of pulmonary island may also cause bleeding , stenosis, and thrombosis which may need to be reoperated.

3) The new operation aims to reshape the left atrium from a pathological to a physiological one, but this benefit may be lost because of unknown reasons which could

cause some side effects.

The majority of these side effects may be experienced by patients receiving most open heart surgery. Complications of some of the above side effects may lead to life-threatening events such as severe arrhythmia, heart failure, stoke, infections, kidney failure, bleeding, and possibly death. There is always a risk involved in receiving a new surgery especially a new cardiac surgery but every precaution will be taken to minimize the risk.

Side effects can sometimes be serious or life threatening. Your doctor should be informed of all side effects you experience.

Risks and Discomforts Associated with Study Procedures

Holter Monitoring for 7 days

The 7-day Holter Monitoring are painless. This is a non-significant risk, noninvasive medical monitoring device. The potential risks from wearing the device may include discomfort, skin irritation, itching, rash, contact dermatitis, or breaching of skin if the patch adhesive is the removed too quickly

Echocardiogram

The echocardiogram are also painless. This is a non-significant risk, noninvasive medical exam device. No significant discomfort were reported at our center.

X-rays

You may have chest x-rays during the study. You will be exposed to a small amount of radiation during the test. The radiation that you receive from each test is about the same about what you would get in 12 days normally from all sources (natural and man-made). You may feel slightly uncomfortable as you stand for the chest x-ray.

Other Risks
In addition to the risks named above, the study procedures might have other unknown risks.

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In addition to the risks named above, the study procedures might have other unknown risks.

What If New Information Becomes Available?

You will be told about any important new information that is found during this study that might affect your health, well-being or willingness to stay in the study.

Will This Study Help Me?

This new operation now has early clinical outcomes, combination of left atrial geometric volume reduction and left atrial appendage base closure is being proved by our preliminary study that it can restore 100% sinus rhythm in 20 strictly selected patients and reshape the left atrium from a pathological to a physiological one. Thus, we speculate that this new operation may also do well in this portion of study. Although you may not receive benefit of AF termination from taking part in this study, your concomitant heart disease is cured certainly by surgery.

You might receive information about your health from any study procedures that are done during this study.

Information obtained from this study will benefit the sponsor of the study, Fujian Medical University, and might help patients in the future.

You may not take part in this study to be treated for your AF. There are other treatments and therapies available to you. These might include traditional Cox-Maze III or IV procedure. Your study doctor can discuss these treatments and therapies with you.

Do I Have To Take Part In This Study?

Your taking part in this study is entirely voluntary. Whether or not you take part is completely up to you to decide. You will continue to receive the best possible care no matter what you decide.

If you choose to take part and later change your mind, you can stop participating at any time. A decision to stop being in the study will not affect how your health care is provided to you. If you decide to stop the treatment, please talk to the study doctor or one of the staff members. They can tell you about any other treatments, and arrange to continue your usual care.

Your study doctor or the sponsor might decide, at any time and for any reason, to stop your taking part in the study, even though you might want to continue. The study doctor or one of the staff members will explain the reasons why you must stop and arrange for your health care to continue.

Treatment and Compensation for Injury

Signing this form does not mean you give up any of your legal rights. The study doctor, sponsor or hospital would still have legal and professional responsibilities to you.

What Will The Study Cost Me?

There are no extra Study device for patients. However, you might have to pay for some expenses related to your taking part in this study, such as *[transportation, parking, meals or others]*.

Who Is Paying For The Research Study?

None.

Who Do I Contact If I Want To Report Health Problems Or Have Questions?

If you have any injury, bad effect, or any other unusual health experience during this study, make sure that you immediately tell the study doctor or other study staff. You can call at any time, day or night, to report such health experiences, [insert contact details] If you have any questions about this study or your rights, please contact Dr. [insert study physicians name] at [insert address and phone #].

If you have any questions about your rights as a research subject, please contact [insert ethics contact or other neutral or disinterested party] at [insert address and phone number].

Will My Taking Part In This Study Be Kept Confidential?

The study doctor and staff will handle your personal health information in a confidential manner. Your health information will be used and disclosed as explained in the following Data Privacy Statements.

In this section, "personal health information" means information about a person that relates to things like the person's physical or family health history, health care, health care provider or substitute decision-maker and that directly identifies the person, and "study data" means study-related health information that does not directly identify a person (that is, it does not contain the person's name, address, health number or other identifying information) but that does contain an assigned code number for the person and/or the person's initials.

By signing the consent document for this study, you will give permission for the uses and disclosures of your personal health information that are described in this Data Privacy Statement. If you do not want to allow these uses, you should not participate in this study.

If you agree to participate in the study, your personal health information and study data will be maintained, used and shared in the following ways:

- The study monitor, the study auditor, the sponsor's clinical research staff and regulatory authorities might have access to your personal health information. This personal health information may include information from your health records such as your medical history, all lab results, ECG readings, specialist reports, and medications that you have been on in the past or currently. The records will be kept and disposed of in accordance with all applicable laws and regulations.

- The study doctor and staff will send your study data to the study sponsor, its associated companies and its representatives (the "sponsor"). Because the sponsor conducts business related to clinical research in many countries around the world, this may involve sending your study data outside of Canada. If your study data is sent to other countries, your privacy will remain protected as described in this section.

- Your study data will be used by the sponsor for research purposes to support the scientific objectives of the study. This may include studying how well the drug(s) or treatment(s) associated with the study worked and/or how safe they were; to better understand the conditions or illnesses being studied; and/or to improve the design of future studies.

- Your study data, either alone or combined with data from other studies, might be shared with regulatory authorities in China, and similar government agencies from other countries, as well as the ethics review board

overseeing this study.

- The sponsor works with business partners in drug development. The sponsor might share your study data with a business partner but only if the business partner signs a contract that requires it to protect your study data in the same way as the sponsor.

- Study data (which does not identify you) might be published in medical journals or shared with others as part of scientific discussions.

- To the extent permitted by applicable laws, the sponsor, the ethics review board, National Health Commission of the People's Republic of China and/or regulatory agencies in other countries, might review your original health records, which contain information that directly identifies you, to verify the accuracy and completeness of study data collected during the study.

You will have the right to see and copy your personal health information related to the study for as long as the study doctor or research institution holds this information, subject to applicable laws. However, you will not be able to see or copy this information until after the study has been completed.

You may withdraw your permission at any time by providing notice to the study doctor. The study doctor and staff would then no longer use or share your personal health information in connection with the study, unless it is essential to ensure that the study is scientifically reliable. However, the sponsor would still use your study data that was collected before you withdrew your permission. In addition, you would no longer be able to participate in the study.

Subject Information and Consent Form

Signature Page

To take part in this study and to allow the use and disclosure of my personal health information for the purposes of the study, I must sign and date this page.

By signing this page, I confirm the following:

- I give permission for my personal health information and study data to be maintained, used and shared as described in this document

- I have read the Subject Information and Consent Form, and have had time to think about whether or not I want to take part in this study.

- All of my questions about the study or this form were answered to my satisfaction. If I did not understand any of the words in this form, the study doctor or a member of the study staff explained them to me.

- I voluntarily agree to allow photographs to be taken of my wound for the study.

- I voluntarily agree to take part in the study, to follow the study procedures, and to provide necessary information to the study doctor or other staff members, as requested.

- I understand that I may freely choose to stop being a part of this study at any time.
- I have received a copy of the Subject Information and Consent Form.

Signature of Subject	Date (*ddMMMyy*) [Subject must p
Subject's Name (Print or Type)	Subject Number
Signature of Individual Conducting Informed Consent Discussion	Date (*ddMMMyy*) [Individual cond date]
Name of Individual Conducting Informed Consent Discussion (Print or Type)	

Study Procedures (Attachment 1)

Study: /

Study Visit	Time Between Visits	Approx Visit Length	Study Procedures/ Activities
Baseline (Visit 0)	Before operation		This visit will determine if you are eligible to participate in this study. • Your consent will be requested before you participate in this study • Information on your health, medical and smoking history as well as medications you are taking will be collected. • Physical exam including measurement of weight, height, blood pressure and pulse will be performed. • Echocadiogram, electrocardiogram and radiologic exam (CT scan, MRI or chest X-Ray as applicable) will be done. • Blood samples will be taken for excluding contraindication for surgery.
Visits 1	Visit 1:About 1-2 week(s) after operation	24 hours*7d	At each visit the following tests will be done: • Physical exam will be performed; information on your health and

			about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Echocadiogram, electrocardiogram and 7-day Holter monitoring will be done.
Follow-up Visit 1	Approximately 3 months after visit 0	24 hours*7d	At each visit the following tests will be done: • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Echocadiogram, electrocardiogram and 7-day Holter monitoring will be done.
Follow-up Visit 2	Approximately 6 months after visit 0	24 hours*7d	At each visit the following tests will be done: • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Echocadiogram, electrocardiogram and 7-day Holter monitoring will be done.
Follow-up Visit 3	Approximately 12 months after visit 0	24 hours*7d	At each visit the following tests will be done: • Physical exam will be performed; information on your health and about any side effects will be collected. • Medications you are taking besides the drug, information on treatment-related hospitalization will be noted. • Echocadiogram, electrocardiogram and 7-day Holter monitoring will be done.