RIPCOM 1

The right ventricular pulmonary circulation in mitral valve disease study 1

Version 3 31/12/2016
IRAS ID 199676

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MAIN SPONSOR: Imperial College London
FUNDERS: Applications to Heart Research UK, Rosetrees Trust and British Heart Foundation pending
STUDY COORDINATION CENTRE: Department of Cardiothoracic Surgery, Hammersmith Hospital
NRES reference: 199676

Protocol authorised by:

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Version 3
31/12/2016

Study Management Group

Chief Investigator: Mr Prakash Punjabi

Co-investigators: Dr Jonathan Afoke, Dr Simon Gibbs, Dr Joseph Boyle

Study Management: Department of Cardiothoracic Surgery, Hammersmith Hospital

Study Coordination Centre

For general queries, supply of study documentation, and collection of data, please contact:

Study Coordinator: Dr Jonathan Afoke
E-mail: jonathan.afoke@nhs.net
Address: BN2/25 B Block, Hammersmith Hospital
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Clinical Queries

Clinical queries should be directed to Dr Jonathan Afoke who will direct the query to the appropriate person

Sponsor

Imperial College, London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
Imperial College London & Imperial College Healthcare NHS Trust
2nd Floor Medical School Building
St Mary's Hospital
Praed Street
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Funder

Funding applications to Heart Research UK, Rosetrees Trust and British Heart Foundation are currently pending

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This protocol describes the RIPCOM1 study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CPET	Cardiopulmonary exercise testing
cMRI	Cardiac magnetic resonance imaging
MR	Mitral regurgitation
MS	Mitral stenosis
NYHA	New York Heart Association
PFT	Pulmonary function tests
RHC	Right heart catheterization
QoL	Quality of life
TTE	Transthoracic echocardiogram

KEYWORDS

Mitral regurgitation, mitral stenosis, mitral valve disease, pulmonary hypertension, cardiopulmonary exercise testing, quality of life

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STUDY SUMMARY

TITLE The right ventricular pulmonary circulation continuum in mitral valve disease study 1

DESIGN Observational clinical study

AIMS

1. To correlate pre-operative exercise capacity on cardiopulmonary exercise testing with measurements of quality of life, cardiac function on transthoracic echocardiogram and cardiac magnetic resonance imaging and respiratory function on lung function tests.
2. To define the histological changes in the left and right ventricular in severe mitral valve disease with or without pulmonary hypertension.
3. To obtain pilot data in changes in exercise capacity early after surgery.
4. To measure the accuracy of measurements of pulmonary artery pressures on transthoracic echocardiogram against the gold standard measurement of right heart catheterization in a prospective mitral valve disease cohort.

OUTCOME MEASURES

1. The accuracy of transthoracic echocardiogram compared to right heart catheterization in measuring pulmonary artery pressures in a prospective severe mitral valve disease cohort.
2. Correlation between objective measurements of exercise capacity on cardiopulmonary exercise testing with quality of life and measurement of cardiac function on transthoracic echocardiogram and cardiac MRI in severe mitral valve disease.
3. Histological changes in the left and right ventricle in severe mitral valve disease.
4. Pilot data on changes in exercise capacity and quality of life and relationship to transthoracic echocardiogram, cardiac MRI and pulmonary function tests early after mitral valve surgery.

POPULATION 50 patients

ELIGIBILITY Patients undergoing cardiac surgery for severe mitral valve disease with or without concomitant coronary artery bypass grafting or tricuspid valve surgery or atrial fibrillation surgery.

This will be an observational study since all patients will already be accepted for surgery under the current guidelines.

DURATION 2 years (January 2017-March 2019)

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1. INTRODUCTION

1.1 BACKGROUND

Mitral regurgitation (MR) is one of the most prevalent valvular heart conditions in population based studies (1) and the hospital and outpatient patient population (2). The incidence of mitral valve surgery has been shown to be increasing in a European series (3) and the United States (4). One of the major driving forces has been an appreciation of the benefits of successful mitral valve repair over mitral valve replacement in terms of operative mortality, potential avoidance of lifelong anticoagulation and long term survival. This has resulted in an increase in mitral valve repair rates in Europe and the United States.

The current indications for surgery for MR include symptomatic status; asymptomatic status with echocardiographic features such as impaired left ventricular function or increased left ventricular dimensions; new onset atrial fibrillation or pulmonary hypertension; asymptomatic status with a high likelihood of durable repair and low co-morbidity (5). The limitation in strength of the current evidence base is reflected by the class of evidence being expert opinion (level C) for all of the above indications with the sole exception of symptomatic patients, which is level B.

The fulcrum point between asymptomatic status and symptomatic status at which patients would derive prognostic benefit and thus should be referred for surgery on prognostic grounds still remains unclear and controversial. Although elective mitral valve repair carries a low risk of mortality (4), it has been demonstrated that asymptomatic patients with severe degenerative MR can be safely followed up before becoming symptomatic or reaching cutoff values for left ventricular dimensions, size or pulmonary hypertension; with no significant difference with expected survival. As a result, prophylactic surgery for all patients with asymptomatic severe degenerative MR can not be recommended on prognostic grounds (6).

At the other end of the clinical spectrum, the increased operative mortality and worse long term prognosis of symptomatic patients is well proven. Patients with New York Heart Association Class III or IV status have excessive operative mortality and significantly increased mortality at 10 years (7). Both this study and another (8) have demonstrated that preoperative ejection fraction is an independent predictor of long term survival. Although this evidence base does not support prophylactic surgery on asymptomatic patients, it does highlight the importance of avoiding the long term sequelae of MR in causing symptomatic status or left ventricular impairment. Hence attention has turned to objective markers or investigations independent of symptomatic status that may be subjectively assessed in the early phases; to help identify patients who would prognostically benefit from earlier surgical intervention.

As a result of rheumatic fever being the most common etiology, mitral stenosis (MS) is the least common valvular lesion in the hospital population (2) and has a low prevalence rate in epidemiological studies (1) in industrialized countries. However, it still causes significant morbidity and mortality worldwide. The preferred treatment for severe mitral stenosis in those patients with favourable valvular anatomy is percutaneous mitral commissurotomy. In one single centre follow up, there was a low immediate risk of the procedure with 89% of patients obtaining good immediate results defined as a final mitral valve area greater than 1.5cm^2 without significant mitral regurgitation and a 20 year rate of good functional results of 30.2% (9).

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However, in those patients with unfavourable valvular anatomy; there are no randomised trials to guide the best timing of surgery. Survival benefit increases with more advanced symptoms, but surgical risk increases with pulmonary hypertension so it has been suggested to intervene when symptoms are more than mild, but before the development of pulmonary hypertension (10). An area of uncertainty exists in asymptomatic patients with severe MS or those with symptoms out of proportion with the severity of MS. Current guidelines suggest the use of stress echocardiography and intervention if the mean transmitral pressure gradient is greater than 15mmHg during exercise or peak pulmonary artery systolic pressure exceeds 60mmHg (11). However, this guidelines is based on level C evidence and there is no data comparing these parameters with objective measurements of exercise capacity and its relationship with operative risk or long term prognosis.

In summary, severe mitral valve disease is a common valvular pathology that causes a significant burden of disease in the United Kingdom and worldwide. Current guidelines for timing of operative intervention are mostly based on expert opinion rather than randomised trials or studies. There is currently no proven prognostic benefit from surgery on asymptomatic patients. Patients with significant symptoms benefit from surgery, but have worse long term prognosis than the general population. It is difficult to assess early or mild symptoms and there is no significant evidence base objectively measuring exercise capacity and its correlation with quality of life and markers of cardiac or respiratory function before and after surgery.

Pathophysiology of severe mitral valve disease

In the initial compensated phase of MR, there is eccentric hypertrophy of the left ventricle and enlargement of the left atrium to accommodate volume overload. As a result of the increased capacitance there is a normal pulmonary vascular resistance and transpulmonary pressure gradient. In the final decompensated phase, there is heart failure characterized by increase in left ventricular dimensions, elevation of left sided filling pressures, increase in transpulmonary pressure gradient and decline in biventricular contractile function (12). This is associated with progressive histological changes to the pulmonary vasculature which range from medial hypertrophy and intimal proliferation in small muscular pulmonary arteries to progressive fibrous vascular occlusion and arterial dilatation and the end stage of haemosiderin deposition and necrotizing arteritis (13). This in turn affects the alveolar-capillary unit and can increase impedance to gas transfer. From a clinical end point, this results in pulmonary hypertension and potentially reduced gas transfer factor.

Right heart catheterisation (RHC) is regarded as the gold standard for establishing a diagnosis of pulmonary hypertension and allows invasive haemodynamic assessment. Transthoracic echocardiogram allows a non-invasive assessment of pulmonary pressures by calculating transtricuspid pressure gradient using the modified Bernoulli equation and adding right atrial pressure. However, this method is restricted by the limitations of acquiring a continuous wave signal and severe tricuspid regurgitation (14). One metaanalysis comparing the accuracy of echocardiography and RHC in 29 studies reported modest correlation between the two methods and that RHC remains the gold standard. Of the 29 studies, only 8 evaluated cardiac disease, none evaluated a mitral disease cohort and the studies were subject to significant biases (15).

Although pulmonary hypertension is an important risk factor and indication for surgery, there is currently no prospective comparison of measurements on transthoracic echocardiogram and RHC. In addition, the changes in the histology of the left and right ventricle and changes in pulmonary function have not been related to changes in pulmonary haemodynamics.

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1.2 RATIONALE FOR CURRENT STUDY

To identify objective markers of exercise capacity, cardiac or respiratory function that will demonstrate the earliest point at which patients with severe mitral valve disease derive prognostic benefit from surgery.

Patients with severe mitral valve disease and symptoms although gaining benefit from surgery have a worse long term prognosis and quality of life than the general population. There is currently no proven prognostic benefit for surgery on asymptomatic patients. Therefore there will be an objective point between the two ends of the disease spectrum at which patients will derive early prognostic benefit and enable a return to a normal life expectancy and quality of life.

2. STUDY OBJECTIVES

Primary objective

Correlation between objective measurements of exercise capacity on cardiopulmonary exercise testing with quality of life and measurement of cardiac function on transthoracic echocardiogram and cardiac MRI in severe mitral valve disease.

Secondary objective

1. The accuracy of transthoracic echocardiogram compared to right heart catheterization in measuring pulmonary artery pressures in a prospective severe mitral valve disease cohort.

2. Histological changes in the left and right ventricle in severe mitral valve disease.

3. STUDY DESIGN

Observational clinical study with tissue collection lasting two years (October 2016-October 2018). According to the validated returns to the national audit for the Society For Cardiothoracic Surgery, Mr Punjabi operates on 40-50 patients a year who meet the inclusion criteria.

This will be an observational study since all patients will already be accepted for surgery under the current guidelines. For the purposes of comparison, the cohort will be stratified into three groups: asymptomatic patients with preserved left ventricular function (defined as ejection fraction greater than 60%), symptomatic patients with preserved left ventricular function and patients with impaired left ventricular function (defined as ejection fraction less than 60%).

Recruitment and consent process

Patients will be identified at their initial surgical consultation or from the surgical waiting list (mitral valve surgery with or without coronary artery bypass grafting or tricuspid valve surgery or atrial fibrillation surgery) by the direct care team.

For patients identified at initial surgical consultation, the Patient Information Sheet and Patient Invitation Letter will be given to the patient and the patient given an opportunity to ask questions and give consent before the investigations are arranged.

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For patients identified from the surgical waiting list, the patient will be contacted by phone and Patient Information Sheet and Patient Invitation Letter sent to the patient. After confirming initial interest, the investigations will be arranged. The patient will be given the opportunity to ask further questions and give consent at the initial study visit.

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Pre-operative investigations

The additional pre-operative investigations will be co-ordinated with the preassessment team to minimize changes to the normal patient pathway. If patients have already had pre-operative investigations required as part of the study protocol prior to enrolment, the data from these investigations may be used for the purposes of research.

Clinical history and examination- Patients will be reviewed at initial surgical consultation, 6-8 weeks after surgery and one year after surgery.

Right heart catheterisation- It is the usual gold standard practice at our institution for patients to have a right heart catheterisation before being referred for surgery. The few patients who have not had one before surgery will be referred to the Department of Pulmonary Hypertension at Hammersmith Hospital for this test to be performed.

Cardiac MRI- patients will have a T1 weighted non-contrast cardiac MRI. One strength of cardiac MRI over transthoracic echocardiogram is the ability to provide objective measurements of right heart function. Parameters measured will be left and right ventricular ejection fraction, cardiac chamber dimensions, patterns of myocardial fibrosis.

Cardiopulmonary exercise testing (CPET)- CPET is a quantitative and validated method of assessing cardiorespiratory function and exercise capacity with commonly measured variables including maximal oxygen consumption (VO2 max) and the clearance of carbon dioxide during exercise (Ve/VCO2). The patient's gaseous exchange is monitored during a 3 minute rest period, a three minute "rolling basal" period when they perform exercise on a bicycle with no load; and subsequently during the exercise phase when the work load increases at a rate of 30 Watts per minute. The exercise continues until the patient has to stop or predicted maximum heart rate is achieved.

Pulmonary function tests- Patients will have routine spirometry tests and also assessment of transfer factor (DLCO and KCO). It is normal practice for patients to have spirometry at preassessment clinic and those with abnormal spirometry or a significant history of respiratory disease to have transfer factor measured.

Transthoracic echocardiogram- It is normal practice for patients to have a transthoracic echocardiogram at preassessment clinic to assess biventricular function, dimensions and cardiac structural disease.

Quality of life questionnaire- At the preassessment clinic, patients will be asked to fill out a validated quality of life questionnaire (SF-36 health survey).

Intra-operative specimens

Heart muscle biopsies will be obtained at the time of clinically indicated heart surgery. Two small heart samples approximately 0.8 grams each or the size of a cooked rice grain will be taken from the left and right ventricle. The specimens will be preserved in formalin and processed and analysed at the Department of Pathology by a pathologist with a specialist interest in cardiac pathology. The samples will be fixed and analysed with haematoxylin and eosin for structure, Elastin van Gieson stain for elastin, Martius, Scarlet and Blue stain for fibrin, Picrosirius red stain for collagen, Perls' Prussian blue stain for iron, Periodic acid-Schiff stain for polysaccharides, Desmin stain for smooth muscle, CD68 for monocytes, CD45 for leucocytes, smooth muscle actin for smooth muscle and CD31 for vascular endothelium.

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By correlating the results of the histological analysis with clinical markers such as left and right ventricle function and pulmonary hypertension, and the cardiac imaging on transthoracic echocardiogram and cardiac MRI this will enable us to grade microscopic changes in the myocardium throughout the spectrum of mitral valve disease from asymptomatic to symptomatic.

In addition, the results of the histological analysis will be the basis of further collaborative work with the Myocardial Function group at the Imperial Centre for Translational and Experimental Medicine.

Post-operative follow up

6-8 weeks- it is normal practice for patients to be reviewed at 6-8 weeks after surgery in clinic with clinical history and examination. Patients will be asked to fill in a quality of life questionnaire at this time.

6-9 months- Patients will have a repeat transthoracic echocardiogram, cardiac MRI, CPET, pulmonary function tests. A quality of life questionnaire will be mailed to patients with a self-addressed envelope.

12 months- it is normal practice for patients to be followed up at 12 months after surgery with clinical history and examination.

Review of investigations

All pre and post-operative investigations will be reviewed on an individual basis with the Chief Investigators and if there are any abnormalities, these and any additional investigations will be discussed with the patient. The patient's GP and referring cardiologist will be informed of any progress with the permission of the patient.

3.1 STUDY OUTCOME MEASURES

1. The accuracy of transthoracic echocardiogram compared to right heart catheterization in measuring pulmonary artery pressures in a prospective severe mitral valve disease cohort.
2. Correlation between objective measurements of exercise capacity on cardiopulmonary exercise testing with quality of life and measurement of cardiac function on transthoracic echocardiogram and cardiac MRI in severe mitral valve disease.
3. Histological changes in the left and right ventricle in severe mitral valve disease.
4. Pilot data on changes in exercise capacity and quality of life and relationship to transthoracic echocardiogram, cardiac MRI and pulmonary function tests early after mitral valve surgery.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Transthoracic echocardiogram showing severe mitral valve disease meeting the current indications for open heart surgery.

4.2 INCLUSION CRITERIA

Patients undergoing cardiac surgery for severe mitral valve disease with or without concomitant coronary artery bypass grafting or tricuspid valve surgery or atrial fibrillation surgery.

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4.3 EXCLUSION CRITERIA

Age <18 years or >85 years, pregnancy, critical preoperative status with multi-organ dysfunction, emergency cardiac surgical intervention, unable to give informed consent or unwilling to participate in research, patients with definite contraindication for MRI would be excluded from the cardiac MRI element of the study, patients unable to take adequate biopsies due to technical difficulties would be excluded from the myocardial biopsy element of the study, other significant valve lesions requiring concomitant surgery.

4.4 WITHDRAWAL CRITERIA

Patients who develop a life expectancy limiting medical condition subsequent to enrolment will be withdrawn from the study. Patients will have the right to withdraw from the study at any time. Patients who lose capacity will be withdrawn from the study but data and tissue already collected with consent will be retained and used in the study with no further data or tissue collected.

5. ADVERSE EVENTS

5.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- **Results in death**
- **Is life-threatening** – *refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing inpatients' hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.3 REPORTING PROCEDURES

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.3.1 Non serious AEs

All such events, whether expected or not, should be recorded.

5.3.2 Serious AEs

An SAE form should be completed and faxed to the Chief Investigator within 24 hours. However, relapse and death due to mitral valve disease, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the <name of REC> where in the opinion of the Chief Investigator, the event was:

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- ‘related’, ie resulted from the administration of any of the research procedures; and
- ‘unexpected’, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

Contact details for reporting SAEs
Fax: 02033132334, attention Dr Jonathan Afoke
Please send SAE forms to: Bn2/25 B Block, Hammersmith Hospital
Tel: 02033132025 (Mon to Fri 09.00 – 17.00)

6. ASSESSMENT AND FOLLOW-UP

Patients will be followed up at 6-8 weeks after surgery in clinic as normal practice and will be asked to fill in a quality of life questionnaire at this time.

It is normal practice for patients to be followed up at one year after surgery with a repeat transthoracic echocardiogram prior to this appointment. Before this appointment, they will have an additional repeat cardiac MRI, CPET, pulmonary function tests and quality of life questionnaire at 6-9 months after surgery.

7. STATISTICS AND DATA ANALYSIS

The myocardial specimens will be preserved in formalin and transferred to the pathology laboratory at Hammersmith Hospital for processing and histological analysis. Spare sections will be fixed in Polysine slides and stored in the pathology laboratory at Hammersmith Hospital.

All data will be expressed as mean with standard error. Statistical comparison will be performed by one-way ANOVA followed by unpaired t-test as appropriate. Results will be considered statistically significant if $P<0.05$.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study at Imperial College.

8. REGULATORY ISSUES

8.1 ETHICS APPROVAL

The Chief Investigator has obtained approval from the xxx Research Ethics Committee and the HRA. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

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8.2 CONSENT

Consent to enter the study must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Signed participant consent should be obtained. The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. All patients will be anonymised by assigning a study number. The code to this and study data will be kept on Imperial College NHS Trust computers. Only anonymised data will be analysed by the statisticians at Imperial College, London.

8.4 INDEMNITY

Imperial College, London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 SPONSOR

Imperial College, London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 FUNDING

This study is pending funding applications to Heart Research UK, Rosetrees Trust and British Heart Foundation.

8.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Dr Jonathan Afoke and Mr Prakash Punjabi, Department of Cardiothoracic Surgery, Hammersmith Hospital.

10. PUBLICATION POLICY

Study data will be disseminated through academic presentations and publications.

10. REFERENCES

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Appendix 1. Summary of investigations, treatment and assessments

Exam			**Months after operation**		
	Pre-operative	Operation	2	6-9	12
Clinical history/examination	X		X		X
Transthoracic echocardiogram	X			X	
Informed consent	X				
Cardiac MRI	X			X	
Right heart catheterization	X				
Cardiopulmonary exercise test/lung function tests	X			X	
Quality of life questionnaire	X		X	X	
Intra-op myocardial biopsies		X			

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