Study Protocol

A Secondary Mitral Regurgitation Assessment Using Three-dimensional Transesophageal Echocardiography: A Multicenter Clinical Study

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1. Background

Secondary mitral regurgitation (SMR) occurs in a structurally normal mitral valve when left ventricular or left atrial dilatation or dysfunction prevents complete leaflet closure. Associated conditions include ischemic cardiomyopathy, heart failure, atrial fibrillation, and atrial cardiomyopathy.

SMR results from left ventricular (LV) and/or left atrial (LA) remodeling, altered geometry, annular dilatation, leaflet tethering, mechanical dyssynchrony, and papillary muscle displacement. Its global prevalence is approximately 1-2%, with a higher prevalence among older adults and patients with heart failure. SMR can worsen cardiac function and heart failure, increase hospitalization and mortality, and independently predict adverse cardiovascular outcomes.

Conventional echocardiography, including transthoracic echocardiography, has limitations in assessing SMR severity, mechanisms, and contributing factors. It may incompletely characterize three-dimensional structural changes, including mitral annular geometry.

Three-dimensional transesophageal echocardiography (3D-TEE) provides high-resolution imaging and enables non-invasive, precise quantification of regurgitant volume and mitral annular remodeling. This information supports clinical decision-making. Existing studies are predominantly small, single-center investigations. Multicenter data supporting SMR prediction models and individualized treatment strategies remain limited.

This study will use the Liaoning Provincial Clinical Research Center for Medical Imaging platform to coordinate participating imaging centers across China. It will combine 3D-TEE and transthoracic echocardiography for multimodal assessment. The study will characterize SMR and examine its associations with clinical outcomes. Findings will inform treatment, including mitral valve repair and medical therapy.

2. Study Objectives

1. To assess the severity of SMR and its contributing factors using 3D-TEE.
2. To compare mitral valve structure and left ventricular functional parameters between patients with SMR and controls.
3. To investigate predictors of adverse events in patients with SMR. Events of interest include atrial fibrillation recurrence, heart failure rehospitalization, catheter-based or surgical mitral valve treatment, and cardiovascular death.

3. Study Methods

3.1 Overall Design and Procedures

This prospective multicenter clinical study will be conducted in the People's Republic of China.

Preparatory work and training are planned to begin in January 2026. Study implementation is planned to start in February 2026 and continue for 23 months. The first 11 months will cover data collection. The subsequent 12 months will cover patient follow-up, data analysis, and reporting.

The sample-size calculation requires multimodal ultrasound data from 1,600 patients with SMR and 800 controls. The study includes 93 participating centers and will use competitive enrollment.

Accounting for valid cases and loss to follow-up, each center has a minimum baseline target of 40 patients and 10 controls. Baseline enrollment will end when the overall target sample size is reached.

Each participating institution will designate registered physicians with echocardiography experience as its lead investigator and study personnel. All personnel will receive centralized training before study implementation.

Participants will be screened strictly according to clinical diagnoses and echocardiographic findings. Standardized images will be acquired in accordance with the Chinese adult echocardiographic measurement guidelines. All selected images will be transferred to the First Hospital of China Medical University.

Images will be imported into the Ultrasound Workspace workstation. Conventional two-dimensional, Doppler, and three-dimensional echocardiographic parameters will be measured using uniform procedures.

Each institution will record participant data in the case report form (CRF) accurately, completely, truthfully, and promptly. A designated person will retain the CRFs. Echocardiographic data will be verified using common procedures and analyzed by trained personnel.

3.2 Study Schedule

- February-December 2026: data collection.
- January-December 2027: patient follow-up, data analysis, and study reporting.

3.3 Equipment

Examinations will use a Philips EPIQ CVX ultrasound system. Multiplane transesophageal probes will be X8-2t or X7-2t, with frequencies of 2-8 MHz or 2-7 MHz, respectively. An X5-1 probe, operating at 1-5 MHz, will also be used.

3.4 Study Population

Patient Group: Secondary Mitral Regurgitation

Inclusion criteria

1. Age 18 years or older.
2. At least mild atrial secondary mitral regurgitation (A-SMR), meeting all of the following criteria:
    - Structurally normal mitral valve without primary mitral valve disease.
    - Left ventricular ejection fraction at least 50%, without regional wall motion abnormalities or mitral leaflet tethering.
    - Normal or mildly enlarged left ventricle, meeting either of the following sex-specific criteria. The end-diastolic diameter must be below 56 mm in women or 63 mm in men. Alternatively, the end-diastolic volume index must be below 71 mL/m² in women or 79 mL/m² in men.
    - Mitral annular dilatation, with an anteroposterior diameter above 35 mm, together with left atrial enlargement. Left atrial enlargement is defined by either of two criteria. The volume index must be above 34 mL/m². Alternatively, the anteroposterior diameter must be above 37 mm in women or 39 mm in men.

3. Undergoing both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE), with standardized images retained.

Exclusion criteria

1. Primary mitral regurgitation caused by organic mitral valve disease, including degenerative changes, rheumatic involvement, congenital mitral valve abnormalities, or vegetations.
2. Moderate or greater aortic valve disease.
3. Previous cardiac valve surgery, including surgical or catheter-based procedures.
4. Congenital heart disease.
5. Inadequate three-dimensional TEE image quality that prevents reliable assessment of mitral valve structure and motion.
6. Contraindications to TEE or inability to tolerate the examination.
7. Refusal to sign the informed consent form.

Control Group

Inclusion criteria

1. Age 18 years or older.
2. Undergoing TEE for clinical indications, such as suspected patent foramen ovale or infective endocarditis.
3. TTE showing no substantial abnormalities in cardiac structure or function, with less than mild regurgitation of all cardiac valves.

Exclusion criteria

Individuals will be excluded if they do not meet the control-group inclusion criteria or meet any exclusion criterion specified for the patient group.

3.5 Eligibility and Recruitment

Participants must meet all applicable inclusion criteria, meet none of the exclusion criteria, and provide written informed consent. Patients will be enrolled through participant recruitment. Recruitment information is provided in Appendix 3.

3.6 Follow-up

Participants will undergo clinical follow-up every three months after the baseline examination. Follow-up will include symptom assessment and repeat TTE. Primary endpoint events include heart failure rehospitalization, cardiovascular death, and mitral valve intervention. Follow-up will use outpatient visits or telephone interviews, supplemented by medical records.

3.7 Confidentiality

Personal information in the case records will be concealed to protect participant privacy.

4. Quality Control

4.1 Initial Investigator Qualifications

1. All study personnel must have at least five years of relevant echocardiography experience and have performed at least 1,000 TTE examinations. They must be proficient in three-dimensional TEE.
2. Each participating center must have a Philips EPIQ CVx ultrasound system equipped with X8-2t or X7-2t and X5-1 probes.
3. All personnel must follow the same echocardiographic reporting principles, including standardized images and measurement methods.

4.2 Training

Centralized training will cover basic operation, standardized images, quality-control methods, influencing factors, CRFs, and reporting tools.

After centralized training, each center must complete the following:

1. Standardized presets: establish uniform settings for two-dimensional grayscale, color Doppler, spectral Doppler, tissue Doppler, and three-dimensional ultrasound imaging, as specified during training.
2. Image-acquisition quality control: complete image acquisition for one case using the standardized workflow and upload all required materials.
3. CRF quality control: complete and submit the data for that case using the standard CRF workflow. The principal investigator will review the information and request corrections when requirements are not met. Routine image acquisition may begin only after all materials for two cases meet the required standard.

4.3 Quality Standards for Participating Institutions

Following confirmation by the principal investigator, institutions that fail institutional or personnel qualification review will withdraw from the study. Centers must submit more than their assigned number of cases each month. Failure to provide cases on schedule may also result in withdrawal.

The proportion of unusable or lost samples must not exceed 20%. This includes inadequate images, inaccurate data, and incomplete or delayed submission of forms. If this proportion exceeds 20%, the principal investigator will assess the center and issue reminders or warnings, potentially leading to withdrawal.

Lead investigators and study personnel must fulfill their responsibilities, follow the clinical protocol and standard operating procedures, and verify all measurements. These measures support implementation of the study's quality-control and quality-assurance systems.

5. Risk Assessment and Management

5.1 Preliminary Risk Assessment

Medical ultrasound imaging systems have been established as among the safest imaging systems and are used in routine diagnosis and treatment. Ultrasound is non-invasive and does not involve ionizing radiation. The likelihood that participants will experience risk from ultrasound examinations is therefore almost zero.

5.2 Participant Safety

Ultrasound safety management will follow the ALARA principle: As Low As Reasonably Achievable. The lowest ultrasound output that provides adequate data will be used.

6. Research Ethics

The study will follow the Declaration of Helsinki and other applicable requirements. Implementation will begin only after the ethics committee has approved the protocol.

Before enrollment, investigators will explain the study purpose, procedures, and potential risks to each participant or legally authorized representative. Written informed consent will be obtained. Participants will be informed of their right to withdraw at any time. Consent documents will be retained as study records. Participant privacy and data confidentiality will be protected throughout the study.

7. Study Personnel

Name	**Professional Title / Department**	**Responsibilities**	**GCP Training**
Chunyan Ma	Chief Physician / Cardiovascular Ultrasound	Quality control and study design at the lead institution	February 2021
Yonghuai Wang	Associate Chief Physician / Cardiovascular Ultrasound	Study implementation	December 2024
Meng Li	Attending Physician / Cardiovascular Ultrasound	Study implementation	September 2021