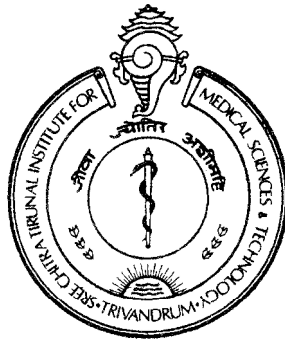


**SREE CHITRA TIRUNAL INSTITUTE FOR  
MEDICAL SCIENCES AND TECHNOLOGY  
TRIVANDRUM, KERALA**



**PROJECT REPORT**

Submitted during the course of  
DM Cardiology

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**DEPARTMENT OF CARDIOLOGY**

Jan 2012 – Dec 2014

## **DECLARATION**

I, **Dr. Panneer Selvam.S**, hereby declare that the project in this book was undertaken by me under the supervision of the faculty, Department of Cardiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

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The candidate, **Panneer selvam.S**, has carried out the minimum required project.

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**Cardiac MRI in Rheumatic heart disease patients  
with significant Left ventricular dysfunction**

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## **Abstract**

**Background:** Rheumatic heart disease (RHD) is the most common cause of valvular heart disease in India and other developing countries accounting for 25-45% of acquired heart disease. Patients with aortic stenosis, aortic and mitral regurgitation and about 30% with mitral stenosis may develop left ventricular systolic dysfunction. Whether these rheumatic valvular heart disease patients with left ventricular dysfunction have myocardial fibrosis has not been studied.

**Objectives:** The study was conducted to evaluate the pattern and degree of myocardial fibrosis in RHD patients with significant LV dysfunction by Cardiac MRI and to assess whether the severity of myocardial fibrosis correlates with the degree of LV dysfunction.

**Methods:** We retrospectively reviewed the records of RHD patients with LV (Left ventricular) dysfunction (Left ventricular ejection fraction, LVEF < 50%) by echocardiogram who underwent Cardiac MRI. Patients with history or any evidence of previous acute coronary syndrome or coronary artery disease, any other cardiomyopathies were excluded. We analysed what percentage of these patients had late gadolinium enhancement (LGE) suggestive of fibrosis on cardiac

MRI, whether there was any correlation of LGE with the degree of LV dysfunction and whether any specific pattern of LGE was present in RHD patients.

**Results:** Cardiac MRI data of 17 patients (14 (83%) male) with mean age 47.5 years (range 29-61) were analysed. 15 of the 17 patients underwent a coronary angiogram which was normal. 13 patients has dominant mitral involvement alone and 4 patients had combined mitral and aortic valve disease. Six patients (35%) had mild LV dysfunction (LVEF 41-50%), 9 patients (53%) had moderate LV dysfunction (LVEF 31-40%) and 2 patients (12%) had severe LV dysfunction (LVEF $\leq$  30%). Thirteen patients (76.5%) were in atrial fibrillation and 4 patients (23.5%) were in sinus rhythm. Two out of the seventeen patients (12%) had ventricular LGE on cardiac MRI. One patient had LGE in the basal Inferoseptum and the other patient had LGE of the basal inferior wall. The first one had enhancement in the subepicardial and midmyocardial regions and the second one had enhancement transmurally. There was no correlation between the severity of left ventricular dysfunction and presence of LGE. Enhancement of atrium (IAS or Left atrium or both) was seen in 94% and the LGE of LA correlated with the presence of atrial fibrillation. LGE of mitral, aortic and tricuspid valves were seen in 100%, 47% and 47% of the patients respectively.

**Conclusion:** Among patients with rheumatic valvular heart disease, about 12% of the patients have myocardial fibrosis as indicated by the presence of LGE in cardiac MRI. The patterns of LGE seen in these patients were transmural, subepicardial or midmyocardial. The presence of LGE did not correlate with the severity of the left ventricular dysfunction. Additionally atrial and valvar LGE were found in most of the patients.

## **Introduction**

Valvular heart diseases account for an important cause of cardiovascular morbidity and mortality, next to ischemic heart disease. Valvular heart diseases accounts for more than one fourth of all cardiac surgeries performed all over the world. Valve surgeries contributed to 57% of all adult cardiac surgeries in a large study of 1000 consecutive patients conducted at a tertiary centre at Delhi<sup>1</sup>. The primary causes of valve disease are Rheumatic heart disease (RHD), age-associated calcific valve changes and inherited or congenital conditions. Though the prevalence of RHD has reduced in the west, it still is the most common cause of valvular heart disease in India. In India, rheumatic fever is endemic and remains one of the major causes of cardiovascular disease, accounting for nearly 25-45% of the acquired heart disease<sup>2</sup>. The prevalence of RHD in population surveys in India ranged from 1.8 to 2.2 per 1000 population and school based studies showed a prevalence of 0.67 to 4.54 per 1000 population aged 5- 18 years of age<sup>3</sup>. RHD patients account for up to 45% of all cardiology admissions in Indian hospitals contributing significantly to the economic burden of the healthcare system<sup>4</sup>. Though many suitable patients with RHD are managed by Percutaneous transluminal balloon commissurotomy, open heart surgeries are required in a significant proportion of patients. Valve surgeries are associated with significant

morbidity and mortality. Adverse outcomes are significantly higher in patients presenting late with left ventricular dysfunction.

Aortic stenosis and regurgitant lesions of mitral and aortic valve on the later part of their natural history can lead to left ventricular (LV) systolic dysfunction. As this LV dysfunction develops because of a mechanical problem, it is said that the correction of this mechanical problem by valve surgery leads to improvement of LV function. This improvement is presumably time-dependent, although it is not clear till what point the ventricular dysfunction is irreversible. This irreversibility of left ventricular dysfunction may be related to a significant degree of myocardial fibrosis. Cardiac MRI based studies have demonstrated significant myocardial fibrosis in subsets of patients with valvular heart diseases, especially degenerative aortic stenosis and those patients with fibrosis had poor outcomes with surgical treatment. Also specific patterns of fibrosis like midwall fibrosis were associated with adverse outcomes. There is no data on the prevalence of myocardial fibrosis and their patterns in patients with rheumatic heart disease till date except isolated case reports.

## Review of literature

### **Outcomes of valve surgeries in patients with Left ventricular dysfunction**

Duarte and coworkers did a study to analyse the late survival of patients with left ventricular dysfunction undergoing valve surgery<sup>5</sup>. In a study of 257 patients with a preoperative ejection fraction of 0.40 or less who underwent aortic (n =177), mitral (n =72), or combined (n = 8) valve operations from 1980 to 1993, they found a hospital mortality of 12.5%. Logistic regression analysis showed that an ejection fraction of less than 0.30, mitral regurgitation, concomitant coronary artery bypass grafting, emergency operation, and reoperation were independent correlates of hospital mortality (all at  $p < 0.05$ ). Kaplan-Meier survival curves of the 220 hospital survivors showed a 65% 5-year survival. Multivariate analysis revealed preoperative use of diuretics, male sex, reoperation, age exceeding 60 years, and aortic regurgitation to be independent predictors of poor late outcome (all at  $p < 0.05$ ). They concluded that the liability of left ventricular dysfunction with regard to diminished long-term survival is not completely reversed by valve operation.

Haan et al performed a study to decide whether patients with left ventricular dysfunction may safely undergo mitral valve surgery for MR, and if so, which ones<sup>6</sup>. The mortality and morbidity outcomes were compared by EF

category (< 30% vs > 30%), and observed mortality compared by EF group, stratified by predicted risk for mortality. They studied 14,582 patients who had mitral valve surgery for mitral regurgitation, 727 had an EF of 30% or less and 13,855 had an EF of more than 30%. Observed mortality rates were higher for patients with an EF of 30% or less (5.4% vs 3.1%). However, for low-risk to medium-risk patients, mortality rates remained fairly constant across levels of EF. Mortality is notably increased in the high-risk patients (predicted risk > 10%). A classification tree identifies three key characteristics for high risk: age more than 75 years, renal failure, and emergent or salvage procedure. They concluded that when the predicted mortality risk is less than 10%, EF has minimal impact on operative mortality for mitral regurgitation.

Acar and coworkers analyzed treatment options for valvular regurgitation with severe left ventricular dysfunction by studying the results of valvular surgery in 98 patients with mitral or aortic regurgitation and severe systolic left ventricular dysfunction<sup>7</sup>. In patients with aortic regurgitation (n = 46) operative mortality was higher but not significantly so than in a control group of 238 cases (6.5% vs. 3.4%). The actuarial survival rates at five and 10 years were 84% and 55% vs. 84% and 67%, respectively. In patients with mitral regurgitation (n = 52), operative mortality was not significantly different from that of a control group of 273 cases (3.8% vs. 2.6%), whether the surgical procedure was valve replacement or valve

repair. The actuarial survival rates at eight years were respectively for the groups with and without LVD: 81% and 89% after valve repair, 60% and 75% after valve replacement. They concluded that concluded that a low EF is not a predictive factor of operative mortality but it influences late survival as do the degree of left ventricular dilatation.

Tarantini et al evaluated 85 consecutive patients with severe aortic stenosis (aortic valve area  $<1 \text{ cm}^2$ ) and severe depression of LV ejection fraction (EF)  $<35\%$  to examine the outcome and the preoperative predictors of postoperative cardiac death and of LV function recovery in these patients<sup>8</sup>. Among them, 52 underwent aortic valve replacement and they were compared to patients who were not operated on. In-hospital mortality was 8%. Postoperative NYHA functional class changed from  $2.84 \pm 0.67$  to  $1.43 \pm 0.44$  ( $P < 0.001$ ) and LVEF from  $29 \pm 6\%$  to  $43 \pm 10\%$  ( $P < 0.001$ ). At follow-up 10 patients died of heart disease. By multivariate analysis, preoperative LV end-systolic volume index (ESVI) was the only covariate of cardiac death (LV ESVI/10 ml/m<sup>2</sup>, OR 1.3, CI 1.1–1.8,  $P < 0.028$ ). By using a receiver operating characteristic curve, LVESVI  $\geq 90 \text{ ml/m}^2$  was the best cut-off value (sensitivity and specificity 78%) to fit with a better survival (93% vs. 63%,  $P < 0.01$ ) and with LVEF recovery after aortic valve replacement (EF improved by  $15 \pm 10\%$  vs.  $8 \pm 5\%$ ,  $P < 0.001$ ). Their conclusion

was that despite LV dysfunction, aortic valve replacement appears to change drastically the natural history of severe aortic stenosis.

Similar studies were conducted by several authors focussing on patients with severe aortic regurgitation with left ventricular dysfunction showing varying clinical outcomes in different studies.

Bhudia et al evaluated the surgical outcome of 724 Severe AR patients undergoing AVR<sup>9</sup>. Of these, 88 (12%) had severe LV dysfunction defined as left ventricular ejection fraction (LVEF) <30%. Patients with severe LV dysfunction tended to be older (56 vs. 50 years) and male (91% vs. 67%). Propensity-matching was used to select 77 well-matched pairs of subjects with and without severe LV dysfunction. In this group, hospital mortality before 1985 was 17% in those with severe LV dysfunction compared with 3% without it ( $p < 0.03$ ). In patients who underwent surgery after 1985, there were no hospital deaths in either group. Long-term survival was worse with severe LV dysfunction (81% vs. 92% at 1 year, 68% vs. 81% at 5 years, 46% vs. 62% at 10 years), but this was mostly the result of hospital mortality in the patients undergoing surgery before 1985. In those patients who underwent surgery after 1985, there was no significant difference in long-term survival. Importantly, the mean LV end-diastolic and -systolic diameters were  $7.5 \pm 0.7$  cm and  $5.9 \pm 0.8$  cm, respectively. Thus, the patients in this study had not

only depressed LVEF but also increased LV dimensions, which would indicate a poor surgical outcome based on older studies.

Chaliki and coworkers studied 450 patients who had AVR for isolated AR between 1980 and 1995<sup>10</sup>. Patients with markedly reduced left ventricular function (EF <35%, n=43) were compared with those with moderate reduction in left ventricular function (EF 35% to 50%, n=134) and those with normal left ventricular function (EF >50%, n=273). The operative mortality rate was higher with EF<35% (14%) than with EF 35-50% and EF>50% (6.7% and 3.7%, respectively, P<0.02). At 10 years, 41%±9% of patients with EF<35% had survived compared with 56%±5% and 70%±3% of patients with EF 35-50% and >50%, respectively (P<0.0001). Congestive heart failure occurred at 10 years in 25%±9% with EF <35% compared with 17%±4% and 9%±2% EF 35-50% and >50%, respectively (P<0.003). Postoperative EF improved by 4.9%±13.8% in the EF<35% group and by 4%±11.9% in the EF 35-50% group compared with -2.3%±10.9% in the EF >50%group (P<0.002 and P<0.0001, respectively). They concluded that Patients with severe AR and markedly low EF incur excess operative mortality rates, postoperative mortality rates, and congestive heart failure after AVR. However, postoperative EF improves markedly, and most patients enjoy a long postoperative survival without recurrence of heart failure after AVR; thus they should not be denied the benefits of AVR.

Bonow et al studied 37 patients with aortic regurgitation who preoperatively had left ventricular dysfunction to determine the influence of duration of preoperative left ventricular dysfunction on postoperative reversal of left ventricular dysfunction<sup>11</sup>. In 11 patients left ventricular dysfunction was documented 18 to 57 months preoperatively (prolonged); in 10 patients left ventricular dysfunction developed in an interval of 14 months or less preoperatively (brief); in 16 patients duration of left ventricular dysfunction was unknown. Patients with brief versus those with prolonged left ventricular dysfunction did not differ with respect to severity of preoperative symptoms or exercise tolerance, echocardiographically determined left ventricular dimensions or fractional shortening or radionuclide angiographic ejection fraction ( $42 \pm 5\%$  vs  $42 \pm 5\%$ ). After operation, however, patients with brief left ventricular dysfunction developed a smaller left ventricular diastolic dimension ( $50 \pm 3$  vs  $59 \pm 8$  mm;  $p < .005$ ) and a higher ejection fraction ( $63 \pm 7\%$  vs  $43 \pm 12\%$ ;  $p < .001$ ) than patients with prolonged left ventricular dysfunction; postoperative ejection fraction was intermediate in patients with unknown duration of preoperative left ventricular dysfunction ( $48 \pm 11\%$ ;  $p < .001$ ). All deaths occurred in patients with either prolonged or unknown duration of left ventricular dysfunction. They concluded the duration of preoperative left ventricular dysfunction in patients with aortic

regurgitation is an important determinant of the reversibility of left ventricular dysfunction after aortic valve replacement.

Kamath et al did a retrospective study of 166 patients with severe AR and LV ejection fraction (EF)  $\leq 35\%$ . 69% of these were men, age  $65 \pm 16$  years, and LV EF was  $23 \pm 8\%$ . Kaplan–Meier analysis revealed that performance of AVR (n=53) was associated with a better survival ( $P < 0.001$ ). Adjusted for the propensity score, AVR was associated with a significantly lower mortality hazard (HR 0.59, CI 0.42 to 0.98,  $P < 0.04$ ). One-year, 2-year, and 5-year survival rates among patients with AVR were 88%, 82%, and 70%, respectively, compared to 65%, 50%, and 37%, respectively in those who had no AVR ( $P < 0.001$ ). In patients with EF  $< 20\%$ , five-year survival rate was 35% in patients who did not undergo AVR (n=57) compared with 70% for the 21 patients who underwent AVR ( $P < 0.02$ )<sup>12</sup>.

As most of these studies say that, there is proportion of patients with valvular heart disease who may not show reversal of LV dysfunction or survival benefit after valve surgery. So there is a felt need for tools which may stratify patients with LV dysfunction into whether the LV dysfunction is reversible or not, so that surgery could be deferred in patients with irreversible LV dysfunction thus avoiding the risks of such high risk surgeries.

Nobuchika et al retrospectively analysed 32 patients with LV dysfunction (FS $< 25\%$ ) who underwent valve surgeries, 15 of whom underwent a Dobutamine

stress echo preoperatively<sup>13</sup>. Patients who showed significant improvement in LV function postoperatively had a higher delta FS% ( $12 \pm 3.9\%$ ) compared to patients who showed no improvement in FS% ( $4.0 \pm 3.4\%$ ). Ten patients underwent LV biopsies in the operation, and %fibrosis was assessed by a point-counting's method. In patients with no improvement in FS%, %fibrosis in LV myocardial specimens was higher.

In a recently published study, Milano et al evaluated whether myocardial fibrosis influences left ventricular performance in severe aortic stenosis and to assess its effect on long-term survival after aortic valve replacement<sup>14</sup>. Myocardial fibrosis was evaluated in biopsy specimens taken from the interventricular septum in 99 patients undergoing aortic valve replacement because of severe or prevalent aortic stenosis. The patients were classified according to the myocardial fibrosis severity (none or mild in 28, moderate in 52, and severe in 19). Patients with a higher grade of myocardial fibrosis had a significantly lower freedom from cardiac death at 10 years ( $42\% \pm 19\%$  vs  $89\% \pm 6\%$ ,  $P = .002$ ), with congestive heart failure the most common cause of death. Based on these results new strategies for the earlier detection of myocardial fibrosis are needed to achieve a better prognostic outcome.

Based on these data, LV myocardial fibrosis may be a good risk stratification tool in valvular heart disease including rheumatic heart disease (RHD) patients

with LV dysfunction taken up for surgery. Cardiac MRI with late Gadolinium enhancement (LGE) has been a good modality for diagnosis of myocardial fibrosis in ischemic and nonischemic cardiomyopathies.

### **Assesment of myocardial fibrosis in valvular heart diseases using Cardiac MRI and correlation with clinical outcome:**

Dweck and coworkers did a study with the goal of assessing the prognostic significance of midwall and infarct patterns of late gadolinium enhancement (LGE) in aortic stenosis<sup>15</sup>. They followed 143 patients with moderate to severe aortic stenosis who underwent cardiac MRI with assessment of fibrosis by late gadolinium enhancement and out of whom 72 underwent aortic valve replacement for  $2.0 \pm 1.4$  years. 27 died (24 cardiac, 3 sudden cardiac deaths). Compared with those with no LGE (n = 49), univariate analysis revealed that patients with midwall fibrosis (n = 54) had an 8-fold increase in all-cause mortality despite similar aortic stenosis severity and coronary artery disease burden. Patients with an infarct pattern (n = 40) had a 6-fold increase. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16 to 24.56; p = 0.03) and ejection fraction (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.99; p < 0.01) were independent predictors of all-cause mortality by multivariate analysis.. According to them , Midwall fibrosis was an independent predictor of mortality in patients with moderate and

severe aortic stenosis and it has incremental prognostic value to ejection fraction and may provide a useful method of risk stratification.

In a prospective observational study of 63 patients undergoing CMR with LGE imaging within 1 year of subsequent AVR, Quarto and coworkers demonstrated that patients with midwall fibrosis (n=20) had significantly high 30 day MACCE compared with those with absent LGE (n=25) and infarct patterns (n=18) (25% vs 0% vs 5%, p=0.013)<sup>16</sup>. Incidence of CVA and heart blocks were higher in patients with midwall fibrosis. Patients with no LGE had no 30 day MACCE and no mortality on 2 year follow up.

In a prospective cohort study of 83 patients with aortic stenosis (AS), Hermann and coworkers aimed to identify surrogates of myocardial fibrosis that are easy to derive in clinical practice, allow the differentiation of low-gradient severe AS from moderate AS, and have an impact on clinical outcome<sup>17</sup>. In all the patients, replacement fibrosis was quantified by late-enhancement magnetic resonance imaging. Biopsy samples were taken from patients with severe AS (n = 69) at aortic valve replacement. All patients were followed for 9 months. Patients were divided into 4 groups according to aortic valve area (<1.0 cm<sup>2</sup>), mean valve gradient >40 mmHg, and EF (<50%): group 1, moderate AS (n = 17); group 2, severe AS/high gradient (n = 49); group 3, severe AS/low gradient/preserved EF (n = 11); and group 4, severe AS/low gradient/decreased EF (n = 9). At baseline,

a significant decrease in mitral ring displacement and systolic strain rate was detected in patients with low gradient AS. In low-gradient groups, a higher degree of interstitial fibrosis in biopsy samples and more late enhancement magnetic resonance imaging segments were observed. A close inverse correlation was found between interstitial fibrosis and mitral ring displacement ( $r = -0.79$ ,  $p < 0.0001$ ). Clinical outcome was best for patients in group 1, whereas mortality risk increased substantially in groups 2 through 4.

The effect of myocardial fibrosis on myocardial performance in symptomatic severe aortic stenosis was investigated, and the impact of fibrosis on clinical outcome after aortic valve replacement (AVR) was estimated in a prospective follow-up study by Weidemann et al<sup>18</sup>. They evaluated 58 consecutive patients with isolated symptomatic severe aortic stenosis. Standard and tissue Doppler echocardiography and cardiac magnetic resonance imaging (late-enhancement imaging for replacement fibrosis) were performed at baseline and 9 months after AVR. Endomyocardial biopsies were obtained intraoperatively to determine the degree of myocardial fibrosis. Patients were analyzed according to the severity of interstitial fibrosis in cardiac biopsies (severe,  $n=21$ ; mild,  $n=15$ ; none,  $n=22$ ). The extent of histologically determined cardiac fibrosis at baseline correlated closely with New York Heart Association functional class and markers of longitudinal systolic function (all  $P < 0.001$ ) but not global ejection fraction or

aortic valve area. Nine months after AVR, the degree of late enhancement remained unchanged, implying that AVR failed to reduce the degree of replacement fibrosis. Patients with no fibrosis experienced a marked improvement in New York Heart Association class from 2.8 $\pm$ 0.4 to 1.4 $\pm$ 0.5 ( $P < 0.001$ ). Only parameters of longitudinal systolic function predicted this functional improvement. Four patients with severe fibrosis died during follow-up, but no patient from the other groups died. They concluded that the markers of longitudinal systolic function appear to indicate sensitively both the severity of myocardial fibrosis and the clinical outcome, they may prove valuable for preoperative risk assessment in patients with aortic stenosis.

Choi et al reported a case of rheumatic AR with left ventricular dysfunction who had a 80% transmural LGE in lateral LV segment from base to mid level<sup>19</sup>. Coronary angiogram was normal. Endomyocardial biopsies taken during surgery from segments with LGE showed interstitial fibrosis and myocyte disarray.

Rochette et al prospectively evaluated survival (all-cause and cardiovascular disease related) according to LGE-CMR status in 154 consecutive AS patients (96 men; mean age: 74  $\pm$  6 years) without a history of myocardial infarction undergoing surgical AVR and in 40 AS patients undergoing

transcatheter aortic valve replacement (TAVR)<sup>20</sup>. LGE was present in 29% of patients undergoing surgical AVR and in 50% undergoing TAVR. During a median follow-up of 2.9 years, 21 patients undergoing surgical AVR and 20 undergoing TAVR died. In surgical AVR, the presence of LGE predicted higher post-operative mortality (odds ratio: 10.9; 95% confidence interval [CI]: 1.2 to 100.0;  $p = 0.02$ ) and worse all-cause survival (73% vs. 88%;  $p = 0.02$  by log-rank test) and cardiovascular disease related survival (85% vs. 95%;  $p = 0.03$  by log-rank test) on 5-year Kaplan-Meier estimates of survival after surgical AVR. Multivariate Cox analysis identified the presence of LGE (hazard ratio: 2.8; 95% CI: 1.3 to 6.9;  $p = 0.025$ ) and New York Heart Association functional class III/IV (hazard ratio: 3.2; 95% CI: 1.1 to 8.1;  $p < 0.01$ ) as the sole independent predictors of all-cause mortality after surgical AVR. The presence of LGE also predicted higher all-cause mortality ( $p < 0.05$ ) and cardiovascular disease related mortality ( $p = 0.03$ ) in the subgroup of patients without angiographic coronary artery disease ( $n = 110$ ) and higher cardiovascular disease related mortality in 25 patients undergoing transfemoral TAVR.

Heyninng and colleagues sought to investigate the prevalence and significance of delayed enhancement in primary MR<sup>21</sup>. They prospectively included 41 patients with at least moderate primary MR and without overt signs of left ventricular (LV) dysfunction. Patients with evidence of coronary artery

disease, arrhythmias or significant concomitant valvular disease were excluded. All patients were evaluated with LGE CMR. 39 MRIs were interpretable. Among them, 12 (31%) had late contrast uptake of the LV wall. LGE CMR showed an infarct pattern in three patients, a pattern of mid-wall fibrosis in seven patients and two patients had a combined pattern. Patients with delayed enhancement on CMR had significant higher LV diameters (LV end-systolic diameter  $39 \pm 4$  vs.  $34 \pm 5$  mm,  $P = 0.002$ ; LV end-diastolic diameter  $57 \pm 5$  vs.  $50 \pm 5$  mm,  $P = 0.001$ ). There was a trend towards a higher indexed left atrial volume ( $55 \pm 21$  vs.  $44 \pm 13$  mL/m<sup>2</sup>,  $P = 0.06$ ). By contrast, there was no significant association between myocardial contrast uptake and age, LV ejection fraction and MR severity. They concluded that left ventricular remodelling seems to be associated with the presence of delayed enhancement on CMR in primary MR.

The role of cardiac MRI and patterns of of enhancement in RHD patients has not been studied in detail till date. This study was planned to study the patterns of LGE by CMRI in RHD patients with LV dysfunction and to look for the correlation of the degree of enhancement with the severity of the LV dysfunction.

### **Aims and objectives**

1. To study the pattern and degree of myocardial fibrosis in RHD patients with significant LV dysfunction by CMRI
2. Whether the severity of myocardial fibrosis correlates with the degree of LV dysfunction

## **Methods**

**Setting:** Cardiology out-patient department (OPD), Sree Chitra Tirunal Institute for Medical Sciences and Technology

**Study period:** January 2014 to July 2014

**Study Design:** Cross Sectional study

All patients of rheumatic heart disease of any valve (Aortic stenosis, Mitral stenosis, Aortic regurgitation, Mitral regurgitation) with LV systolic dysfunction ( LV ejection fraction <50%) who were under treatment from the cardiology services, SCTIMST and who had underwent Cardiac MRI as a part of their evaluation were eligible for the study.

Retrospective data of RHD patients with LV dysfunction who underwent CMRI in the past were collected from the medical records department of the institute and prospective patients who are undergoing CMRI as per departmental decision during the study period were also enrolled. All patients meeting the inclusion criteria were included in the analysis.

### **Exclusion criteria:**

- 1) Patients with known coronary artery disease with history of acute coronary syndrome (ACS) before.

- 2) Patients without known coronary artery disease (CAD) with significant Regional wall motion abnormalities or evidence of Old ACS in electrocardiogram (ECG)
- 3) Patient with features highly suggestive of known forms of non ischemic cardiomyopathy known to have LGE on CMRI

Baseline demographic data of all enrolled patients were recorded including full history and symptomatic status at the time of Cardiac MRI (Noted from the hospital records). Chest roentgenogram and Electrocardiogram findings were also recorded.

Echocardiographic details of all enrolled patients were recorded from their echocardiogram report just before undergoing the cardiac MRI with emphasis on parameters like LV internal dimension in diastole (LVIDD), LV internal dimension in systole (LVIDS), Septal thickness in diastole (Sd), Septal thickness in systole (Ss), Posterior wall thickness in diastole (PWd), Posterior wall thickness ( PWs), LVEF (M Mode), End diastolic volume (EDV), End systolic volume (ESV), EF (Modified simpson), Left atrial (LA) dimension, Aorta (AO) Dimension, Mitral Valve E and A velocities , E deceleration time (Edt), Mitral gradient if any, Aortic valve Velocity ( gradient if any), MR grade, AR grade, Aortic regurgitation pressure half time (ARPHT), Mitral valve

area (MVA) (2D/ PHT- If mitral stenosis), Right ventricular systolic pressure (RVSP) (by Tricuspid regurgitation (TRjet)), Regional wall motion abnormalities (RWMA).

### **Cardiac MRI:**

The following parameters were recorded from the cardiac MRI of the patient

1. LV volumes – LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV)
2. LV Ejection Fraction -LVEF (%)
3. Presence or absence of Late Gadolinium enhancement (LGE )
4. Territories of LGE using 17 segment model
5. Pattern of LGE (whether Subendocardial, Midmyocardial, Transmural etc)
6. Severity of LGE( Based on overall number of segments having LGE): Mild / moderate / Severe

### **Statistical analysis:**

Continuous variables were expressed as mean with standard deviations. The data was analysed by the principal investigator with advice from statistician and was analysed with commercially available statistical software (SPSS version 16.0, SPSS Inc., Chicago, IL, USA) to study the percentage of patients having LGE, percentage of patients with specific patterns of LGE, any other patient parameters

by other investigations correlating with the presence of LGE on CMRI, Correlation of the degree of LGE with the severity of LV dysfunction. The correlation between the LVEF obtained by echocardiography and by cardiac MRI was analysed using the Pearson correlation coefficient.

## Results

A total of 19 Rheumatic heart disease have undergone cardiac MRI in our institute as a part of their evaluation. Seventeen of these 19 patients had Left ventricular ejection fraction  $<50\%$  and were included in the analysis. None of them had historical, Electrocardiographic or echocardiographic evidence of coronary artery disease or any other form of cardiomyopathy associated with late gadolinium enhancement on Cardiac MRI. Fourteen of them (83%) were male and 3 of them female. The mean age of the patients was 47.5 years (range 29-61) and 11 patients  $\geq 50$  years. Six patients (35%) had history of rheumatic fever in the past and diagnosis of RHD in others was based on the echocardiographic appearance of the valves on echocardiography. Most of them (n=13, 76.5%) were mildly symptomatic with NYHA functional class II dyspnoea on exertion and 23.5% were having FC III dyspnoea.

Twelve patients were having no modifiable risk factors for CAD. One patient had hypertension, 1 had dyslipidemia and 3 patients were smokers.

Rhythm was sinus in 4 of the patients (23.5%). Thirteen patients (76.5%) were in atrial fibrillation, out of them 69% had controlled ventricular rate on drugs. Fifteen patients had normal QRS axis (88%), 1 patient had Left axis deviation and

other had right axis deviation. None of them had AV conduction abnormalities. None of them had ischemic changes or infarct pattern.

Cardiac enlargement on chest roentgenogram (Cardiothoracic ratio, CTR > 0.5) was seen in 82% of the patients, with  $CTR \geq 0.6$  in 47%. Left atrial enlargement was seen in 88% and right atrial enlargement was seen in 70% of them. Changes suggestive of pulmonary venous hypertension were present in 88% of the cases and pulmonary arteries were enlarged in 3 of the patients.

Fifteen out of the 17 patients had undergone a coronary angiogram and all of them had been normal.

**Table 1: Baseline characteristics**

Mean age (years)	47.5 years (range 29-61)
Male (%)	83%
Functional class	NYHA FC II – 76.5% NYHA FCIII – 23.5%
H/o Rheumatic fever	35%
Rhythm	Sinus rhythm - 23.5% Atrial fibrillation- 76.5%
Cardiomegaly (CTR >50%)	82%
% of patients who had a prior CAG	88% ( All were normal)

NYHA FC- New York heart association functional class, CTR-Cardiothoracic ratio

Echocardiography showed mild left ventricular dysfunction (LVEF 41-50%) in 6 patients (35%), moderate LV dysfunction (LVEF, 31-40%) in 9 patients (53%) and severe LV dysfunction (LV EF $\leq$  30%) in 2 patients (12%). Both patients with severe left ventricular dysfunction were cases of severe mitral stenosis. Significant dilatation of the left ventricle (LVIDD  $\geq$  60mm) was seen in 8 patients (47%). Left atrium was enlarged in size in all the patients and gross left atrial enlargement (LA size  $\geq$  50mm) was present in 8 patients (47%). Right ventricular dysfunction was noted in 2 patients, both of them by visual assessment and objective parameters were not recorded.

**Table 2: Stratification based on LVEF**

LVEF	No of patients
41-50%	6 (35%)
31-40%	9 (53%)
$\leq$ 30%	2 (12%)

LVEF – Left ventricular ejection fraction

Thirteen patients had dominant mitral valve disease (76%), 4 patients had significant aortic valve disease along with mitral valve disease. None had dominant aortic valve involvement without mitral valve involvement. Among patients with

significant mitral valve disease alone, 6 patients had only significant mitral stenosis with mild or lesser degrees of mitral or aortic regurgitation.

Among patients with prominent mitral valve involvement alone, 4 had significant mitral regurgitation. Among them 2 had severe mitral regurgitation (1 with severe mitral stenosis (MS) and other with mild MS), 2 had moderate mitral regurgitation (both with associated moderate mitral stenosis). Among patients with significant aortic valve involvement (n=4), 1 patient had severe aortic regurgitation (with moderate MS), 3 had moderate aortic regurgitation (1 with severe MS, 1 with severe MR and other with moderate MS). None of them had more than mild aortic stenosis.

**Table 3: Categorisation based on predominant valve involvement**

Dominant valve involvement	No of patients
Dominant mitral valve involvement alone	13 patients (76.5%) <ul style="list-style-type: none"> <li>• 6 patients had dominant MS alone (<math>\geq</math> moderate severity)</li> <li>• 4 patients had significant MR ( associated with any degree of MS)</li> <li>• 3 patients had mild MS with mild MR</li> </ul>
Aortic +Mitral valve involvement	4 patients (23.5%) <ul style="list-style-type: none"> <li>• 1 had severe AR (with moderate MS),</li> <li>• 3 had moderate AR ( 1 with severe MS, 1 with severe MR and other with moderate MS)</li> </ul>
Organic tricuspid valve disease	1 patient (6%)

MS – Mitral stenosis, MR-Mitral regurgitation, AR-Aortic regurgitation

As seen above, only 8 of the 17 patients were associated with conditions associated with increased load on the left ventricle (volume overload in all the cases). Six patients had isolated mitral stenosis which does not impose any pressure or volume overload on the left ventricle. Three patients had mitral valve involvement with mild mitral stenosis and mild mitral regurgitation

Significant tricuspid valve lesions ( $\geq$  moderate tricuspid valve lesions) were seen only in 4 of the 17 patients. None of them had tricuspid stenosis. 3 patients had severe tricuspid regurgitation and 1 had moderate TR. Out of them 3 had functional TR related to pulmonary hypertension and 1 patient had severe organic tricuspid regurgitation.

### **Cardiac MRI data:**

Out of the 17 patients, fifteen patients had no late gadolinium enhancement of the ventricular myocardium. Two patients had late gadolinium enhancement of the ventricular myocardium. One patient had LGE in the basal Inferoseptum and the other patient had LGE of the basal inferior wall. The first one had enhancement in the subepicardial and midmyocardial regions and the second one had enhancement transmurally. Both patients had only mild or moderate left ventricular dysfunction. Both of the patients had severe mitral stenosis with not more than mild mitral regurgitation.

**Table 4: Comparison of baseline data in patients with and without LGE**

Parameters	Ventricular LGE+ (n=2)	Ventricular LGE- (n=15)
Mean age (yrs)	44.5	44.8 <50 yrs- 6 ≥50yrs -9
Males	2(100%)	11 (73%)
Atrial fibrillation	2 (100%)	11 (73%)
Predominant Valve involvement	2 - Isolated severe MS	4/15- Isolated severe MS 4/15- Severe MR (associated with MS) 4/15 – Moderate or severe AR - 3 with moderate to severe MS - 1 with severe MR 3/15 – Mild MS with mild MR
LVEF	Patient1-34% Patient2-44%	>30%-2 31-40%- 7 41-50% -6
Mean EDVI in ml/m <sup>2</sup> (range)	93.4 (69-117.8)	83.6( 38.7-199.4)
% with Increased EDVI (EDVI>92ml/m <sup>2</sup> )	50%	27%
ESVI (ml/m <sup>2</sup> )	45.2	56.2
RV dysfunction	0	2 (13%)

MS –Mitral stenosis, MR-Mitral regurgitation, AR- Aortic regurgitation, LVEF- Left Ventricular ejection fraction, EDVI,ESVI-End diastolic and systolic volume index

**Table 5: Valve involvement in relation to ventricular LGE**

Valve involvement	EF%	Ventricular LGE
Isolated Moderate or Severe MS (n=6)	41-50% - 1 31-40% - 3 <30% - 2	2 (33%)
Moderate / Severe MR (Associated with MS)(n=4)	41-50% - 1 31-40% - 3	0
Moderate / Severe AR ( with associated MS/MR)(n=4)	41-50%-2 31-40%-2	0
Mild MS/Mild MR (n=3)	41-50% - 2 31-40% - 1	0

MS –Mitral stenosis, MR-Mitral regurgitation, AR- Aortic regurgitation, EF- Ejection fraction, LGE- Late gadolinium enhancement

There was an apparent trend towards the presence of ventricular LGE in patients with isolated severe MS compared to other valve lesions. But the association is not statistically significant as 4 other patients with isolated severe mitral stenosis also didn't have any demonstrable Late gadolinium enhancement.

Even among patients with severe MS only one third had LGE of the ventricular myocardium. As all the patients with ventricular LGE and most patients without LGE (73%) were in atrial fibrillation, the impact of the rhythm on the presence of ventricular fibrosis could not be assessed. The positive correlation between the severity of the left ventricular dysfunction on the presence of ventricular LGE was analysed. But there was no significant correlation between

the severity of LV dysfunction and LGE as both the patients with the most depressed left ventricular function didn't show any myocardial enhancement and those who had LGE only had either mild or moderate left ventricular dysfunction.

Though there was no enhancement of the ventricular myocardium in many patients, there was enhancement of the left atrium and interatrial septum (IAS) in many patients. 7 Patients had LGE of the interatrial septum and 8 patients had enhancement of both the left atrium and the interatrial septum. One of them had enhancement of the Left atrium alone.

**Table 6: Atrial enhancement characteristics**

Area of LGE	No of patients
Posterior wall of LA+ Interatrial septum	8 (47%)( 1 of them had LGE of RA also)
Interatrial septum only	7 (41%)
Left atrium only	1
No atrial enhancement	1

LGE- Late gadolinium enhancement LA- Left atrium, RA- Right atrium

Patients with sinus rhythm (n=4) had no enhancement of the left atrial free wall though all of them had enhancement of the interatrial septum. Among patients with atrial fibrillation (n=13), 8 patients had enhancement of the left atrium along

with enhancement of the interatrial septum, 1 had isolated LGE of the left atrium, 3 had enhancement of the IAS alone and one had no enhancement of both IAS and the left atrium.

**Table 7: Atrial enhancement and relation to atrial rhythm**

Rhythm	LGE of atrium
Sinus (n=4)	LGE OF IAS alone -4 (100%) LGE of LA + IAS -0 (LA LGE-0%)
AF (n=13)	LGE of IAS alone -3 LGE of LA + IAS- 8 (61%) LGE of LA alone- 1 No LGE of atria -1 (LA LGE- 69%)

LGE- Late gadolinium enhancement, LA- Left atrium, IAS- Interatrial septum

**Table 8: Valve involvement in relation to atrial LGE**

Site of atrial enhancement	Valve involvement
IAS+ Left atrium (n=8)	Isolated Moderate or severe MS – 5 Severe MR with severe MS - 1 Mild MS/Mild MR - 2
IAS alone (n=7)	Moderate/ Severe AR - 3 Isolated moderate / Severe MS -1 Moderate / Severe MR – 2 Mild MS/Mild MR -1
LA alone (n=1)	Severe MS with moderate MR -1
No atrial LGE (n=1)	Severe AR with moderate MS -1

MS –Mitral stenosis, MR-Mitral regurgitation, AR- Aortic regurgitation, IAS- Interatrial septum, LA-Left atrium, LGE- Late gadolinium enhancement

**Table 9: Comparison of LV function among patients with different patterns of atrial enhancement**

Pattern of LGE in atria	EF (%)
IAS (n=7)	41-50% - 3 31-40% - 4
LA+IAS (n=8)	41-50% - 2 31-40% - 4 <30% - 2
LA alone (n=1)	41-50% - 1
No atrial LGE ( n=1)	31-40% - 1

IAS-Interatrial septum, LA-Left atrium, LGE- Late gadolinium enhancement

EF- Ejection fraction

From the above table, it appears that the presence of left atrial enhancement IAS is more commonly seen in patients with significant mitral stenosis. Among patients

with left atrial LGE, 78% has moderate or severe mitral stenosis. Among patients with significant mitral regurgitation, only two of the four (50%) had LA enhancement. That patient also has associated severe MS

One new finding of this study was the enhancement of the valve leaflets and in some cases the mitral subvalvular apparatus. Mitral valve enhancement was seen in all the seventeen cases. Aortic valve enhancement was seen in 8 patients, out of whom 4 of whom had hemodynamically significant aortic valve involvement. Tricuspid valve involvement was noted in 8 patients (47%) though significant lesion of the tricuspid valve was noted only in 4 patients of whom 3 appeared to have functional tricuspid regurgitation and only one had organic tricuspid valve disease.

**Table 10: Valve enhancement in MRI**

	Mitral valve	Aortic valve	Tricuspid valve
Clinical involvement	17(100%)	4(23.5%)	1(6%)
MRI detected fibrosis	17(100%)	8(47%) (Only half had clinical involvement)	8(47%) (only 12.5% had clinical disease)

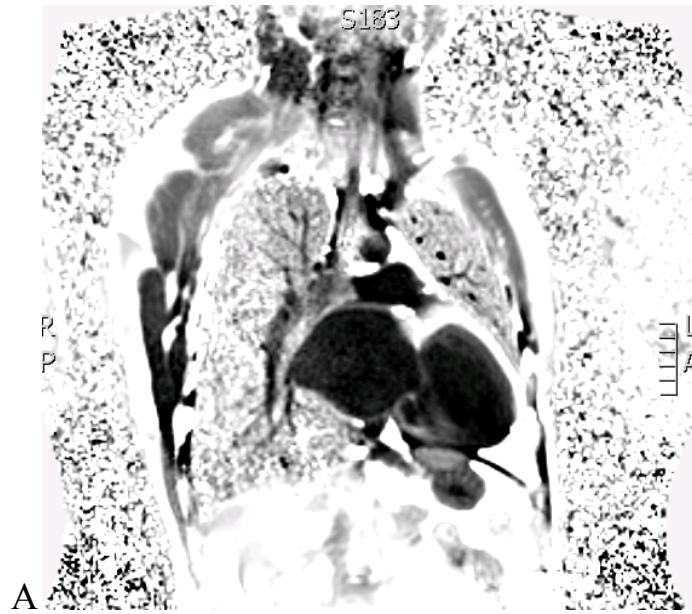
MRI- Magnetic resonance imaging

The overall pattern of LGE in rheumatic valvular heart disease patients is summarized below

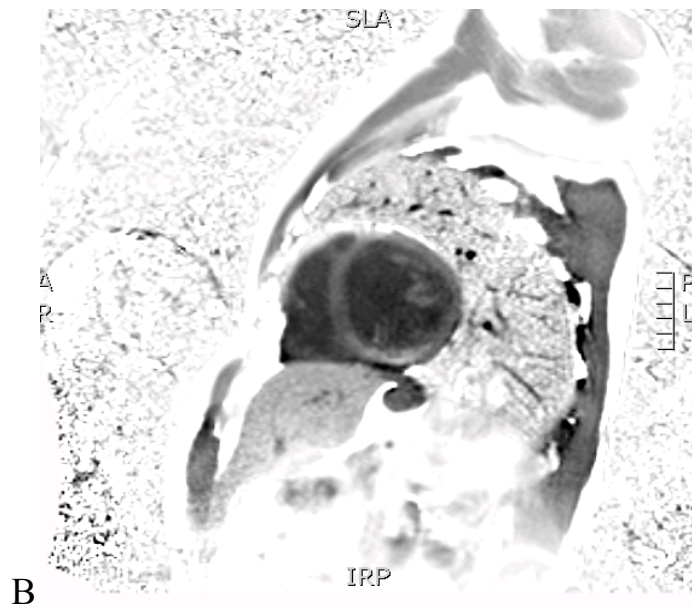
**Table 11: Summary of LGE data**

Site of LGE	No of patients (%)
<ul style="list-style-type: none"> <li>Ventricular myocardial LGE</li> </ul>	2/17 (12%) <ul style="list-style-type: none"> <li>1 patient had Subepicardial and midmyocardial LGE of basal Inferoseptum</li> <li>1 patient had transmural LGE of basal inferior wall</li> </ul>
Atrial LGE	16/17 (94%) <ul style="list-style-type: none"> <li>IAS - 44%</li> <li>LA wall + IAS - 50%</li> <li>LA - 6%</li> </ul>
Valvular LGE	17/17 (100%) <ul style="list-style-type: none"> <li>Mitral valve - 100%</li> <li>Aortic valve - 47%</li> <li>Tricuspid valve -47%</li> </ul>

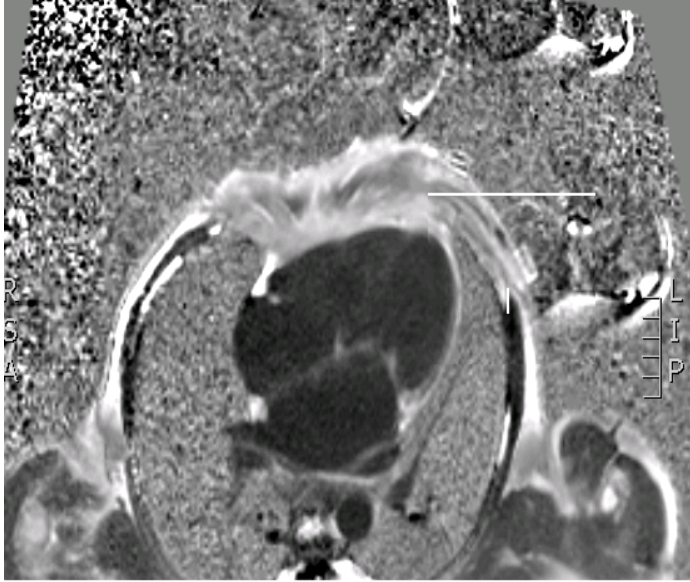
LGE- Late gadolinium enhancement, LA-Left atrium IAS- Inter atrial septum



A. Cardiac MRI image 30 minutes postcontrast showing the late gadolinium enhancement of the mitral valve



B. Cardiac MRI image 30 minutes postcontrast showing transmurular late gadolinium enhancement of inferior wall



C.

C. Cardiac MRI image 30 minutes postcontrast showing the late gadolinium enhancement of the left atrial

## **Discussion**

Rheumatic heart disease being one of the commonest causes of valvular heart disease in our part of the world, is a common indication for valve replacement surgeries and valve interventions (balloon mitral valvotomy). Left ventricular dysfunction has been reported in rheumatic mitral regurgitation and aortic valve lesions once they decompensate after a long stable course. It has also been reported that about 30% of mitral stenosis patients have left ventricular dysfunction. Though the onset of left ventricular dysfunction has been a standard indication for surgery in these patients, there have been reservations about their immediate post operative course and long term outcome compared to patients with these valve lesions with otherwise normal LV function. There have been controversial reports on the outcomes of these patients after valve surgeries.

It has been believed that, among this group, unintervened patients with left ventricular dysfunction for a prolonged period of time, may have fibrotic changes in the myocardium which affects the recovery of the myocardial function after the valve lesions have been addressed. There is a search for tools to stratify this group of patients into those who have chances of significant recovery of left ventricular dysfunction and those who may not improve. Medical treatment may be better in

the group of patients whose left ventricular dysfunction may be irreversible as surgeries in these patients may not worth the risk involved.

Cardiac MRI has become one such tool to stratify the outcomes of patients undergoing valve surgeries. Many researchers have studied the role of delayed enhancement cardiac MRI in prediction of postoperative and long term outcomes in aortic stenosis patients, mostly degenerative etiology and reported good correlation of late gadolinium enhancement with long term outcomes. There is also a suggestion that specific patterns of enhancement are predictive of worse outcomes in aortic stenosis patients. Similar studies in other valvular heart lesions like mitral stenosis, aortic regurgitation or mitral regurgitation and other etiologies like rheumatic are sparse.

The present study is the first of its kind reporting patients with rheumatic heart disease who underwent late gadolinium enhancement cardiac MRI. Also there have been reports of smoldering myocarditis as a part of the underlying rheumatic process in these patients with left ventricular dysfunction. This study provided chance to study the existence of myocardial fibrosis in such patients.

Many patients in the study including those with severe left ventricular dysfunction did not show any myocardial involvement by the fibrotic process. Only 2 out of the seventeen patients had myocardial LGE and both of them had

either mild or moderate left ventricular dysfunction by echocardiography and both of them had involvement of only small segment of the left ventricle. This shows that rheumatic heart disease even in those with severe left ventricular dysfunction does not produce significant myocardial fibrosis.

Both patients with LGE on MRI had isolated severe mitral stenosis. Regarding the site of LGE seen in both the patients, both correspond to previous reports of the fibrosis of the posterobasal region of the left ventricles previously reported in angiographic and echocardiographic studies of mitral stenosis patients with left ventricular dysfunction . One patient had a transmural pattern and the other had a subepicardial and midmyocardial enhancement. Similar transmural enhancement was reported in a case of Rheumatic AR by Choi et al<sup>19</sup>. Whether the presence of the localized enhancement or the pattern of the enhancement affects outcome is not clear as of now, as it was seen only in 2 patients and there is no sufficient follow up duration to comment on this.

### **Atrial Late gadolinium enhancement and correlation with atrial fibrillation:**

Another important finding of the present study was the presence of LGE of the interatrial septum and the left ventricle mainly the posterior wall. Except one patient, all others had enhancement of the intratrial septum or the left atrium or both. One patient had enhancement of the right atrium along with the left atrium.

The presence of atrial fibrosis may be related to the prolonged pressure overload of the left atrial with mitral stenosis and mitral regurgitation. But direct involvement of the atrial tissue, especially the appendages by the rheumatic process have been documented in some studies, documenting a prevalence between 19 to 74%<sup>22, 23</sup>. In a study published by Rubner et al of 316 mitral stenosis patients undergoing closed mitral commissurotomy, they did biopsy of the atrial appendages and found Aschoff Bodies in Atrial Appendages of 41% patients<sup>24</sup>. These report reports indicate direct involvement of the atrial tissues in rheumatic activity and these lesions may become fibrosed as seen in present study.

Association between the fibrosis of the atrial tissues and the presence of atrial fibrillation, both in rheumatic and nonrheumatic patients has been reported by various authors based on histopathologies obtained during cardiac surgeries. Alessandri et al analysed the histopathological findings of 243 patients who underwent mitral commissurotomy or mitral valve replacement. They compared the biopsy findings of patients in sinus rhythm and atrial fibrillation. Left atrial biopsy showed in patients of SR a normal atrial tissue in the 48% of cases and lightly altered in remaining 52%. On the contrary in patients of AF there was strong fibrosis in the 100% of cases<sup>25</sup>. Similarly atrial fibrosis was shown to be predictive of atrial fibrillation in patients undergoing coronary artery bypass surgery<sup>26, 27</sup>. Studies have also shown the increased expression of profibrotic factors like TGF-  $\beta$

and downregulation of antifibrotic MMP-1 in patients with valvular AF patients with persistent AF<sup>28, 29</sup>.

Leon et al analysed the biopsies of the atrial appendages (66 left and 62 right), obtained from 72 patients with rheumatic valve disease and chronic AF undergoing cardiac surgery for valve replacement. They found Amyloid deposition in 33 (46%) valvular patients with chronic persistent AF. They concluded that patients with long-standing AF and rheumatic heart disease have a very high prevalence of atrial amyloidosis. Amyloid deposition is more frequent in left than in right atrial appendage and correlates with AF duration. Amyloid deposition could constitute an additional histological feature in the structural remodeling of atria during long-standing AF, at least in rheumatic valve disease<sup>30</sup>.

Thirteen out of 17 patients (76%) in the present study were in atrial fibrillation. This is more than the expected prevalence of atrial fibrillation in rheumatic heart disease. The increased prevalence of atrial fibrillation may be related to the presence of more number of risk factors in the study population like older age at evaluation ( 11 patients >50 yrs of age), presence of LA enlargement in 100% of the patients ( 8 patients had LA size  $\geq$  50mm ) and the presence of left ventricular dysfunction itself. Shikano et al, in a study of 33 mitral stenosis patients compared the prevalence of atrial fibrillation between those with low ejection fraction with those with normal ejection fraction<sup>31</sup>. They reported that

incidence of patients with atrial fibrillation in the low ejection fraction group was significantly higher than in the normal ejection fraction group(86% vs 31%,  $p < 0.01$ ). There were no significant differences in the severity of mitral stenosis or other echocardiographic indices between the two groups. This increased prevalence of AF might imply to other other valve lesions with reduced ejection fraction due to common mechanism by which poor LV systolic performance increases the incidence of AF.

In the present study, there was correlation between the presence of atrial fibrosis on cardiac MRI and prevalence of atrial fibrillation. Out of the 13 patients in atrial fibrillation, 9 of them had diffuse LGE of the atrial wall (8 of them has LGE of interatrial septum also). But none of the patients in sinus rhythm ( $n=4$ ) had LGE of the left atrium though they had LGE of the interatrial septum.

There was also correlation between the degree of atrial fibrosis and the response to therapeutic interventions directed towards atrial fibrillation. Geuzebroek and coworkers in a biopsy study in patients undergoing maze procedure in lone AF and in patients with valvular AF undergoing valve surgery with maze, reported that Atria of patients with atrial fibrillation and mitral valve disease have more fibrosis than atria of patients with lone atrial fibrillation. They concluded that that fibrosis plays a more important role in the pathogenesis of atrial fibrillation secondary to mitral valve disease than in lone atrial fibrillation

and potentially explains the relatively poor success of antiarrhythmic surgery in patients with mitral valve disease<sup>32</sup>.

Similarly Singh et al studied the Correlation of left atrial appendage histopathology, cardiac rhythm, and response to maze procedure in patients undergoing surgery for rheumatic valvular heart disease<sup>33</sup>. Their results showed that patient with grade III histological changes in the appendage (diffuse interstitial and endocardial fibrosis with presence mural luminal thrombi and gross myofibril hypertrophy) on follow up have tendency to remain in AF even after modified maze procedure.

Bailey and coworkers studied the biopsies of the posterior wall of the left atrium obtained from 44 patients undergoing mitral surgery and graded them into 3 grades based on the severity of the fibrotic changes<sup>34</sup>. Cardioversion was attempted after surgery whenever feasible. Nine patients were successfully cardioverted, and all had grade II changes. Three additional patients succeeded and then relapsed; one had grade II and two had grade III changes. In seven patients cardioversion failed, and six of these had grade III changes. They proposed that fibrosis after rheumatic inflammatory insults leads to atrial fibrillation by disturbing impulse propagation in the atrium; prolonged atrial fibrillation leads to a disuse atrophy of muscle, and atrial fibrillation becomes irreversible. These pathologic changes may

be used for predicting success or failure of cardioversion and probability of maintaining sinus rhythm.

As late gadolinium enhancement by cardiac MRI has a good potential for assessing myocardial fibrosis, it can be used to select patients for pharmacological and interventional means for achieving and maintaining sinus rhythm. Considerable amount of work has been done in this area, mostly involving patients with paroxysmal atrial fibrillation and no significant structural heart disease. Harrison et al reported that High LGE MRI signal intensity correlates with areas of low endocardial voltage, however, low voltage can still occur in areas of low signal intensity on LGE MRI.<sup>35</sup>

Mahnkopf et al in a study involving 40 'lone AF' patients reported that majority of these 'lone' AF patients showed a mild or even moderate degree of left atrial fibrosis.<sup>36</sup>

Oakes et al reported on the delayed enhancement MRI (DE-MRI) quantification of left atrial structural remodelling in 81 patients with AF. Mild enhancement was found in 43 patients, 28 of these (65%) had paroxysmal AF. However, 15 of these patients (35%) still had only mild enhancement but were already in persistent AF. Furthermore, from the 30 patients with moderate enhancement, 43% still presented with paroxysmal and 57% with persistent AF, respectively, again indicating towards the high variability of structural remodelling

in patients with paroxysmal and persistent AF. When present, LA scar was an independent adverse prognosticator of longterm success of an AF ablation procedure in this series<sup>37</sup>.

Jaddi et al studied 18 patients with persistent (n = 7) and long-standing persistent (n =11)<sup>38</sup>. All patients underwent delayed enhancement MRI and electroanatomical mapping. MRI images were processed to identify DE abnormalities that were regionally categorized as dense (>90% distribution), patchy (20% to 70% distribution), or normal (no DE). The overall DE content (mostly of patchy type) was higher in patients with longstanding persistent versus persistent AF. The investigators concluded that LA DE abnormalities observed using high-resolution CMRI imaging interact uniquely with CFE abnormalities during persistent and long-standing persistent AF. They further concluded that sites manifesting DE and CFE abnormalities have mechanistic implications and so may be more promising ablation targets .

In a multicenter, prospective, observational cohort study of patients diagnosed with paroxysmal and persistent AF patients, Marrocuì et al, studied 369 patients<sup>39</sup>. Atrial tissue fibrosis estimation by delayed enhancement MRI was successfully quantified in 272 of 329 enrolled patients. their results were indicative that among patients with AF undergoing catheter ablation, atrial tissue fibrosis

estimated by delayed enhancement MRI was independently associated with likelihood of recurrent arrhythmia.

Based on these results, it appears clear that cardiac MRI with delayed enhancement may evolve as an important tool to select patients for catheter ablation, to guide ablation strategies and predict the risk of recurrence after catheter ablation. But its role in patient valvar AF is still not clear in view of the poor success rates of catheter ablation by contemporary methods, as substrates for ablation are entirely different for valvar AF patients compared to those of lone AF patients. Delayed enhancement MRI may provide a good idea of the atrial substrate which may help devising better ablation strategies and improve success rates of catheter ablation for valvar AF patients. Studies focusing on cardiac MRI guided AF ablation in valvular AF patients are warranted.

### **Late gadolinium enhancement of the valves:**

One interesting finding in this study was the presence of valve enhancement in late gadolinium sequences. All patients had LGE of the mitral valve and some had involvement of the aortic and tricuspid valves also. Enhancement of the mitral and tricuspid valves was seen in many patients without any hemodynamic significant involvement. Aortic valve enhancement was seen in 8 patients (47%) out of whom 4 of whom had hemodynamically significant aortic valve involvement. Thus only

50% of patients with aortic valve enhancement have clinically significant lesions. This correlates with 25% involvement of aortic valves along with mitral lesions in echocardiographic studies.

Though the clinical involvement of tricuspid valves in the present study correlates with data from echocardiographic studies on the prevalence of individual valve lesions in rheumatic heart disease, but the late enhancement data correlates better with the autopsy data. In an autopsy study by Chopra et al, Organic involvement of the tricuspid valve was documented in 38.4% of cases<sup>40</sup>. Organic involvement of the tricuspid valve by echocardiographic studies was 4.7% in a study in a study by Manjunath et al<sup>41</sup>. Involvement of tricuspid valve was reported in other echocardiographic studies was reported in upto 8% of the patients<sup>42</sup>. But is not clear whether the fibrosis in valves without hemodynamic significance can evolve over time to cause clinically significant lesions.

The presence of late enhancement in valves may be related to the excessive fibrosis in the valves affected by the rheumatic process. Excess fibrocollagenous deposition in rheumatic valves has been demonstrated by histopathological examination of affected valves excised during valve surgeries and by autopsies. Microscopically there is diffuse fibrosis and often neovascularization that obliterate the originally layered and avascular leaflet architecture. In a study of 50

excised mitral valves and 43 aortic valves, Malhotra et al have shown that, chronic rheumatic process is associated with loss of architecture and extensive fibrosis<sup>43</sup>.

Except for report in a single patient with mitral stenosis by Shikri et al<sup>44</sup>, LGE of rheumatic valves has not been studied that exclusively. The present study shows that even clinically unaffected valves can have significant degrees of fibrosis, but the clinical significance of this finding is not clear at present.

### **Reduced systolic performance in mitral stenosis patients:**

About 30% of patients with isolated mitral stenosis were reported to have reduced Left ventricular systolic function (LVEF< 50%) as assessed by angiographic and echocardiographic methods<sup>48, 49, 50</sup>. Variable postulates have been put forward to explain the mechanism of LV systolic dysfunction in these patients with mitral stenosis. Many studies attributed altered loading conditions like reduced preload (chronically underfilled LV) or increased afterload as the primary cause for reduced systolic performance in mitral stenosis and some have focused on intrinsic myocardial pathology including focal fibrosis of the posterobasal LV wall caused by the chronic rheumatic process<sup>51</sup>.

Carabello et al compared different hemodynamic parameters indicative of preload conditions( End diastolic volume index EDVI), afterload ( Endsystolic wall stress,ESS) , EF, Velocity of circumferential fiber shortening [Vcf] stroke

work index [SWI], and an index of LV contractile function thought to be independent of loading conditions (end-systolic wall stress/end-systolic volume index [ESS/ESVI]) in nine normal subject and 16 patients with isolated MS. 31% of their patients had reduced LV ejection fraction<sup>48</sup>. After comparing the parameters, they found MS patients with EF<50% had higher ESS (afterload) yet similar preload (EDVI) compared to those with EF >50%. Mitral stenosis patients as a group had lower EDVI. So they postulated that the reduction in ejection performance is due to increased afterload without adequate Frank-Starling compensation. LV muscle function, however, is normal in most MS patients with reduced LVEF. Similar results were put forward by Wisenbaugh and coworkers who found similar EDVI in mitral stenosis with reduced LVEF compared to those with normal EF and concluded that excessive vasoconstriction with increased afterload may be cause for poor left ventricular performance<sup>52</sup>.

In a study of fourteen patients, Bolen et al analysed the LV systolic performance of mitral stenosis patients in response to afterload augmentation and reduction<sup>53</sup>. Afterload reduction did not improve Left ventricular performance and they concluded that contraction abnormalities in posterobasal area correlated well with the abnormal left ventricular function curves. Some old publications also claimed similar localised contraction abnormalities in mitral stenosis patients

involving the posterobasal LV caused by the extension of the fibrotic process from the submittal apparatus<sup>54, 55</sup>.

Ibrahim et al did an echocardiographic analysis on 20 patients, found EF <55% in 50% and <50% in 30% of the patients<sup>56</sup>. After analyzing multiple factors, they postulated that the abnormalities in contractility of the left ventricular myocardium can be responsible for the impaired myocardial function in patients with mitral stenosis.

The present study includes 6 patients with isolated mitral stenosis with no hemodynamically significant mitral regurgitation or involvement of the aortic valve, providing an opportunity to study the mechanism of the left ventricular dysfunction in these patients. End diastolic volumes indexed to the body surface area (EDVI) of all the patients were either within the normal range or increased. Two patients had grossly dilated left ventricles. This fairly excludes chronic underfilling of the left ventricle as a cause of poor systolic performance in these patients. Five patients have no significant tricuspid regurgitation or pulmonary hypertension, causing the pressure or volume overloaded right ventricle to cause paradoxical septal motion to cause reduced LVEF. Only one of them had severe TR with severe pulmonary hypertension.

**Table 12: LV EF and End diastolic volumes in patients with MS**

Patient No.	LVEF(%)	EDVI(ml/m2) Normal (47—92)	Late gadolinium enhancement
1	40	69	LGE in basal Inferoseptum
2	34	117.8	LGE in basal Inferior wall
3	40	51.7	None
4	38	76.6	None
5	21	67	None
6	20	155.6	None

LVEF- Left Ventricular ejection Fraction EDVI- End diastolic volume index

LGE –Late gadolinium enhancement

Four out of the six patients with MS did not show any delayed enhancement changes in the left ventricle post gadolinium injection. Two of them showed focal LGE in the basal regions, one in the Inferior wall and the other showed LGE of the inferoseptum. One of the patients had subepicardial and midmyocardial enhancement doubting the older postulate that the regional wall abnormalities are due to the extension of the fibrotic process form the submitral apparatus. And the presence of the LGE in only two of the six patients may not explain the LV

systolic dysfunction in the other 4 patients. The extent of the myocardial fibrosis in those 2 patients is very small to contribute to global reduction in LVEF. Also those 2 patients with severe LV dysfunction ( $LVEF \leq 30\%$ ) did not show any fibrotic changes. These results may explain that intrinsic myocardial factors may not play a key role in the poor systolic function in a subset of mitral stenosis patients. So unknown factors causing altered loading conditions may be most probable cause for the LV dysfunction in mitral stenosis cases, as all explained load related factors studied till date may be common to all patients with mitral stenosis and not specifically present in the subgroup with left ventricular dysfunction.

Also the cause of LV dysfunction in 3 patients with mild mitral stenosis with left ventricular dysfunction could not be explained by conventional factors contributing to loading conditions of the ventricle, also the valve lesions per se was only mild to contribute to reduced preload or increased afterload due to reduced cardiac output.

Some recent reports have shown improvement of left ventricular dysfunction in mitral stenosis patients after addressing the stenotic valve either surgically or by balloon mitral valvotomy. Mathur et al in a study of 60 patients with mitral stenosis ( 16 of them had  $LVEF < 50\%$ ) compared the left ventricular volumes and systolic function before and after balloon mitral valvotomy<sup>57</sup> . There was a trend

towards improvement in LVEF at 1 week (pre  $47\pm 4\%$ , 1 week post BMV  $50\pm 4.9\%$ ) and 3 months ( $52\pm 6$ ). Whether a longer follow up would have produced a further improvement in LV function is not clear.

In a study by Mangoni and coworkers, compared the clinical outcomes following mitral valve replacement of 16 mitral stenosis patients with LVEF  $<50\%$  with those with normal ejection fraction<sup>58</sup>. Though they did not report regarding the improvement in LVEF, they reported similar survival in both group of patients. There was increased incidence of heart failure in patients in patients with LV dysfunction in the immediate postoperative period. They concluded that moderately reduced LV ejection fraction should not be a contraindication to mitral valve surgery in patients with severe MS.

## **Limitations**

The important limitation of the study was that most patients in the study had only mild or moderate left ventricular dysfunction creating speculation whether analysis of more patients with severe forms of LV dysfunction might have shown more cases with myocardial fibrosis. But even in the patients studied in this study, those 2 patients with LVEF<30% didn't show enhancement but those 2 who had enhancement belonged to the group with mild or moderate LV dysfunction. Another limitation is that the number of patients in the study is low which may affect the generalisability of the results. Still it is the only study reporting the noninvasive assessment of myocardial fibrosis in rheumatic heart disease patients. Also the patients studied are heterogeneous and a lesion specific analysis was also not feasible because the total number of patients were less causing number of patients with significant aortic valve lesions to be less. It is not clear why some patients without significant valve lesion had ventricular dysfunction. Whether they are cases of unrelated cardiomyopathies with associated mild RHD is not clear.

## **Conclusions**

Among patients with rheumatic valvular heart disease, about 12% of the patients have myocardial fibrosis as indicated by the presence of LGE in cardiac MRI. The patterns of LGE seen in these patients were transmural, subepicardial or midmyocardial. The presence of LGE does not correlate with the severity of the left ventricular dysfunction.

Many patients with isolated mitral stenosis having significant left ventricular systolic dysfunction did not have myocardial fibrosis as proposed by earlier studies. Left ventricular dysfunction in many of them may be due to altered loading conditions mainly afterload.

Atrial fibrosis was seen in a significant number of patients with rheumatic valvular heart disease patients and presence of left atrial LGE positively correlated with the prevalence of atrial fibrillation.

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## Abbreviations

ACS- Acute Coronary Syndrome

AF – Atrial fibrillation

AR - Aortic regurgitation

ARPHT - Aortic regurgitation pressure half time

AS – Aortic Stenosis

AV – Atrio ventricular

AVR- Aortic Valve Replacement

CMRI- Cardiac MRI

CVA- Cerebrovascular events

CI – Confidence interval

CAD- Coronary Artery disease

CTR- Cardiothoracic ratio

DE – Delayed enhancement

DE-MRI – Delayed enhancement MRI

Edt – E deceleration time

EF- Ejection fraction

EDV - End diastolic volume

EDVI - End diastolic volume index

ESV- End systolic volume

ESVI – Left Ventricular end-systolic volume index

FC – Functional class  
FS- Fractional Shortening  
HR- Hazard ratio  
IAS – Interatrial septum  
LA – Left Atrium  
LVEF- Left ventricular Ejection Fraction  
LGE- Late Gadolinium enhancement  
LVIDD -LV internal dimension in diastole  
LVIDS - LV internal dimension in systole  
LV – Left ventricle  
LVD- Left ventricular dysfunction  
MMP – Matrix metalloproteinase  
MRI- Magnetic resonance imaging  
MR- Mitral regurgitation  
MS – Mitral stenosis  
MVA- Mitral valve area  
NYHA- New York Heart Association  
OPD – Out patient department  
PWd - Posterior wall thickness in diastole  
PWs - Posterior wall thickness in systole  
RHD – Rheumatic heart disease  
RVSP - Right ventricular systolic pressure  
RWMA - Regional wall motion abnormalities

Sd – Septal thickness in diastole

Ss - Septal thickness in systole

SWI - Stroke work index

TAVR - Transcatheter aortic valve replacement

TGF-  $\beta$  – Transforming growth factor-  $\beta$

TR - Tricuspid regurgitation

Vcf - Velocity of circumferential fiber shortening