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

NCT number: NCT03347695

Ethical committee approval:
The study was approved by research ethical committee in Fujian Medical University Union Hospital (Protocol NO. CLW2017AF**).**
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1. ABBREVIATIONS

Atrial Fibrillation AF

Mitral Valvular Surgery MVS

Radiofrequency ablation RFA

Transthoracic Doppler Echocardiography TDE

Electrocardiogram ECG

2. STUDY SUMMARY

Title	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
Objectives	Phase I: To examine the feasibility of our new operation (left atrial geometric volume reduction, pulmonary vein island isolation and left appendage base closure) based on a new concept for AF elimination Phase II: To assess the safety and efficacy of the new operation for the treatment of long-standing persistent AF during mitral valve surgery
Protocol Number	NCT 03347695
Study Design	Phase I: Prospective, single-arm pilot study Phase II: Prospective, single-arm clinical trial
Study Duration	3 years, (Phase I: from 2017 to 2018; Phase II: from 2018 to 2020)
Study Center	Fujian Medical University Union Hospital
Study Population	Adult patients with long-standing persistent AF had clinical indications for mitral valvular surgery (MVS)
Sample Size	The study will enroll a maximum of 140 patients. Phase I: 20 patients with longstanding persistent AF. Phase II: 120 patients with longstanding persistent AF.
Intervention	Evaluation: Transthoracic 2-dimensional echocardiography and Holter Operation: new operation (left atrial geometric volume reduction, pulmonary vein island isolation and left appendage base closure) Routine postoperative management: receiving amiodarone beginning within 24 hours post-operation until the 3-month point.
Primary endpoints	Efficacy: freedom from AF at both 6 months and 12 months after surgery, assessed by 7-days continuous Holter monitoring. Safety: cardiopulmonary bypass time; and a composite of death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, coronary artery injury, anatomical excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, and superior vena cava stenosis, within 30 days after the procedure or hospital discharge (whichever was later)
Secondary endpoints	Efficacy: The left atrial linear dimensions and A wave reappearance measured by transthoracic echocardiography at 3 time points (before surgery, 6 and 12 months after surgery).

	Safety: Major adverse cardiac events, which were defined as a non-weighted composite score of: death, stroke, worsening heart failure (+1 NYHA Class), hospitalization for heart failure, and mitral valve re-intervention within 12 months after surgery; and incidence of protocol-defined serious adverse events (especially thromboembolic and hemorrhagic events) within 12 months after surgery.
Follow-up Schedule	Pre-discharge, and at 30 days, 3, 6, and 12 months after surgery.

3. BACKGROUND

Atrial fibrillation (AF) often occurs in patients with valvular disease, especially in those with mitral valve disease, leading to an elevated mortality.[1] Though valvular replacement and plasty are the effective methods to treat valve disease, valvular procedure alone is not enough to cure AF.[2,3] AF can cause thromboembolism and stroke in approximately 5 -10% of high-risk patients, the risk of which increases with age and the coexistence of structural heart disease.[3-5]

The cut-and-sew Cox-Maze III operation, developed in 1989, has been regarded as the golden standard surgery for AF elimination.[6] In this surgical procedure, the atrial wall is divided into small areas to electrically isolate from each other, which is then not large enough to sustain the macro-reentry circuits. While it has not been widely used because it is complex and time-consuming, and the incisions are risky in both atria. Another procedure, known as Cox-Maze IV, was then developed and broadly accepted as the preferred technique for AF elimination, in which the classic cut and sew lesions are replaced with ablative lines using various energy sources. However, completion of so many ablative lines is still time-consuming.[5]

AF is always accompanied with an enlarged left atrium. Volume reduction of the enlarged atrium can decrease operative morbidity and incidence of AF recurrence after simultaneous mitral and AF surgery.[7] Unfortunately, the additional left atrial volume reduction was rarely performed because it will further prolong the aortic cross-clamp time. In both analogous Cox-Maze III and IV, the division of the entire intact atria into small areas has been proven to negatively affect the restoration of atrial transport function after appearance of sinus rhythm.[8-10] Therefore, it is desirable to develop a simple AF elimination technique which will benefit both atrial appropriate volume restoration and transport function reappearance.

In a cross-sectional study, we found the left atrial spatial enlargement and the fibrosis regional distribution were not uniform. We thus proposed a new concept that reconstructing a new left atrium with appropriate size and shape and a uniform fibrosis distribution for conduction is effective for AF elimination. Based on this concept, a new procedure (left atrial geometric volume reduction, pulmonary veins island isolation and left appendage base closure), was developed to render left atrium appropriate geometry and achieve uniform fibrosis distribution. Therefore, we conduct this proof-of-concept study to determine the feasibility, efficacy and safety of the new procedure.

4. OBJECTIVES

Primary objective

The primary objective is to assess the efficacy and safety of the new procedure (left atrial geometric volume reduction, pulmonary veins island isolation and left appendage base closure) for treating long standing persistent AF elimination. Efficacy will be evaluated by freedom from AF within 6 months and 12 months after surgery. Safety will be assessed by a composite of early adverse outcomes (within 30 days post-procedure or hospital discharge, whichever is later), including death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, coronary artery injury, anatomical excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, and superior vena cava stenosis. We hypothesize that the new procedure will reduce the risk of AF post-MVS reoccurrence and lower the incidence of adverse outcomes, as compared to that was historically reported in patients undergoing MVS concomitantly with COX MAZE IV.

Secondary objectives

(a) To assess the incidence of major adverse cardiac events and protocol-defined and serious adverse events (especially thromboembolic and hemorrhagic events) within 12 months after surgery, which is hypothesized to be lower than MVS concomitantly with COX MAZE IV.

(b) To assess the intra-operation cardiopulmonary bypass time(CPB), which if prolonged could increase risk of poor prognosis within 30 days post-procedure or hospital discharge. CPB time is hypothesized to be shorter than that historically reported in COX MAZE IV procedure.

(c) To assess the changes of size and shape of left atrium. The post-surgical shape and size of left atrium is hypothesized to be closer to normal status.

(d) To assess the function of left atrium. The incidence of peak late trans-mitral flow velocity (A) at 12 months post-surgery is supposed to be high.

5. STUDY DESIGN

This is a prospective, single-arm objective performance criteria study, consisting of two phases.

Phase I: A single-arm pilot study, 20 patients will be enrolled to test the feasibility of the procedure.

Phase II: A single-arm clinical trial, 120 patients will be enrolled to determine the safety and efficacy of the procedure.

Total study period is expected to take 40 months, and all patients will be followed for 12 months after surgery.

6. STUDY POPULATION

Recruitment

Patients admitted to our center will be enrolled in this study. Based on the average hospitalization admissions in our center, it is estimated that approximately 50 patients could be enrolled annually.

Characterization of Patient Population

The patient population for the pilot study is adult patients with both longstanding persistent AF and mitral valve disease requiring surgical intervention. Longstanding persistent AF is defined as continuous AF of greater than one year duration. This definition applies only to AF episodes that are of at least 30 seconds' duration and do not have a reversible cause such as acute pulmonary disease or hyperthyroidism. All patients who meet the eligibility criteria will be included in the study regardless of gender, race or ethnicity.

Phase I

Inclusion Criteria

1. Able to sign Informed Consent and Release of Medical Information forms
2. Age ≥ 18 years and ≤ 60 years old
3. Clinical indications for only mitral valve surgery for the following:
   Organic mitral valve disease without other cardiac disorders (functional or structural).
4. Longstanding persistent AF is defined as continuous AF of greater than one year duration.
   Duration of AF must be documented by medical history and
   Presence of AF must be documented by a direct electrocardiographic assessment upon arrival in the clinic.
5. Able to use heart rhythm monitor
6. Anteroposterior diameter of left atrial between 45mm and 60mm
7. Without history of stroke.

Exclusion Criteria

1. AF without indication for mitral valve surgery; or
2. Ischemic mitral regurgitation with evidence of concomitant structural mitral valve disease; or

3. Functional tricuspid regurgitation; or

4. AF is only or paroxysmal persistent; or

5. Evidence of active infection; or

6. Mental impairment or other conditions that may not allow patient to understand the nature, significance, and scope of study; or

7. Surgical management of hypertrophic obstructive cardiomyopathy; or

8. Previous catheter ablation for AF; or

9. Life expectancy of less than one year; or

10. Absolute contraindications for anticoagulation therapy; or

11. Enrollment in concomitant drug or device trials; or

12. Uncontrolled hypo- or hyperthyroidism; or

13. FEV1 < 30% of predicted value; or

14. Women who are pregnant as evidenced by positive pregnancy test; or

15. Women of childbearing age who do not agree to be on adequate birth control throughout the period of the trial; or

16. Diagnosed with infective endocarditis; or

17. Need emergency surgery.

Phase II

Inclusion Criteria

1. Able to sign Informed Consent and Release of Medical Information forms

2. Age ≥ 18 years

3. 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.

4. Longstanding persistent AF is defined as continuous AF of greater than one year duration.

Duration of AF must be documented by medical history and

Presence of AF must be documented by a direct electrocardiographic assessment upon arrival in the clinic.

5. Able to use heart rhythm monitor

Exclusion Criteria

1. AF without indication for mitral valve surgery; or
2. AF is only or paroxysmal persistent; or
3. Evidence of active infection; or
4. Mental impairment or other conditions that may not allow patient to understand the nature, significance, and scope of study; or
5. Surgical management of hypertrophic obstructive cardiomyopathy; or
6. Previous catheter ablation for AF; or
7. Life expectancy of less than one year; or
8. Absolute contraindications for anticoagulation therapy; or
9. Enrollment in concomitant drug or device trials; or
10. Uncontrolled hypo- or hyperthyroidism; or
11. Women who are pregnant as evidenced by positive pregnancy test; or
12. Women of childbearing age who do not agree to be on adequate birth control throughout the period of the trial; or
13. Diagnosed with infective endocarditis; or
14. Need emergency surgery.

7. INTERVENTIONS

The new procedure

All patients will have their left atrial geometric volume reduced, pulmonary vein island isolated and left appendage ligated or suture closed. After the superior vena cava was transected, two circular incisions were usually made in the left atrial wall between the pulmonary veins and the mitral annulus for circumferential atrial strip resection and pulmonary vein island isolation. The first circular incision was performed around the pulmonary veins. With this incision, pulmonary vein island was isolated and the left atrium was opened. The second one was performed in the interatrial groove and extended around the mitral annulus, leaving a 2 cm inferior wall margin from the annulus and the appendage in situ. With those two incisions, a circumferential strip of the left atrium was excised. Then the base of the left atrial appendage was ligated or excised and sutured. After the mitral manipulations, the center of the pulmonary vein island was longitudinally reef-imbricated with a 3-0 polypropylene continuous running suture to exclude toward the outside of the left atrial cavity. This plicated pulmonary vein island was directly anastomosed to the resected margin around the mitral annulus and the intraatrial septum instead of the interatrial groove. Finally, caval continuity was restored after aortic cross-clamp removal using a running 4-0 polypropylene suture.

Mitral Valve Surgery

For mitral regurgitation, the procedures will be a valve repair in the majority of cases. For valves that are not amenable to repair, and for most cases of mitral stenosis, a valve replacement will be performed. And the cardiopulmonary bypass time will be recorded.

Transthoracic Doppler Echocardiography

Transthoracic Doppler Echocardiography(TDE) will be used to measure left atrial size and volumes, quantify mitral valve function, detect intracardiac thrombi, and to assess left atrial and left ventricular function. TDE will be used to measure LA size as well as diameters in LA.

Electrocardiogram (ECG)

An ECG will be done upon arrival in the operating room. This tracing will be used to assess heart rhythm on all patients and provide part of the documentation needed to establish the diagnosis of longstanding persistent AF.

Postoperative management

Standardization of Anti-arrhythmic Drug Use during Follow-up

Unless contraindicated (hypotension or bradycardia defined as heart rate less than 60 beats per minute), all patients will receive prophylactic amiodarone beginning within 24 hours post-operation. Patients will be discharged on the anti-arrhythmic agent. At the 3-month point, antiarrhythmic agents will be terminated in all patients and this recommendation communicated by study personnel to the managing physician. Direct current cardioversion will be performed as clinically indicated by managing physicians and recorded by study personnel for the duration of follow-up.

Anticoagulation

Unless specifically contraindicated, warfarin will be prescribed for all patients at hospital discharge, with a target INR of 2.0-2.5. It is recommended that warfarin be continued in patients for the entire duration of the study if in mechanical valve replacement status or AF was detected at follow-up time points.

8. ENDPOINTS

Primary Endpoints

Efficacy

Freedom from AF in patients with longstanding persistent AF undergoing MVS at 6 months and 12 months. AF will be measured by 7 days continuous Holter monitoring at 6 months and 12 months post-surgery; and freedom of AF will be defined by absence of AF lasting > 30 seconds at 12 months.

Patients will be considered as treatment failures (not free of AF) if: 1) they die prior to the 12-month assessment; 2) or they are determined by an independent adjudicator to be too ill to undergo AF assessment; 3) or they require additional ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure.

Safety

(a)Cardiopulmonary bypass time, which if prolonged could increase risk of poor prognosis within 30 days post-procedure or hospital discharge;

(b)The adverse events within 30 days after surgery, including: death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism, peripheral embolism, coronary artery injury, anatomical excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, and superior vena cava stenosis.

Secondary Endpoints

Efficacy

(a)The changes of size and shape of left atrium, which will be measured by comparing the anteroposterior, transversal, and superoinferior diameters of left atrium between 3 time points (i.e., before surgery, 6 months and 12 months post-surgery) by using transthoracic echocardiography.

(b)The peak late trans-mitral flow velocity (A) at 6 months and 12 months post-surgery, which will be measured by transthoracic echocardiography.

Safety

(a)MACEs within 12 months after surgery: defined as a non-weighted composite score

of: death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, and mitral valve [MV] re-intervention.

(b)Protocol-defined and serious cerebrovascular adverse events (especially thromboembolic and hemorrhagic events) within 12 months after surgery.

(c)All-cause mortality at 12 months after surgery.

9. DATA COLLECTION

Data collected at hospital admission

Demographics

A screened patient is defined as an individual (a consented patient) who was referred to, or identified at a clinical site for consideration of entry into the study, and for whom some preliminary (i.e. medical record) data have been collected and/or reviewed. For all patients screened, the first, middle, and last initial, date of birth, ethnic origin, and sex will be captured on the screening log and registration form. The EDC will generate a unique 8-digit identification code that will identify the patient throughout the course of the study.

Medical History

Within 30 days prior to surgery

This form captures the information pertaining to the medical history, including but not limited to previous myocardial infarction, myocardial revascularization, arrhythmias, automatic implantable cardioverter-defibrillator, permanent right ventricular or biventricular pacemaker, stroke and other comorbidities such as diabetes and peripheral vascular disease. Information regarding the current medical condition is also captured, including but not limited to disposition at time of screening (outpatient, inpatient, ICU monitoring, etc) and intra-aortic balloon pump use.

Medications

Within 30 days prior to surgery

This form captures all protocol-defined medications taken within 7 days prior to surgery.

Physical Examination

Within 30 days prior to surgery

This form captures the comprehensive physical examination including vital signs cardiopulmonary examination, abdominal examination, and anthropometrics (height, weight and BSA).

Laboratory Assessment

Within 30 days prior to randomization

- White blood cell ($10^3/\mu L$)
- Hemoglobin (g/dL)
- Hematocrit (%)
- Platelet count ($10^{3}/\mu L$)

- Prothrombin time (PT/sec), partial thromboplastin time (PTT/sec)
- International Normalized Ratio (INR)
- Blood chemistries, including sodium (mM/L), potassium (mM/L), blood urea nitrogen (mg/dL), creatinine (mg/dL).
- Liver function tests, including total bilirubin (mg/dL), alanine aminotransferase (ALT U/L), aspartate aminotransferase AST (U/L), albumin (g/dL), lactate dehydrogenase (LDH).
- Urine or serum beta HCG (IU/L) is required for women who have the potential to
- become pregnant

Cardiovascular Rhythm Assessment

Prior to surgery

Physicians must document in the Medical History Form the timing and duration of AF. An ECG or other direct assessment of heart rhythm will be obtained within 1 year prior to document the presence of long-standing persistent AF. All long-standing persistent AF patients will undergo an ECG upon arrival in the operating room (OR).Furthermore, there will be a baseline transthoracic Doppler echocardiogram performed within 3 months prior to surgery.

Data collected during hospitalization

Informed consent

A detailed explanation of the risks and benefits of the study will be outlined by the investigator to each patient or their legally authorized representative before any preoperative assessments that are not part of the routine preparation and they will be asked to sign a consent form.

Surgical Procedures

Initial surgical intervention and event driven

Includes information regarding specific primary procedure, operative variables, lesion sets created, additional procedures performed at time of initial operation, intra-operative pharmacological agents, intra-operative blood transfusions, the cardiopulmonary bypass time.

Medications

All cardiovascular medications are recorded, including amiodarone given prophylactically since surgery.

Physical Examination (including vital signs and cardiopulmonary examination)

Electrocardiogram (12-lead ECG)

Adverse Events

Detailed information regarding adverse events is recorded at the time an event occurs during hospitalization. Investigators are asked to make a judgment as to the seriousness and relationship of the event to the surgical intervention.

Patient Discharge

Patients clinically stable for discharge may be discharged to an affiliated rehabilitation center, intermediate care center, long-term care facility, step-down facility or home.

Data collected at follow-up

Follow-up visits will be conducted at 30 days, 3 months, 6 months and 12 months after surgery (±30 days) after surgery provided that the patient is still alive. The following assessments are scheduled at each visit:

Transthoracic Doppler Echocardiogram

All patients will undergo follow-up transthoracic Doppler echocardiography at the investigative center*. Transthoracic Doppler echocardiography will be used to measure LA function (a) atrial filling, (b) LA ejection fraction, (c) atrial systolic mitral annular velocity (TDI). MV function, mitral regurgitation and LV function will be measured.

24-hour Holter Monitoring

The 24-hour holter monitoring provided to patients will be used for this assessment.

Medications

All cardiovascular, inotropic, antiplatelet agents, and anticoagulants will be recorded. Medications (including AADs) will be recorded at the study visit, and also as indicated at the time of associated adverse events. Response to DC cardioversions (success or failure) will also be recorded.

Functional Status

NYHA classification will be determined by a coordinator or physician not otherwise involved in this trial and blinded to the treatment assignment. The NYHA class will be documented on the "New York Heart Association Classification" form.

Adverse Events, Anti-arrhythmic Interventions, and Hospitalizations

Patients will be asked to recall any adverse events (including stroke and bleeding) and the number of hospitalizations that occurred out of network since the last contact. Patients will also be asked if they had a permanent pacemaker insertion, cardioversion or subsequent ablation since the last contact.

10. DATA MANAGEMENT

Source data

All source data for this study will be maintained in the Electronic Medical Record system, in accordance with hospital regulatory and requirements for the protection of confidentiality of patients. The investigator will be responsible to ensure the accuracy and completeness of the data reported timely. Incoming data will be double checked to detect inconsistent or missing data. All related hard copies will be secured to ensure confidentiality. Access to the clinical information will be based on individuals' roles and responsibilities.

Investigator Records

Investigators will maintain complete and accurate records of this study, which will be maintained until two years after the date of the study completeness/termination. The following materials will be included in investigator records:

(a) Correspondence: Documentation of all verbal and written correspondence with investigator, the Clinical Monitor, the Clinical Events Committee (CEC), and patients enrolled in this study.

(b) Patient records: Signed informed consent forms and copies of all documents (medical records, laboratory reports, reports of diagnostic tests, etc.).

(c) Clinical Study Protocol: A copy of the Clinical Study Protocol.

(d) Ethics Committee (EC) Information: All information related to EC review and approval of this clinical study.

(e) Other: Any other records that may be required.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Protocol deviations

A protocol deviation is a failure to comply with the requirements of this clinical study protocol. Each investigator shall conduct this clinical study in compliance with this clinical study protocol, hospital regulations, ISO guidelines, Good Clinical Practices (GCP), and other study requirements.

The protocol deviations include, but not limited to the following:

- Failure to obtain patient's informed consent
- Failure to meet all of the inclusion/exclusion criteria
- Failure to conduct follow-ups required by this protocol

All deviations shall be assessed for the impact by investigators. Continued protocol deviations may result in termination of the study. The investigators reserve the right to terminate the study at any time.

Investigator and monitor training

The investigators and monitors will be trained appropriately to monitor study progress.

Clinical Events Committee (CEC)

An independent group of physicians that are not involved in the clinical investigations will act as the Clinical Events Committee (CEC), which will be responsible for the review and validation of reported potential adverse events. The CEC will be. The CEC will be developed before the study start and blinded to the study details during the study period. This CEC shall include consistent definitions for each type of event and outline the review process.

Data and Safety Monitoring Board

To meet the study's ethical responsibility to its subjects, an independent data safety monitoring board (DSMB) will monitor the progress of the study. The board consists of physicians, biostatisticians, ethicists and bioengineers, who have no formal involvement or conflict of interest with the participants or the investigators. The DSMB will act in a senior advisory capacity regarding data and safety matters and review interim summary results of the accumulating data every 6 months. These data include adverse events (e.g., infection, bleeding, right heart failure) and mortality.

12. ANALYTICAL PLAN

Statistical overview

The aim of this study is to assess the safety and efficacy of our new operation (left atrial geometric volume reduction, pulmonary vein island isolation and left appendage base closure) in patients with MV disease and longstanding persistent AF. This study included a pilot study and a clinical trial, both of which are prospective, single-arm studies with similar statistical analysis plan.

Sample size

Sample size is based on previously published data, and on ensuring the ability to detect, with high probability, a clinically meaningful presumed benefit for our new operation. To date there have been some studies examining effect of COX MAZE IV in treating AF in MVS patients. The reported absence of AF one year post MVS with COX MAZE IV is about 60%-80%. For computing sample size, according to our pilot study, a reasonable proportion of patients free from AF at 1 year, will be assumed.

As observed in the pilot study that 20/20 (100%) patients free from AF at 6-month follow-up, we assume that 90% of patients treated with our new operation will be free of AF at 1-year post-surgery. A total of 120 patients enrolled in the clinical trial provides 80% power to detect an absolute increase of 10% (80% versus 90%) in the proportion of patients free of AF, based on a single-tailed 0.025 level continuity corrected chi-squared test and 10% drop-out rate. (ADDED at August 2018)

Primary analysis

The primary outcome of efficacy is freedom from AF over one year post surgery. The rate of free of AF will be calculated after finishing 1-year follow-up for 120 patients. Patients who die within 12 months will be considered treatment failures (not free of AF). Patients who die prior to the 12-month assessment, or who are determined by an independent adjudicator to be too ill to undergo AF measurement, will be considered as treatment failures (not free of AF). In the primary analysis, patients who undergo ablation therapy for AF (including surgical ablation or percutaneous catheter ablation) subsequent to the index procedure will be considered treatment failures (not free of AF).

The primary safety endpoint of this trial include:

(a) CPB time will be recorded.

(b)a composite of death, stroke, serious cardiac events (heart failure, myocardial infarction), cardiac re-hospitalizations, transient ischemic attack, pulmonary embolism,

peripheral embolism, coronary artery injury, anatomical excessive bleeding, deep sternal wound infection/mediastinitis, damage to specialized conduction system requiring permanent pacemaker, and superior vena cava stenosis, within 30 days post-procedure or hospital discharge (whichever is later). The rate of these safety endpoints will be calculated within 30 days after surgery.

Secondary Analyses

Efficacy

(a)The size and shape of left atrium. The anteroposterior, transversal, and superoinferior diameters, as well as their ratios, of left atrium between two time points (i.e., before surgery and 12 months post-surgery), will be measured by transthoracic echocardiography. The absolute change and reduction rate of each diameter will be analyzed, and the post-surgery size and shape will be compared with Chinese standards.

(b)Left ventricular ejection fraction and peak late transmitral flow velocity (A) at 12 months post-surgery will be measured by transthoracic echocardiography. These measurements evaluate the function of heart pump.

Safety

(a)Major adverse cardiac events (MACE) defined as a non-weighted composite score of: death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, and mitral valve [MV] re-intervention within 12 months of surgery. The rate of MACE will be calculated and compared with MACE rate historically reported in COX MAZE IV procedure.

(b)Incidence of protocol-defined and serious adverse events (especially thromboembolic and hemorrhagic events) within 12 months of surgery. The rate of SAE will be calculated and compared with MACE rate historically reported in COX MAZE IV procedure.

(c)All-cause mortality at 12 months post-surgery. The Kaplan-Meier curve will be plotted to show the probability of death at a respective time interval and compared with 1-year deaths historically reported in COX MAZE IV procedure.

13. SPECIFIC ADVERSE EVENT DEFINITIONS

Bleeding

A bleeding event is defined by any one of the following:

- Transfusion of > 2 units RBC within the first 24 hours following surgery
- Death due to hemorrhage
- Re-operation for hemorrhage or tamponade

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., hemodynamic compromise, oliguria, pre-syncope or syncope) that requires hospitalization or requires a physician visit or occurs during a hospital stay.

Cardiac arrhythmias are classified as:

1. Sustained ventricular arrhythmia requiring defibrillation or cardioversion
2. Sustained supraventricular arrhythmia requiring drug treatment or cardioversion
3. Cardiac conduction abnormalities requiring permanent pacemaker

Pericardial Fluid Collection

Accumulation of fluid or clot in the pericardial space that requires surgical intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Pleural Effusion

Accumulation of fluid or clot in the pleural space documented by chest radiogram or chest CT that requires evacuation with surgical intervention or chest tube placement.

Atrial Rupture

Disruption in the integrity of the left or right atrial wall, documented by direct inspection or diagnostic testing, that necessitates surgical repair.

Valvular Injury

Injury to a cardiac valve (excluding the mitral valve), as evidenced by new regurgitation or stenosis following the treatment intervention. This definition excludes changes to the mitral valve because it will be surgically repaired at the time of the treatment intervention.

Non-infectious Pericarditis

Signs and symptoms of pericardial inflammation, with or without electrocardiographic evidence, requiring pharmacologic anti-inflammatory therapy. This definition excludes infectious pericarditis (see Major Infection infectious pericarditis definition below).

Superior vena cava Stenosis

A ⩾ 50% decrease in the diameter of the superior vena cava as documented by echocardiography.

Diaphragmatic Paralysis

Phrenic nerve injury as evidenced by new elevation of a hemi-diaphragm on chest radiogram.

Pneumothorax

Presence of gas in the pleural space, documented by chest radiogram or chest CT, that requires evacuation or prolongs the duration of chest tube drainage.

Hepatic Dysfunction

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotranferease/ALT) to a level greater than three times the upper limit of normal for the hospital, (or if hepatic dysfunction is the primary cause of death).

Major Infection

A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

Endocarditis

Signs, symptoms and laboratory findings consistent with endocarditis, including but not limited to fever ⩾ 38.0o C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of a new intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.

Mediastinitis/Deep Sternal Wound Infection

Signs and symptoms consistent with mediastinitis, include but are not limited to fever, chills, leukocytosis and chest or back pain, and mediastinal inflammation documented by diagnostic testing (e.g., chest CT). Information regarding deep sternal wound infections will be collected.

Infectious Pericarditis

Signs and symptoms, including but not limited to fever, leukocytosis and pericardial inflammation, necessitating surgical exploration, drainage and treatment with intravenous antibiotics.

Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension. In addition, we will record systemic antibiotic use for presumptive sepsis.

Localized Infection

Infection localized to any organ system or region other than the mediastinum, pericardium, or endocardium without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

Heart Failure

New onset of signs or symptoms of congestive heart failure or worsening of preexisting heart failure by $\geqslant$ 1 NYHA class.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction4:

Myocardial Infarction

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia;

- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Peri-CABG Myocardial Infarction

For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Peri-Percutaneous Intervention (PCI) Myocardial Infarction

For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indiciative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Neurologic Dysfunction

Any new, temporary or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale (NIHSS) must be administered at time of event (within 72 hours following the event) and 90 days following the event

to document the presence and severity of neurological deficits. The Modified Rankin Scale and NIHSS can be found in Appendix III.

Each neurological event must be subcategorized as: Transient Ischemic Attack

Defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.

Ischemic or Hemorrhagic Stroke (Cerebrovascular Accident)

Defined as an event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.

Toxic Metabolic Encephalopathy

Defined as a disorder of the brain function that arises from abnormal systemic metabolism or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.

Other Neurologic Dysfunction

Renal Events

Two categories of renal events will be identified:

- Renal Dysfunction: Abnormal kidney function defined by > 100% rise in serum creatinine (Cr) from baseline, and Cr > 2.0
- Renal Failure: New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

Respiratory Failure

Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilatory support within 48 hours post-surgical intervention. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure

Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (> 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation, inhaled nitric oxide or inotropic therapy, for a duration of > 7 days.

Arterial Non-CNS Thromboembolism

An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

Venous Thromboembolic Event

Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence

Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other

An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

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