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PROJECT REPORT

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DECLARATION

I, Dr. Hitesh Yadav, 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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TITLE

"Atrial fibrosis by CMR in RHD Patients with mitral and aortic valve involvement and its correlation with atrial fibrillation"

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Hitesh Yadav

Atrial fibrosis by CMR in RHD Patients with mitral and aortic valve involvement and its correlation with atrial fibrillation

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Abstract

Background: Rheumatic heart disease (RHD) is the most common valvular heart disease in India and other developing countries accounting for 25-45% of acquired heart disease. RHD Patients may have involvement of mitral and aortic valve as stenotic and regurgitant lesions in various combination. In RHD patients with or without AF, left atrial structural remodelling caused by atrial fibrosis. Late gadolinium enhancement MRI (LGE-MRI) has been proved to be a powerful tool for detecting atrial fibrosis. LGE-MRI: establish atrial disease (fibrotic tissue) and quantify this. Atrial fibrosis is the basis of etiopathogenesis of atrial fibrillation (AF) and AF itself promotes atrial fibrosis. Involvement of atrial myocardium and its correlation with AF in rheumatic valvular heart disease patients have not been studied so far, except for few available case reports.

Objectives: The study was conducted to assess impact of RHD process on atrial myocardium, to correlate atrial remodeling leading to risk of AF and other atrial arrhythmias with outcomes of the AF treatments.

Methods: We retrospectively-prospectively reviewed the records of RHD patients with LV (Left ventricular) dysfunction (Left ventricular ejection fraction, (LVEF < 50%) by echocardiogram underwent Cardiac MRI. RHD patient with Post valve replacement, history or any evidence of Heart failure, Cardiomyopathy (Ischaemic/Idiopathic) and Contraindication to cardiac MRI were excluded. We analyzed the extent of atrial fibrosis by Cardiac MRI late gadolinium enhancement (LGE) in RHD patients with any degree of LV dysfunction and whether there was any correlation of atrial LGE (specific pattern of LGE) with the degree of LV dysfunction, valvular lesion severity, Atrial arrhythmias.

Results: Cardiac MRI data of 26 patients (19 (73%) male and 7(27%) female) with median age 49 years (range 32-62) were analyzed. 18 of the 26 patients underwent a coronary angiogram which was normal. 19 patients had dominant mitral involvement alone and 7 patients had combined mitral and aortic valve disease. 18 patients (69.2%) had mild LV dysfunction (LVEF 41-50%), 6 patients (23.1%) had moderate LV dysfunction (LVEF 31-40%) and 2 patients (7.7%) had severe LV dysfunction (LVEF≤ 30%). twenty-two patients (84.6%)

were in atrial fibrillation and 4 patients (15.4%) were in sinus rhythm. Twenty-five patients out of the twenty-six patients (96.2%) had transmural left atrial LGE, remaining one patient had LGE of left atrial side of IAS. LA LGE correlated well with mitral valvular severity, LA size and AF. LGE of mitral, aortic and tricuspid valve was present in 100%, 96.2% and 92.3% respectively. Two patient had LV LGE, one in the basal Inferoseptum and other patient had LGE of the basal inferior wall. The first one had enhancement the epicardial 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.

Conclusion: Among patients with rheumatic valvular heart disease, about 96% of the patients have atrial fibrosis as indicated by the presence of LGE in cardiac MRI. The patterns of LGE seen in these patients were transmural and correlated with valvular lesion severity, valvular LGE, LA size, PAH status, presence of AF and status post mitral intervention but was not related to LV systolic dysfunction. The presence of LV LGE was not correlated with the severity of the left ventricular dysfunction. So we concluded that atrial myocardial involvement by rheumatic process is much more common than

ventricular myocardium, it appears to be direct involvement of atria or by hemodynamic burden imposed by valvular lesions or presence of AF, most likely all the factors contributing in various proportion. Rhythm does not correlate to atrial or ventricular LGE suggest that Atrial LGE is the result of direct involvement of atria however presence of longstanding AF may increase the atrial LGE.

Introduction

Valvular heart diseases particularly rheumatic is an important cause of cardiovascular morbidity and mortality, next to ischemic heart disease. Valvular heart diseases accounts for >25% of all cardiac surgeries performed all over the world. In Indian Scenario Valve surgeries accounts 57% of all adult cardiac surgeries, shown by a large study of 1000 consecutive patients conducted at a tertiary center at Delhi[1]. The main causes of valvular heart disease are Rheumatic heart disease (RHD), degenerative calcific valve changes and inherited or congenital conditions. RHD is still the most common cause of valvular heart disease in India, Though the prevalence of RHD has reduced in the western countries. Rheumatic fever is endemic in India and remains the major causes of cardiovascular disease, accounts 25-45% of the acquired heart disease[2]. RHD prevalence by 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[3]. RHD accounts up to 45% of cardiology admission in Indian hospitals contribute significant economic burden to the healthcare

system[4]. Patient with suitable mitral valve are managed by balloon mitral valvotomy, significant proportion of patients with unsuitable anatomy require open heart surgeries. Valve surgeries per se lead to significant morbidity and mortality, that is further increased by presence of left ventricular dysfunction due to late presentation.

RHD can involve mitral and Aortic valve (less commonly tricuspid valve) as stenotic and regurgitant lesions in various combinations, each has different natural history. RHD lesions of mitral and aortic valve lead to left ventricular systolic dysfunction due to LV fibrosis in later part of natural history. Similar to LV myocardial fibrosis, atrial myocardium is also prone to fibrosis either as a cause or result of atrial remodeling by rheumatic process.

In RHD patients with or without AF, left atrial structural remodeling caused by atrial fibrosis. Late gadolinium enhancement MRI (LGE-MRI) has been proved to be a powerful tool for detecting atrial fibrosis. LGE-MRI establish atrial disease (fibrotic tissue) and quantify this. Atrial fibrosis may cause AF and AF itself promotes atrial fibrosis. There is no data on the prevalence of myocardial fibrosis and their patterns in patients with RHD till date except isolated case reports.

Review of literature

Atrial tissue LGE and correlation with various factors

Most important finding of this study was the documentation of atrial tissue (LA/RA/IAS/PV) LGE. The atrial fibrosis may be explained by either direct involvement of atria by rheumatic fever that is proved histologically by previous studies or by hemodynamic burden imposed by valvular lesion and associated AF.

In our study we found that most of the pt. was in AF had biatrial delayed gadolinium enhancement, but few patients who was in SR also had biatrial gadolinium enhancement. So it was concluded that rheumatic process that involves cardiac valvular tissue also involves atrial myocardium. AF is late manifestation due to atrial structural, morphological and functional changes that further perpetuate the rheumatic fibrosis process.

Jabi Shriki et al.[5] firstly reported the 3 cases of clinically and Echo proved RHD, in whom LGE by CMR was revealed in the one or both atria. In one patient they also found evident LGE in both left sided atrioventricular valves. Authors concluded that atrial LGE is seen in

RHD is likely more often than in other diseases and this leads to atrial fibrillation. Authors attributed that Atrial-wall fibrosis is from atrial fibrillation or myocardial inflammation from rheumatic carditis.

Previous left atrial appendage (LAA) histopathological studies done in rheumatic and nonrheumatic valvular heart disease has demonstrated the Association between atrial fibrosis and the presence and persistence of atrial fibrillation post-surgery including maze procedure. Direct involvement of the atrial myocardium by rheumatic process have been studied histopathologically and detected to have Aschoff Bodies in Atrial Appendages of 19 to 74 % of patients.[6,7]

Chopra P et al[8] Studied surgically removed mitral valve in 195 RHD patients by histology. One hundred seven patients were from AIIMS, New Delhi and 88 patients from Albuquerque were studied in a similar period. The characteristic finding in Indian patients was presence of moderate or severe valvular calcification and mononuclear cellular infiltration (lymphocytic-plasma cell) of valvular tissue. These distinct findings were not observed among Albuquerque patients. So authors concluded the probability of chronic immune reaction leading to mononuclear cell infiltrates of mitral valve in Indian patients. This influence the natural course of RHD in Indians. Above study support the

valvular LGE in present study.

Lars Wallby et al[9] studied surgically removed aortic valve of 39 patients with aortic stenosis including 29 nonrheumatic AS and 10 rheumatic AS. Immunohistochemical analyses of mononuclear inflammatory cells and apolipoprotein were done. They showed that location of calcification differed in nonrheumatic (tricuspid) valves as comparison to nonrheumatic (bicuspid) and rheumatic valves. Mononuclear lymphocyte infiltration was less in rheumatic valves as compared to nonrheumatic, although macrophages infiltration was indifferent as was apolipoprotein deposition. So Concluded that chronic inflammation is significant and similar in rheumatic and nonrheumatic AS valves. Above findings also highlights the post inflammatory valvular disease in other causes like rheumatic fever.

Rubner et al[10] studied biopsy of the atrial appendages in 316 MS patients who underwent closed mitral commisurotomy and found Aschoff Bodies in Atrial Appendages of 41% patients. This indicate direct involvement of the atrial myocardium by rheumatic activity and these lesions may lead to atrial fibrosis as proved in present study.

Ashutosh Singh et al[11] published study of 50 RHD patients (25 in SR, 25 in AF) who underwent surgery including maze procedure and

correlated left atrial appendage (LAA) histopathology and cardiac rhythm, and its response to maze procedure. They classified LAA histopathology in three grades based on endocardial inflammation and myofibril hypertrophy and post-operatively observed the rhythm of all patients. Patient with AF and MR as predominant lesion were more likely to have gr III changes in LAA histology. Patient with gr I-II changes were more likely to remain in SR, while those with gr III changes remained in AF despite maze. This study showed that higher grade of LAA fibrosis coexist with atrial fibrosis that was responsible for insistence of AF. This study also favors present study atrial fibrotic changes and correlation with AF.

Study based on LAA biopsy and histopathology was published by Connelly JH et al[12] that included 19 patients, whose atrial appendages were removed as part of the surgical procedure including maze. Histopathology of LAA showed myocyte hypertrophy, vacuolar degeneration and intramyocardial lipid deposition that was semi quantitatively measured. LAA vacuolar degeneration were found to be significantly more common in arrhythmias patients.

Saito T et al[13] studied LAA histopathology of 57 patients who underwent surgery for AF treatment, aiming to improve the prediction of

postoperative AF recurrence. LAA from valvular AF patients showed more cardiomyocyte hypertrophy, More nuclear enlargement, more bizarre nuclei, more intercellular fibrosis ($p<0.001$). 37 cases maintained in SR from 7 months to 10 years. 20 patients who had AF recurrence within or after a month of surgery, had more histopathological changes than the patients who remained in SR after surgery.

M Rashed et al[14] aimed to study the histopathological changes in surgically removed rheumatic mitral valves. 25 pediatric RHD cases showed a strong and significant association between absence of Aschoff nodules and AF ($p=0.0070$). Patients with AF and combined mitral dysfunction (MS/MR) had significant mitral calcification. Valvular endothelial ulcerations also significantly associated with MS or combined MS/MR. Clinical-pathologic correlation was concluded to be helpful in evaluating the extent and severity of valvular lesions.

Jayaprakash Shenthar et al[15] analyzed the histopathology of both atria in isolated MS patients underwent MVR who were in SR (10) or AF (13). AF was found to be associated with myocytolysis, whereas SR with myocyte hypertrophy and glycogen deposition. Interstitial fibrosis, LAA Endocardial inflammation was present irrespective of rhythm. Amyloid and Aschoff bodies were not common.

Shruti Sharma et al[16] Studied 30 RHD patients underwent MVR with excision of LAA, of these patients (17 had persistent AF and 13 SR) light and electron microscopic histopathological examination were characterized by cardiomyocyte hypertrophy (CH), nuclear enlargement (NE), perinuclear clearing (PC), sarcoplasmic vacuolation (SV), fibrosis, and inflammation. AF patients had significantly more NE (P=.004), PC (P=.004), SV (P=.06), and fibrosis (P=.001). Extensive interstitial fibrosis, inflammation and CH were observed more commonly in AF as compared to SR patients. AF patients was lacking contractile elements (Z-bands), with glycogen particle accumulation and an increase in mitochondria on electron microscopy.

Alessandri et al[17] published a histopathological study of 243 patients who underwent balloon mitral commisurotomy or MVR. Atrial biopsy findings were compared in patients with SR and AF. Patients with SR had either normal (48%) or mild alteration (52%) in atrial tissue. While all patients with AF had severely fibrosed atrial tissue. Similarly studies in patients with AF underwent coronary artery bypass surgery showed atrial fibrosis that was predictive of rhythm abnormality[18,19]. Molecular studies in persistent valvular AF patients have shown increased expression Transforming growth factor beta (TGF-β), a

profibrotic factor and decrease expression of MMP-1(anti-fibrotic).[20,21]

Leon et al[22] studied the atrial appendages biopsies (66 left and 62 right), of 72 patients with RHD and chronic AF underwent surgical mitral valve repair or replacement. Patients with chronic persistent AF (46%) and RHD had very high prevalence of atrial amyloidosis. Left atrial appendage Amyloid deposition was more frequent than right. So Amyloid deposition could be implicated as an additional histological finding in RHD patients with atrial remodelling leading to long-standing AF.

Above histopathological studies have shown chronic inflammatory changes in atrial myocardium in most of patients and these changes are exaggerated in patients who are in AF.

Higuchi K. et al.[23] studied nonvalvular AF patient with atrial LGE-MRI prior to AF ablation. They evaluated the location, extent and amount of atrial LGE that correlated with low voltage area in three dimensional (3D) electroanatomical mapping during AF ablation. There was significant association between atrial LGE areas and Low voltage areas by electroanatomical mapping. AF recurrence after ablation was correctly predicted by the extent of LA LGE. LGE-MRI became an important modality for atrial disease (fibrotic tissue) detection and

quantification tool after this study. In this study LASRM (Left atrial structural remodeling) was divided into four stages that was Based on the amount of preablation LA LGE as follows- Utah stage I ≤5% LA LGE (minimal), Utah stage II >5% and ≤20% LGE (mild), Utah stage III as >20% and ≤35% LA enhancement (moderate), and Utah stage IV as >35% LA enhancement (extensive). Results of AF ablation strongly correlated with extent of LA LGE particularly LA posterior wall LGE as Patients with Utah stage I had excellent outcome whereas poor with stage IV. Result of this study are important from point of view of clinical decision making, both for patient and physicians.

As per result of this study ablation (PV isolation and posterior wall debulking) is preferred therapy for patients in Utah stage I and II and Utah stage III with localised fibrosis. While rate control and anticoagulation is advised for Utah stage III with diffuse fibrosis and for all Utah stage IV. This study also highlighted the correlation of LASRM (LA LGE) and left atrial appendage (LAA) thrombus by transoesophageal echocardiography (TEE), So predict the risk of thrombus formation and stroke in AF.

Nazem Akoum et al.[24] demonstrated the utility of LGE-MRI to study LA in AF patient and identify the poor responder to RFA, risk of

significant sinus node function and stroke. LA fibrosis by CMR was a strong predictor of AF recurrence following ablation. Post RFA CMR assessed LA LGE that was used as guidance for repeat RFA. Patients who underwent cardiac surgery, their LA biopsy correlated with LGE areas by CMR. AF Patient with fibrosis burden of greater than 20% by LGE had sinus node dysfunction and required pacing post ablation.

Nassir F. Marrouche et al[25] DECAAF study, 260 patients with paroxysmal AF underwent CMR, Fibrosis was blinded to treating physician according to categories as stage 1 (<10% of the atrial wall), 2 (≥10%-<20%), 3 (≥20%-<30%), and 4 (≥30%) and characterize the AF ablation outcome in relation to extent of atrial fibrosis estimated by LGE-CMR that independently predicted AF recurrence also.

Peter Haemers et al[26] reviewed the extent of LA injury by LGE-CMR in identifying AF pathophysiology and correlated its role in stroke prevention and catheter ablation. CMR was proposed as valuable tool for AF in therapeutic decision making.

Marcos Daccarett et al[27] proposed that LGE-MRI allow assessment of left atrial structural remodeling and fibrosis. LA fibrosis was found to correlate with clinical outcomes after ablation and also in assessing individual's risks of LA appendage thrombus and thromboembolic

events. Atrial injury in terms of fibrosis as assessed by LGE-MRI helpful in treatment of atrial fibrillation, predicting recurrence risk and guiding specific ablation techniques.

Above studies done in nonvalvular AF have shown that extent of atrial fibrosis is predictive of its onset and responses to therapy. Based on extent atrial LGE various algorithm have been proposed for AF ablation, they provide both guidance and predict chances of ablation success.

Study by Shikano et al[28], in 33 MS patients has shown that prevalence of AF was significantly higher in the patients with low ejection fraction than normal ejection fraction group (86% vs 31%, $p < 0.01$). Although there were no significant differences in the MS severity between two groups. So increased prevalence of AF in reduced ejection fraction group was related to LV systolic dysfunction per se.

Geuzebroek et al[29] compared the extent of fibrosis in patients with valvular AF and lone AF, this histopathological study enrolled patients undergoing valve surgery with maze and lone AF patient undergoing maze procedure. They showed that valvular AF patients had more fibrosis of atrial tissue in comparison to Lone AF group. So concluded that fibrosis has key role in valvular AF pathogenesis than lone AF and explained the poor success of antiarrhythmic therapy in valvular AF.

Bailey and coworkers[30] 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. Cardioversion was attempted after surgery in whichever 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 LGE by cardiac MRI is good predictor for assessing myocardial fibrosis, it has been studied in nonvalvular AF to select mode of treatment, either ablation or pharmacological for attaining and maintaining sinus rhythm.

Harrison et al[31] correlated High LGE MRI signals with areas of low endocardial voltage, however, low signal areas on LGE CMR may

also have low voltage.

Mahnkopf et al[32] in a study of 40 ‘lone AF’ patients who underwent DGE CMR to quantify atrial fibrosis that is a marker for LA structural remodeling (LASRM), was taken for ablation. Patients was classified on basis of percentage of LA wall enhancement as proposed by Utah. Patients with lesser degree of fibrosis were more likely to have successful ablation.

Oakes et al[33], in a study of 81 atrial fibrillation patients who had LGE CMR for LA structural remodelling. Of 43 patients who had Mild LGE, 15 (35%) and 28 (65%) of these had persistent and paroxysmal AF respectively. Furthermore, of 30 patients who had moderate LGE, 43% and 57% had paroxysmal and persistent AF respectively. So indicating variable extent of LGE in paroxysmal and persistent AF patients. Study also predict the long term success of AF ablation with extent of LA scar as an independent inversely proportional adverse prognosticator.

Jaddi et al[34] published a study of 18 AF patients (7 persistent and 11 long-standing persistent). All patients had LGE CMR and electroanatomical mapping, were classified as dense (>90% distribution), patchy (20% to 70%), or normal (no LGE). Patient with longstanding persistent AF had patchy type of LGE than in persistent

AF. The Authors found that LA LGE abnormalities correlated with complex fractionated electrogram (CFE), so sites manifesting LGE and CFE abnormalities were more promising ablation targets.

In present study twenty-two out of 26 patients (84.61%) had atrial fibrillation. This unexpected high prevalence of atrial fibrillation in RHD patients is likely related to remodeled LA, severe mitral valve disease, presence of LV systolic dysfunction and mean age of 49 years.

Above studies have clearly shown that CMR LGE may evolve as an important tool for patient selection, as guidance for ablation strategy, for prediction of success and risk of recurrence after ablation based on extent of atrial fibrosis. But above studies have shown its role in non-valvular AF patients, so its uses in valvular AF still are not clear. On other hand areas and extent of atrial LGE by CMR in valvular AF patients are different from nonvalvular ones, still chances of successful ablation in patients with valvular AF may be predicted in those with limited atrial fibrosis by LGE. Future studies are needed to focus CMR LGE guided ablation strategy in valvular AF patients. Finally, future advancement in guidance and techniques of ablation may ameliorate the issues of valvular AF.

Correlation of myocardial fibrosis by CMR LGE and clinical outcome:

Biopsy studies assessing myocardial fibrosis have been done in surgical patients. Like Milano et al[35] assessed the influence and survival effect of myocardial fibrosis on LV performance in severe AS. In this study of 99 patients with severe AS who are undergoing AVR, underwent interventricular septum biopsy for Myocardial fibrosis. The patients were classified according to extent of myocardial fibrosis as mild (28), moderate (52) and severe (19) and higher grade of fibrosis had higher cardiac mortality at 10 years (42%± 19%vs 89% ±6%, P ¼ .002), with congestive heart failure being the most common cause of adverse outcome. So CMR LGE is a better tool for detection of myocardial fibrosis and predict prognostic outcome.

Dweck et al[36] studied aortic stenosis patient for midwall and infract pattern of LGE to assess prognostic significance. They analyzed the data of 143 moderate to severe AS patients who underwent CMR for assessment of fibrosis by LGE, of whom 72 patients underwent AVR 2.0 ± 1.4 years and among these 27 died (24 cardiac, 3 sudden cardiac deaths). When these patient were Compared with those with no LGE (n = 49), showed that midwall LGE was a predictor of mortality (8fold

increase) despite no difference in severity of AS and CAD. While infarct pattern (n = 40) had a 6-fold increase in mortality. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16to 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. They concluded that Midwall LGE was an independent predictor of mortality and addition of ejection fraction increase the prognostic value, so this may be a useful tool for risk stratification.

Quarto et al[37] in a prospective observational study of 63 patients undergoing CMR with LGE imaging within 1 year of subsequent AVR, 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)[16]. 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.

Hermann et al[38] in a prospective cohort study of 83 patients with AS, aimed to identify surrogate marker of myocardial fibrosis that, allow the differentiation of low-gradient severe AS from moderate AS

and its impact on clinical outcome. In all the patients LGE MR imaging was used to quantify replacement fibrosis. Biopsy samples of severe AS patients was taken at the time of AVR (n=69). All patients were followed for 9 months. Patients were divided into 4 groups according to aortic valve area (<1.0 cm2), 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). In patients with low gradient AS, systolic strain rate and mitral ring displacement was measured at baseline. Patients with low-gradient groups had higher degree of fibrosis in biopsy that correlated with more LGE segments. Patient in group 1 had best outcome whereas mortality risk increased substantially in groups 2 through 4.

Weidemann et al[39] studied the myocardial fibrosis and myocardial performance interaction in symptomatic severe AS and impact of fibrosis on clinical outcome after AVR was estimated on follow-up. 58 consecutive patients underwent standard and tissue Doppler echocardiography and CMR for LGE at baseline and 9 months' post 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 degree of histologically determined cardiac fibrosis at baseline correlated closely with NYHA functional class and longitudinal systolic function (all P<0.001) but not global EF or aortic valve area. On follow up at Nine months' post AVR CMR LGE pattern remained unchanged, implying that AVR failed to reduce the degree of replacement fibrosis. Patients with no LGE had dramatic improvement in NYHA class from 2.8+/-0.4 to 1.4+/-0.5 (P<0.001). longitudinal systolic function was the major predictor of this NYHA class improvement. Four patients with severe fibrosis died during follow-up, but no patient from the other groups died. They concluded that the longitudinal systolic function appears to predict both the severity of myocardial fibrosis and the clinical outcome, so it may prove valuable for preoperative risk assessment in patients with aortic stenosis.

Rochette et al[40] prospectively 154 patients for survival (all-cause and cardiovascular disease related) according to LGE-CMR status in AS patients (96 men; mean age: 74 ± 6 years) without a history of prior myocardial infarction undergoing surgical AVR and in 40 AS patients undergoing trans catheter aortic valve replacement (TAVR). 29% of

patients undergoing surgical AVR and in 50% undergoing TAVR had LGE. Patients were followed for median period of 2.9 years, 21 surgical AVR patients and 20 TAVR patients died. Presence of LGE predicted higher post-operative mortality in surgical AVR (odds ratio: 10.9; 95% confidence interval [CI]: 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 et al[41] analyzed the prevalence and significance of LGE in primary MR. They studied 41 patients with at least moderate primary MR and without overt signs of LV dysfunction. All patients were

evaluated with LGE CMR. 39 MRIs were interpretable. Among them, 12 (31%) had late contrast uptake of the LV wall, infarct pattern in 3 patients, mid-wall fibrosis in 7 patients and 2 patients had a combined pattern. Patients with LGE on CMR had remodeled LV (LV end-systolic diameter 39 ± 4 vs. 34 ± 5 mm, P = 0·002; LV end-diastolic diameter 57 ± 5 vs. 50 ± 5 mm, P = 0·001). These had a higher indexed left atrial volume (55 ± 21 vs. 44 ± 13 mL/m², P = 0·06). By contrast, there was no significant association between myocardial contrast uptake and age, LV ejection fraction and MR severity. So They concluded that LGE on CMR in primary MR likely associated with left ventricular remodeling.

Aims and objectives:

1. Atrial fibrosis is integral part of rheumatic pathology as valvular and ventricular involvement, and strongly predicts the atrial arrhythmias occurrence.
2. Aim of the study is to assess impact of RHD process on atrial myocardium, to correlate atrial remodeling leading to risk of AF and other atrial arrhythmias with outcomes of the AF treatments.

Methods

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

Study period: June 2014 to June 2016

Study Design: Retrospective Prospective Observational study

All consecutive RHD of mitral and aortic valve involvement with LV systolic dysfunction (LVEF<50%), irrespective of sex, who have undergone CMR for work up at cardiology department, SCTIMST from June 1, 2014 to June 31, 2016, were enrolled. This study aims to know to the impact of RHD process on atrial myocardium and its association with Atrial arrhythmias.

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

Exclusion Criteria:

1. RHD pt. with Post valve replacement
2. Heart failure
3. Cardiomyopathy(Ischaemic/Idiopathic)
4. Contraindication to CMR

Baseline demographic data of all enrolled patients were taken from medical records including full history, symptomatic status, Chest roentgenogram, Electrocardiogram, Echocardiography details and CMRI findings were also recorded.

Detailed Echocardiography was done prior to CMR with emphasis on parameters like diastolic LV dimension (LVIDD), systolic LV dimension (LVIDS), diastolic and systolic Septal thickness (Sd) and (Ss), diastolic and systolic Posterior wall thickness (PWd) and (PWs), LV ejection fraction by M Mode and Area length method (Modified simpson), Dimension of Left atrial (LA) and Aorta (AO), Mitral Valve E and A velocities , E deceleration time (Edt), gradient across Mitral and Aortic valve, grading of MR and AR severity, pressure half times of AR and MS, MVA by 2D, RV systolic pressure (RVSP) (by Tricuspid regurgitation (TR jet)), and Regional wall motion abnormalities (RWMA).

Cardiac MRI:

Cardiac MRI was done with SIEMENS 1.5 T machine. Cine steady-state free-precession CMR sequences (Short axis, four chamber and two chamber views) at a repetition time of 3.6 ms, an echo time of 1.6 ms, and a flip angle of 45° were used for assessing the mitral valve and the subvalvular apparatus like thickening. Late Gadolinium enhancement was assessed using SPIR (Spectral Presaturation with Inversion Recovery) sequences with an inversion time of 200 ms, a repetition time of 8.5 ms, and an echo time of 3.5 ms, after 20-30 mins of intravenous injection of Gadolinium based contrast agent (0.2 mmol/kg body weight).

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

1. LA and RA volumes
2. LV volumes – LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV)
3. LV Ejection Fraction -LVEF (%)
4. Valvular involvement: Mitral, Aortic, Tricuspid and Pulmonary
5. Presence or absence of Late Gadolinium enhancement (LGE) in the walls of LA, RA, IAS, Pulmonary veins(PV), LV, RV and atrio ventricular valves.
6. Pattern of LGE (whether Subendocardial, Midmyocardial, Transmural etc)
7. Severity of LGE (Based on overall number of segments having

LGE): Mild / moderate / Severe

Statistical analysis:

The data will be analyzed by the principal investigator. Data would be expressed as mean of Continuous variables with standard deviations. The data would be analyzed by the principal investigator with advice from statistician if required. All data will be handled with care to maintain patient confidentiality. Records will be maintained in both computer and paper formats.

The closing point for any 1 patient will be the time of their last visit to the follow- up clinic during study period. Data would be interpreted as quantification of LA fibrosis, percentage of patients who had Atrial fibrosis, Correlation of LA fibrosis with valvular lesion severity, LA size, PAH status, and presence or absence of AF. Descriptive summaries will be presented as frequencies and percentages for categorical data, and as means and standard deviations for continuous variables. Continuous variables will be compared using Student's t test or Mann-Whitney U test as appropriate, Group comparisons will be made using $\chi 2$ tests. All statistical analyses were performed using the SPSS statistical software package (release 16.0, SPSS Inc.; Chicago, Ill).

Results

A total of 26 RHD patients had undergone cardiac MRI in our institute as a part of their evaluation. None of patient had evidence of CAD or Cardiomyopathy by history, Electrocardiography and Echocardiography. In study Nineteen (73%) were male and seven (27%) were female. The mean age of the patients was 49 years (range 32-62) and 14 patients ≥ 50 years. Past history of rheumatic fever was present in 9 patients (35%) and other patient was diagnosed as RHD on the basis of echocardiographic appearance of the valves. Most patient (n=19, 73%) was mildly symptomatic with NYHA functional class II dyspnea on exertion and 27% patients were having FC III DOE. (Table:1)

No modifiable CAD risk factor were present in 16 patients, while 10 patient had modifiable CAD risk factors (eight had only one risk factor of diabetes or dyslipidemia or smoker while two patient had multiple CAD risk factors).

22 patients (84.6%) were in atrial fibrillation and duration of AF was ranged from one to thirty years. Six patient had AF of uncertain duration. In AF patient rate was controlled in Fourteen patients (53.8%) and rate was uncontrolled in eight patients (30.8%). Direct current

cardioversion was tried in 2 patients for AF of uncertain duration with minimal LA enlargement, but failed in both the patients.

Four patients had CVA, 3 had Infarct and 1 had TIA, all 4 patients were in AF and 1 infarct patient had CAD risk factor (smoker). Four patients (15.4%) were in sinus rhythm.

ECG showed normal QRS axis in twenty patients (76.9%), 3 patients (11.5%) each had Left axis deviation and right axis deviation respectively. None of patient ECG showed them had ischaemic changes, infarct pattern or AV conduction abnormalities.

Chest X ray showed Cardiac enlargement in (84.6%) 22 patients (Cardiothoracic ratio, CTR > 0.5), 12 patients (46.2%) had CTR ≥ 0.6. 22 patients (84.6%) had Left atrial enlargement and 19 patients (73.1%) had right atrial enlargement. Pulmonary venous hypertension (PVH) and Pulmonary arterial hypertension (PAH) was present in 92.3% and 53.8% of patients respectively. Coronary angiogram was done in 18 patients, all of them had normal coronaries.

Table 1: **Baseline characteristics**

Mean age (years)	49.12 years (range 32-62)
Male (%)	73.1%
Functional class	NYHA FC II – 73.1% NYHA FCIII – 26.9%
H/o Rheumatic fever	34.6%
Rhythm	Sinus rhythm - 15.4% Atrial fibrillation- 84.6%
Cardiomegaly (CTR >50%)	84.6%
% of patients who had a prior CAG	69.2% (All were normal)

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

Echocardiography showed mild left ventricular dysfunction (LVEF 40-50%) in 18 patients (69.2%), moderate LV dysfunction (LVEF, 30-39%) in 6 patients (23.1%) and severe LV dysfunction (LV EF< 30%) in 2 patients (7.7%). (Table:2)

Both Patients with severe LV dysfunction had severe mitral stenosis. Left ventricular diastolic dimension of ≥ 60mm was seen in 10 patients (38.5%). Left atrium enlargement was present in all of the patients and gross left atrial enlargement (LA size > 50mm) was present

in 11 patients (42.3%). 3 patients had Right ventricular dysfunction as noted by visual as well as objective parameter, tricuspid annular plane systolic excursion (TAPSE) by echocardiography assessment.

Table 2: **Stratification based on LVEF**

LVEF	No of patients
40-50%	18(69.2%)
30-39%	6 (23.1%)
<30%	2 (7.7%)

LVEF – Left ventricular ejection fraction

Twenty-two patients had dominant mitral valve disease (84.6%), 16 patients (61.5%) had severe mitral stenosis (MS) as dominant lesion, 5 patients (19.2%) had moderate to severe mitral regurgitant (MR) as dominant lesion and 1 patient had both severe MS/MR. 7 patients (26.9%) had significant aortic valve disease along with Mitral valve disease among these 2 patients had dominant aortic valve involvement (1 patient had severe AR and 1 had moderate AR) with mild mitral valve involvement. None of the patient had more than mild aortic stenosis (AS).

7 of the 26 patients (26.9%) were associated with volume overload of left ventricle due to moderate to severe AR that was associated with severe MS in 4 patients, moderate MS in 1, moderate AR in 1 and 1 had mild MR.

Significant tricuspid valve lesions (≥ moderate tricuspid valve lesions) were see only in 7 of the 26 patients (26.9%). None of them had tricuspid stenosis. 3 patients had severe tricuspid regurgitation and 4 had moderate TR. Out of 3 patients with severe TR, 2 patient had severe functional TR related to pulmonary hypertension and 1 patient had severe organic tricuspid regurgitation. Among 4 moderate TR patients 1 had organic tricuspid valve disease along with moderate PAH. All patients with moderate to severe TR were in NYHA FC III. (Table:3)

Table 3: Categorization based on predominant valve involvement

Dominant valve involvement	No of patients
Dominant mitral valve involvement alone	22 patients (84.6%) • 16 patients had dominant severe MS • 5 patients had dominant moderate to severe MR (associated with mild to moderate MS)
Aortic + Mitral valve involvement	7 patients (26.9%) • 1 had severe AR (with moderate MS), • 6 had moderate AR (3 with severe MS and moderate MR, 1 with severe MS and mild MR, 1 with severe MR, 1 with mild MR
Organic tricuspid valve disease	2 patient with Severe TR (7.7%), 1 had organic TR and other had TV thickening

MS – Mitral stenosis, MR-Mitral regurgitation, AR-Aortic regurgitation, TR tricuspid regurgitation, TV- Tricuspid valve, PAH-

Pulmonary arterial hypertension

Cardiac MRI data:

CMR of all 26 patient showed late gadolinium enhancement (LGE) of atrial chamber and adjacent structures in various combinations. All of 26 patient had LGE of IAS, while 25 patients had LGE of left atrium. Twenty-two of 26 patient had LGE of pulmonary veins, while 17 had LGE of right atrium as well. When various combination of LGE were seen 16 patients (61.55%) had combined LGE of LA/RA/IAS/PV, 6 patients (23.1%) had combined LGE of LA/IAS/PV only, 2 patients (7.7%) had combined LGE of LA/IAS only. One patient (3.8%) had combined LGE of LA/RA/IAS while 1 had LGE of IAS alone.

Three patients (11.5%) Out of the 26 patients had LGE of either LV or RV. Two patient (7.7%) had LGE of LV myocardium, of these first one had LGE in the basal Inferoseptum and the second patient had LGE of the basal inferior wall. The first one had LV enhancement in the subepicardial and midmyocardial regions and the second one had LV enhancement transmurally. Both patients with LV LGE had only mild left ventricular dysfunction. Both of the patients had Severe mitral stenosis with not more than mild mitral regurgitation. One patient who

had isolated RV endomyocardial fibrosis (EMF) along with RHD had LGE of RV myocardium, this patient had mild LV systolic dysfunction and severe MS along with mild MR and mild TR. One patient had perfusion defects of basal and mid LV anterior wall, anteroseptum, anterolateral, inferior wall and inferoseptum regions, this patient had mild LV systolic dysfunction with normal coronary angiography and RHD lesions were severe MS, moderate MR and moderate AR.

Both the patient who had LV LGE had only mild LV dysfunction with severe MS associated with mild MR and AR. Above trend was not true as 14 patients (53.8%) had severe MS and among these only 2 of them had LV myocardial LGE. So association of severe MS and LV LGE was likely incidental. There was also no association between LV systolic dysfunction and LV myocardial LGE as 2 patients who had severe LV dysfunction did not have any LV LGE (Table:4, 5)

When rhythm and atrial structures LGE pattern was evaluated, 4 patients who were in sinus rhythm all showed IAS LGE, while LA, PV and RA LGE were present in 75%, 75%, 25% respectively. In comparison to 22 patients who were in AF, all showed LGE of LA and IAS while PV and RA LGE was present in 86% and 73% respectively.

So concluded from above data that presence of LA, IAS and RA LGE determines the emergence of AF. (Table: 6) (Figure: 1)

When LA, RA, IAS and PV late gadolinium enhancement was analyzed in relation to LV systolic function, no association was found among various LGE pattern and LV dysfunction. 14 Patient with LGE in LA/RA/IAS/PV had mild LV dysfunction while 1 patient with LGE in IAS had moderate LV dysfunction, in other patients also there was no association of atrial LGE and LV systolic function. When atrial LGE, LV function was compared in association with rhythm, there was a negative association between them means most patient those in AF had mild LV dysfunction. (Table: 7)

Correlation of LGE of atrial tissue with sinus rhythm and duration of AF was also analyzed that showed that both patient in SR or AF had LGE of atrial myocardium and pulmonary veins. This analysis effected by number of patient rather than duration of AF as patient with AF duration of 1-10 years was more. Positive correlation might come if quantification of atrial LGE is done. (Table: 8)

When interaction of atrial LGE pattern with valvular lesions and rhythm was looked at, it was found that both groups had atrial LGE

although LGE pattern was more extensive in AF patients and RA involvement was more common in AF group (P=0.10). This was most likely due to advanced RHD lesions in both the groups. When isolated mitral valve was compared with multivalvular lesion there were no significant difference in both the groups (R^2 value 0.8526 vs 0.7293) (Table:9) (Figure:2).

When severity of valvular lesion and atrial LGE was compared, it showed that the presence of left atrial enhancement 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. Patients with moderate AR also had significant atrial LGE, While TR severity did not correlated with atrial LGE pattern. (Table:10, 11, 12, 13, 14)

Correlation of atrial LGE along with PAH status (12 mild to moderate and 3 severe) showed that LGE was more extensive in PAH patients, likely related to advanced rheumatic lesions. (Table:15)

Above combinations of LGE were associated with LGE of

atrioventricular and semilunar valves. Mitral valve LGE was present in all of 26 patients while aortic valve showed LGE in 25 patients and tricuspid valve had LGE in 24 patients. When combined LGE was looked for, 23 patients (88.5%) had LGE of MV/AV/TV. Two patient had combined LGE of MV/AV alone. One patient had combined LGE of MV/TV alone (Table:16)

Twenty patient (76.9) had LGE of ascending and descending thoracic aorta (Table:16)

Patient was analyzed for correlation of atrial LGE and mitral valve intervention (percutaneous and surgical). Five patients were post BMV, 8 were post CMV and 1 underwent both BMV and CMV. Atrial LGE was extensive in post intervention patients and related to direct atrial involvement and hemodynamic burden by severe valvular lesions. Although 1 patient who underwent both BMV and CMV had LA/IAS LGE, RA/PVs were spared. There was no correlation between rhythm and post valvular intervention status. (Table:17, 18)

Table 4: **Comparison of Baseline data in patients with atrial and ventricular LGE**

Parameters	Atrial LGE + (26)	Ventricular LGE+ (n=3)
Mean age (yrs)	49	47.3
Males	73.1%	3 (11.5%)
Atrial fibrillation	84.6%	3 (100%)
Predominant Valve involvement	16 patients dominant MS 10 patients mixed mitral and aortic lesion	3 - Isolated severe MS
LVEF	< 30 (7.7%) 30-39(23.1%) 40-50(69.2%)	Patient1-34% Patient2-44% Patient 3-49%

MS –Mitral stenosis, LGE- Late gadolinium enhancement, LVEF- Left Ventricular ejection fraction

Table 5: **Atrial myocardial and adjacent structures enhancement characteristics**

Area of LGE	No of patients (Frequency)
IAS	1 (3.8%)
LA/IAS	2 (7.7%)
LA/IAS/PV	6 (23.1%)
LA/RA/IAS	1 (3.8)
LA/RA/IAS/PV	16 (61,5%)

LGE- Late gadolinium enhancement, LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins

Table 6: **Pattern of LGE in Atria and relation to rhythm**

Rhythm	LGE of atrium and adjacent structures	Cumulative involvement
Sinus (n=4)	LGE of LA/IAS/PV - 2 (7.7%) LGE of LA/RA/IAS/PV - 1 (3.8%) LGE OF IAS alone - 1 (3.8%) + IAS -0 (LA LGE-0%)	IAS - 100% LA - 75% PV - 75% RA - 25%
AF (n=22)	LGE of LA/RA/IAS/PV - 15 (57.7%) LGE of LA/IAS/PV – 4 (15.4%) LGE of LA/IAS - 2 (7.7%) LGE of LA/RA/IAS -1 (3.8%)	IAS - 100% LA - 100% PV – 86.3% RA – 72.7%

LGE- Late gadolinium enhancement, LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, AF- Atrial fibrillation

Table 7: **Association of Atrial structures LGE with LV function**

Rhythm	LGE of atrium and adjacent structures	LVEF
Sinus (n=4)	LGE of LA/IAS/PV - 2 (7.7%)	40-50% and 30-39%
	LGE of LA/RA/IAS/PV - 1 (3.8%)	<30%
	LGE OF IAS alone - 1 (3.8%)	30-39%
AF (n=22)	LGE of LA/RA/IAS/PV - 15 (57.7%)	40-50%(14 pt.) and 30-39%(1 pt.)
	LGE of LA/IAS/PV – 4 (15.4%)	40-50%(2 pt.) and 30-39%(2pt.)
	LGE of LA/IAS - 2 (7.7%)	40-50% and 30-39%
	LGE of LA/RA/IAS -1 (3.8%)	<30%

LGE- Late gadolinium enhancement, LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, LVEF – left ventricular ejection fraction, AF- Atrial fibrillation

Table 8: Correlation between Atrial fibrosis pattern and AF duration

Atrial LGE	AF Duration								
	SR	1-5yr	5-10yr	10-15yr	15-20yr	20-25yr	25-30yr	U	Total
IAS	1	0	0	0	0	0	0	0	1
LA/IAS	0	0	0	0	0	0	0	2	2
LA/IAS/PV	0	2	2	0	0	0	0	0	4
LA/IAS/PV	2	0	0	0	0	0	0	0	2
LA/RA/IAS	0	0	0	0	0	0	0	1	1
LA/RA/IAS/PV	1	0	0	0	0	0	0	0	1
LA/RA/IAS/PV	0	6	2	1	1	1	1	3	15
Total	4	8	4	1	1	1	1	6	26

LGE- Late gadolinium enhancement, LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, AF- Atrial fibrillation, U- Uncertain

Table 9: **Correlation of Atrial LGE, valvar lesions and AF**

Rhythm	LGE pattern	Valve involvement
SR	LGE of LA/IAS/PV - 2 (7.7%)	Moderate AR and mild MR (1)
	LGE of LA/RA/IAS/PV - 1 (3.8%)	Mild MS/ MR (1)
	LGE OF IAS alone - 1 (3.8%)	Moderate MS/MR
AF	LGE of LA/RA/IAS/PV - 15 (57.7%)	Severe MS/Mild to moderate MR (9) Moderate MS/MR (2), Severe MS/MR (1), Mild MS/MR (1) Severe AR/Moderate MR (1) Severe AR/Mild MS/MR - (1)
	LGE of LA/IAS/PV – 4 (15.4%)	Severe MS/ Mild - Moderate MR
	LGE of LA/IAS- 2(7.7%)	Moderate MS/MR
	LGE of LA/RA/IAS -1 (3.8%)	Severe MS

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

Table 10: Correlation of LGE with MS

LGE	MS				Total
	No	Mild	Moderate	Severe	
IAS	0	1	0	0	1
LA/IAS	0	1	1	0	2
LA/IAS/PV	0	0	0	4	4
LA/IAS/PV SR	1	1	0	0	2
LA/RA/IAS	0	0	0	1	1
LA/RA/IAS/P SR	0	0	1	0	1
LA/RA/IAS/PV	1	1	4	9	15
Total	2	4	6	14	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, MS- Mitral stenosis, SR- Sinus rhythm, LGE- Late gadolinium enhancement

Table 11: Correlation of LGE with MR

LGE	MR				Total
	1	2	3	4	
IAS SR	0	0	0	1	1
LA/IAS	1	1	0	0	2
LA/IAS/PV	1	2	1	0	4
LA/IAS/PV SR	1	1	0	0	2
LA/RA/IAS	1	0	0	0	1
LA/RA/IAS/PV SR	0	0	1	0	1
LA/RA/IAS/PV	3	4	6	2	15
Total	7	8	8	3	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, MR- Mitral regurgitation, SR- Sinus rhythm, LGE- Late gadolinium enhancement

Table 12: Correlation of LGE with AS

LGE	AS		Total
	No	Mild	
IAS SR	1	0	1
LA/IAS	2	0	2
LA/IAS/PV	4	0	4
LA/IAS/PV SR	2	0	2
LA/RA/IAS	1	0	1
LA/RA/IAS/PV SR	1	0	1
LA/RA/IAS/PV	12	3	15
Total	23	3	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, AS- Aortic stenosis, SR- Sinus rhythm, LGE- Late gadolinium enhancement

Table 13: Correlation of LGE with AR

LGE	AR					Total
	No	Trivial	Mild	Moderate	Severe	
IAS SR	0	0	1	0	0	1
LA/IAS	1	1	0	0	0	2
LA/IAS/PV	2	1	1	0	0	4
LA/IAS/PV SR	1	0	0	1	0	2
LA/RA/IAS	0	1	0	0	0	1
LA/RA/IAS/PVSR	1	0	0	0	0	1
LA/RA/IAS/PV	6	0	3	5	1	15
Total	11	3	5	6	1	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, AR- Aortic regurgitation, SR- Sinus rhythm, LGE- Late gadolinium enhancement

Table 14: Correlation of Atrial LGE with TR

LGE	Total				
	none	mild	moderate	severe	
IAS	0	1	0	0	1
LA/IAS	1	1	0	0	2
LA/IAS/PV	2	2	0	2	6
LA/RA/IAS	1	0	0	0	1
LA/RA/IAS/PV	4	7	4	1	16
Total	8	11	4	3	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, TR- Tricuspid regurgitation, LGE- Late gadolinium enhancement

Table 15: Correlation of LGE pattern and PAH

LGE	PAH		Total
	no	yes	
IAS SR	0	1	1
LA/IAS	1	1	2
LA/IAS/PV	2	2	4
LA/IAS/PV SR	2	0	2
LA/RA/IAS	1	0	1
LA/RA/IAS/PV SR	1	0	1
LA/RA/IAS/PV	4	11	15
Total	11	15	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, MR- Mitral regurgitation, SR- Sinus rhythm, LGE- Late gadolinium enhancement, PAH- Pulmonary arterial hypertension

Table 16: CMRI enhancement of valves and Aorta

	MV	AV	TV	AO
Valve LGE	26 (100%)	25 (96.2%)	24 (92.3%)	20 (76.9%)
Clinical involvement	26 (100%)	15 (57.6)	2 (7.7%)	Nil

CMRI- Cardiac magnetic resonance imaging, MV- Mitral valve, AV- Aortic valve, TV- Tricuspid valve, AO- Ascending and descending aorta, LGE- Late gadolinium enhancement

Table 17: Correlation of Atrial LGE and past BMV/CMV/BMV+CMV

LGE	CMV/BMV/BMV+CMV				Total
	0	BMV	CMV	BMV+CMV	
IAS	1	0	0	0	1
LA/IAS	0	0	1	1	2
LA/IAS/PV	4	1	1	0	6
LA/RA/IAS	1	0	0	0	1
LA/RA/IAS/PV	6	4	6	0	16
Total	12	5	8	1	26

LA- Left atrium, RA- Right atrium, IAS- Interatrial septum, PV- Pulmonary veins, MR- Mitral regurgitation, LGE- Late gadolinium enhancement, BMV- Balloon mitral valvotomy, CMV- Closed mitral valvotomy

Table 18: Correlation of Valvular LGE and past BMV/CMV/BMV+CMV

LGE	0	BMV	CMV	BMV+CMV	Total
M/A	1	1	0	0	2
M/T	0	0	0	1	1
M/T/A	11	4	8	0	23
Total	12	5	8	1	26

M- Mitral, A-Aortic, T- Tricuspid, LGE- Late gadolinium enhancement, BMV- Balloon mitral valvotomy, CMV- Closed mitral valvotomy

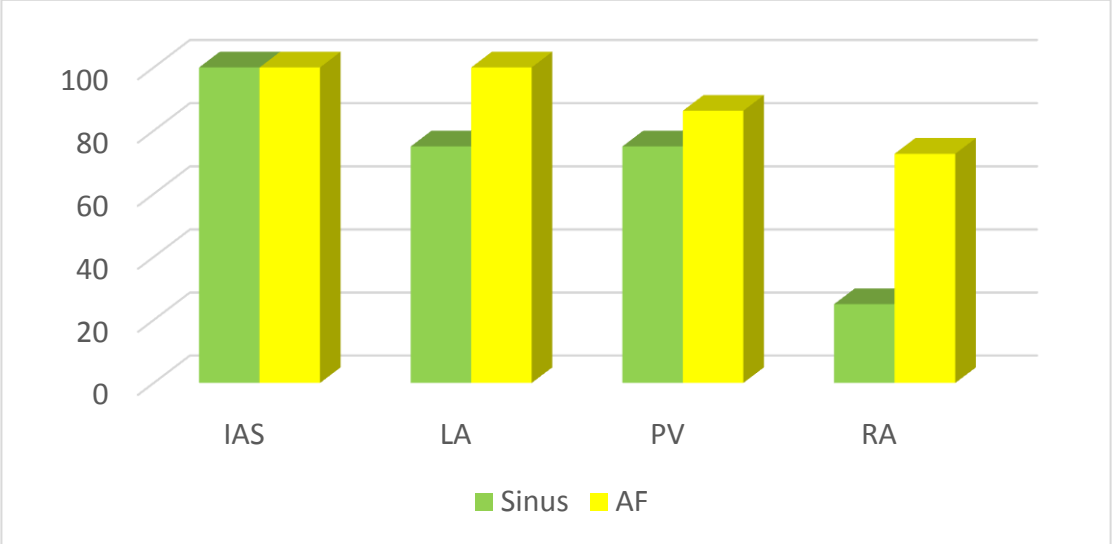


Figure:1

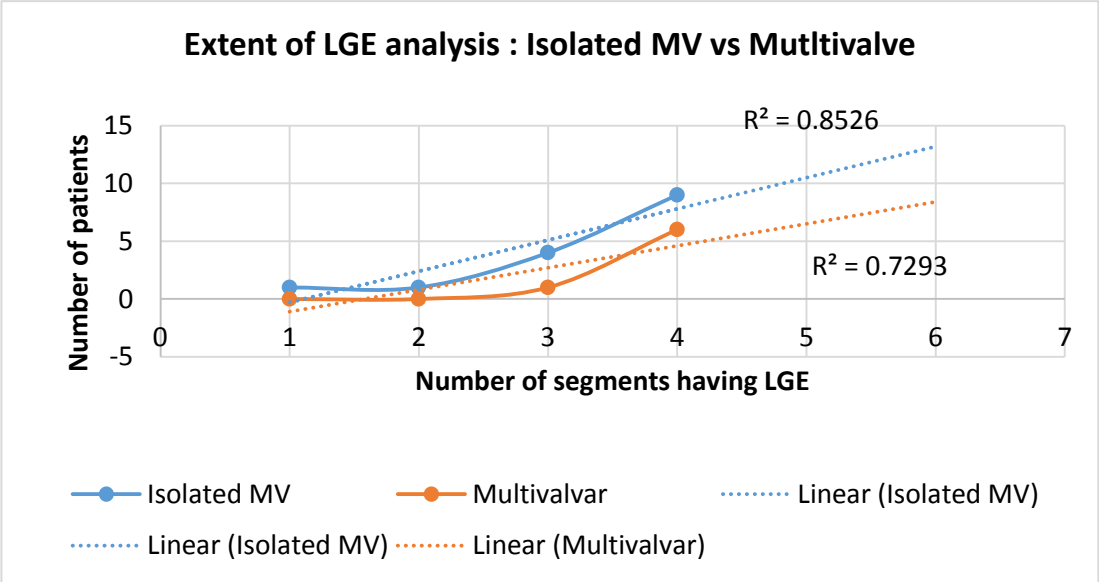


Figure:2

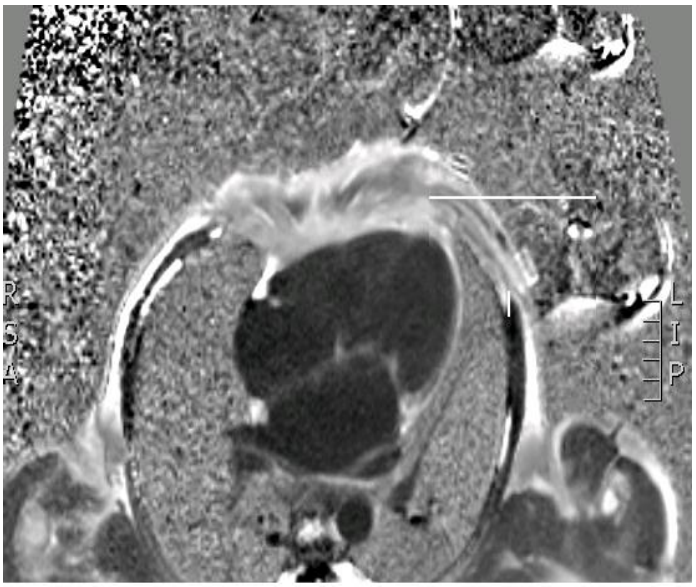
One peculiar finding in this study was presence of LGE of the valve leaflets, mitral subvalvular apparatus (in some patients) and aorta. LGE of Mitral valve was seen in all the twenty-six patients, Aortic valve in 25 patients and in tricuspid valve in 24 patients. Although clinical involvement of aortic and tricuspid valve was not common, so presence of LGE suggest subclinical involvement of above by rheumatic process. LGE in rheumatic valvular heart disease patients are summarized below. (Table:19)

Most of the patients in study showed LGE on CMR likely related to factors discussed above, to further clarify these finding we extended our observation to patients with structurally normal heart underwent CMR eg. RVOT VPCs without tachycardiomyopathy and noninfarcted coronary artery disease patient who underwent CMR for myocardial perfusion imaging. We studied 10 patients (8 RVOT VPCs and 2 CAD), and found that there were no LGE of atrial, ventricular and valvular tissue, this suggest that LGE pattern discussed in above study is specific for RHD.

Table 19: Summary of LGE data

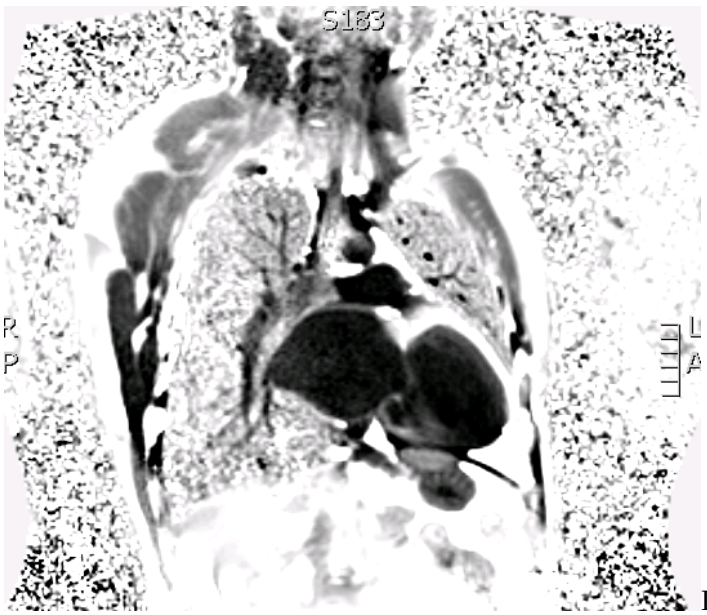
Site of LGE	No of patients (%)
• Atrial myocardial LGE IAS LA/IAS LA/IAS/PV LA/RA/IAS LA/RA/IAS/PV	 1 (3.8%) 2 (7.7%) 6 (23.1%) 1 (3.8%) 16 (61.5%)
• Ventricular myocardial LGE	3/26 (11.5%) • 1 patient had Subepicardial and midmyocardial LGE of basal Inferoseptum • 1 patient had transmural LGE of basal inferior wall • 1 patient had RV LGE due to RVEMF
Valvular LGE	26/26 (100%) • Mitral valve - 100% • Aortic valve - 96.2% • Tricuspid valve - 92.3%
Aorta LGE	20/26 (76.9%)

LGE- Late gadolinium enhancement, LA-Left atrium IAS- Inter atrial septum, RA- Right atrium PV- Pulmonary vein A.



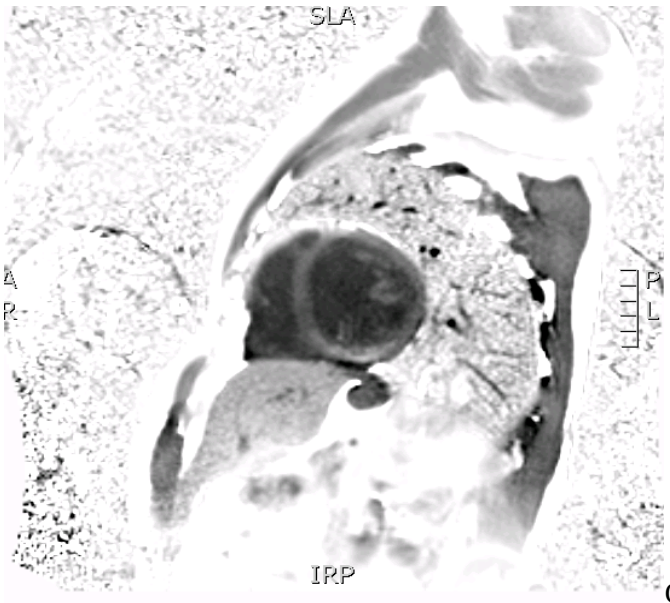
A.

A. CMR image 30 minutes' post contrast showing the late gadolinium enhancement of the left atrium



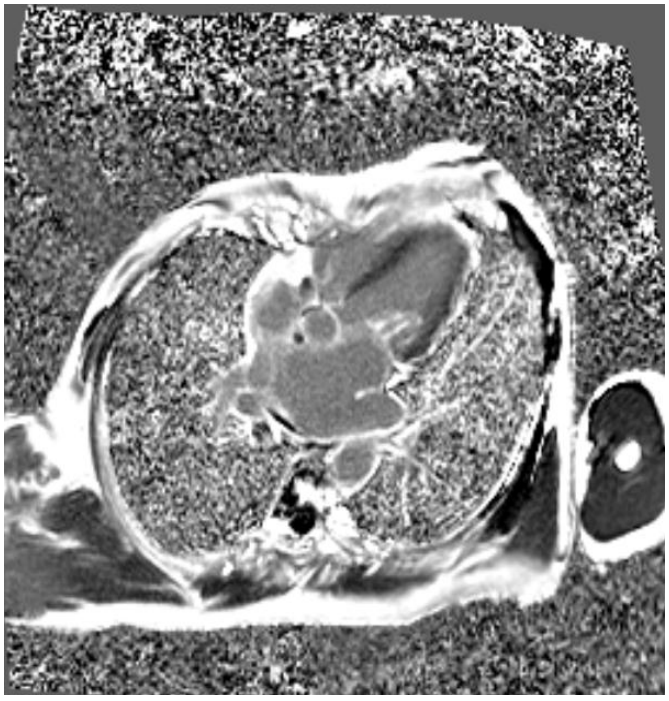
B.

B. Cardiac MRI image 30 minutes' post contrast showing the late gadolinium enhancement of the mitral valve



C.

C. Cardiac MRI image 30 minutes' post contrast showing transmural late gadolinium enhancement of inferior wall



D.

D. Cardiac MRI image 30 minutes' post contrast showing late gadolinium enhancement of RUPV and LLPV

Discussion

Rheumatic heart disease is the most common cause of valvular heart disease in India. RHD is also most common indication for valvular surgeries (Repair or replacement) and percutaneous valvular interventions (balloon mitral valvotomy). Left ventricular systolic dysfunction is well reported in RHD patient with mitral and aortic valvular lesion as part of natural history after a long stable clinical course. Left ventricular systolic dysfunction have also been reported with 25-30% predominant mitral stenotic lesions without significant mitral and aortic regurgitation. Among surgical indication for rheumatic valvular heart disease, onset of left ventricular systolic dysfunction has been a class I indication. Natural history of RHD patient with LV systolic dysfunction is worse as compared to those with normal LV function, whether managed medically or surgically. Patients with LV dysfunction who underwent surgery have guarded immediate post-operative and long term clinical course when compared with counterparts with otherwise normal LV function

We have done study firstly in rheumatic heart disease, that reporting LGE CMR focusing particularly at atrial myocardium. We enrolled 26 RHD patients with mild to severe LV systolic dysfunction

and cardiac MRI was done for evaluation. Spectrum of valvular lesion was ranged from predominant severe MS (16) to mixed mitral and aortic involvement (10). All the patient CMR showed delayed enhancement of atrial myocardial in various pattern involving LA, RA, IAS and PV along with enhancement of cardiac valves and aorta (ascending and descending). Two patient with mild to moderate LV systolic dysfunction had LV myocardial enhancement.

Present study showed correlation between LGE of atria and valvular LGE, which suggest that rheumatic fever likely affect both valvular tissue and atria from very inception. Further exaggeration of atrial changes may be due to recurrent episodes of clinical or subclinical rheumatic fever, by hemodynamic burden imposed due to valvular lesions and latest by rhythm abnormality. In this study, atrial LGE was present even in 3 out of 4 patients with sinus rhythm (with predominant MS), So association between atrial LGE and AF (22 patients) did show exaggeration of changes and correlates in terms of bidirectional relationship. It means atrial fibrosis begets AF and AF begets atrial fibrosis.

Atrial myocardial involvement by rheumatic carditis likely proportionate to valvular lesions severity that can be determined by

biopsy or quantification of CMR LGE in acute rheumatic fever healing phase.

It is already a proven fact that ventricular myocardium is not involved in almost all of rheumatic carditis patients, as shown by previous histopathological studies, although same studies have shown that atrial tissue particularly LA appendage is the most common site for rheumatic carditis inflammation.

As proposed in present study atrial fibrosis might be related to initial episode of rheumatic fever with carditis or may be sequel of recurrent episodes of rheumatic carditis, this needs clarification as above. Other issue that needs clarification is impact of severity of rheumatic carditis on atrial myocardium, means clinically manifested (including mild to severe) or subclinical episodes.

So this study generates the hypothesis that Atrial fibrosis is closely related to valvular fibrosis and its confirmation needs CMR studies during healing phase of rheumatic fever.

Jabi shriki et al 5 Reported 3 cases of RHD and showed atrial wall LGE in one or both atrium in all 3 cases and LGE of both atrioventricular valve in one patient. Authors reasoned atrial LGE as part of atrial inflammation followed by fibrosis, caused by rheumatic carditis and was

also attributed to atrial remodelling by AF.

One study from our institute have reported delayed gadolinium enhancement pattern of ventricular myocardial in RHD patients. In this study 17 RHD patient with mild to severe LV systolic dysfunction by echocardiography was enrolled. Study showed that only 2 patients out of 17 had LGE of LV myocardium, both of these patients had severe MS with mild to moderate LV systolic dysfunction. This study showed various pattern of LV LGE e.g. transmural (1), subepicardial/ midmyocardial (1) and presence of LGE did not correlate with severity of LV dysfunction. This study refuted the concept of smoldering myocarditis in RHD patients which had been described in old case reports. Finally, this study concluded that most of the patients was free of LGE so LV dysfunction was likely due to preload afterload mismatch and surgical risk both immediate and long term is not high in this group, this also suggested that chances of LV function improvement after surgical relief of valvular lesion.

Choi et al 43 reported 1 case of rheumatic severe AR with LV systolic dysfunction, underwent CMR that showed LGE of basal and mid lateral wall LV and CAG revealed normal coronaries. Patient underwent aortic valve replacement with LV endomyocardial biopsy

intraoperatively. Biopsy showed dense fibrosis with calcification suggestive of sequelae of RHD. Author concluded the finding as LV fibrosis is part of rheumatic process and responsible for LV dysfunction.

Significance of valvular LGE:

This study showed an interesting finding of LGE of mitral, aortic and tricuspid valve in 100%, 96% and 92% respectively. Valvular LGE was irrespective of clinical severity as 23 out of 26 patients had tricuspid LGE while only 2 patient had organic tricuspid valve disease clinically, likewise aortic valve LGE was in 96% and clinical involvement was in 27% of patients. All patients in study had mitral valve involvement although it was clinically significant in 22 patients. So clinical valvular severity was discordant with LGE in mitral valve also. Although it is unclear how LGE involved valve did not get affected clinically despite presence of fibrosis, this was supported by CMR study of 3 RHD patients by Jabi Shikri et al42, who showed LGE of both atrioventricular valves. This needs to be studied further with healthy as well as control with various other clinical conditions. Till then significance of this finding is uncertain.

In this study clinical pattern of valve involvement correlates with previous echocardiography based studies however valvular LGE pattern correlates with that of histopathology and autopsy studies.

However, some studies have shown even higher organic involvement as Chopra et al40, showed Organic tricuspid valve disease in 38.4% of cases, Manjunath et al44 showed organic TV involvement of 4.7% by echocardiography. Echocardiography based Studies has even showed up to 8% TV involvement45.

LGE in valvular tissue is likely manifestation of fibrosis caused by rheumatic process. Previous histopathological studies in surgically excised valves of RHD patients have demonstrated fibro collagenous changes. Malhotra et al46 demonstrated extensive fibrotic changes on histopathology in rheumatic mitral (50) and aortic (43) valves.

Limitations

1. The Major limitation of the study was that LA, RA, IAS and PVs CMR scar quantification could not be done.
2. Most patients in the study had moderate to severe valvular heart disease so spectrum of atrial tissue fibrosis in milder valvular lesion could not be assessed.
3. Atrial tissue fibrosis was implicated to be due to direct involvement of atrial myocardium by rheumatic fever, hemodynamic burden related to valvular lesions and LV systolic dysfunction. So individual contribution of above factors could not be separated.
4. Number of the patients in study is small so may have affected the results.
5. Most of the patients in study had predominant mitral valve involvement so effect of other valvular lesion on atrial myocardium is less clear.

Conclusions

Among patients with rheumatic valvular heart disease, about 96% of the patients have atrial fibrosis as indicated by the presence of LGE in cardiac MRI. The patterns of LGE seen in these patients were transmural and correlated with valvular lesion severity, valvular LGE, LA size, PAH status, presence of AF and status post mitral intervention but was not related to LV systolic dysfunction. The presence of LV LGE was not correlated with the severity of the left ventricular dysfunction, atrial LGE and AF. So we concluded that atrial myocardial involvement by rheumatic process is much more common than ventricular myocardium, it appears to be direct involvement of atria, by hemodynamic burden imposed by valvular lesions, rhythm abnormality or LV systolic dysfunction if there. Finally, extent of Atrial fibrosis is determined by interplay of above factors and Most likely rheumatic atrial myocardial injury is the initiating event. Presence of valvular LGE was a distinctive finding.

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Abbreviations

AF	–	Atrial fibrillation
AR	-	Aortic regurgitation
ARPHT	-	Aortic regurgitation pressure half time
AS	–	Aortic Stenosis
AV	–	Atrio ventricular
AVR	-	Aortic Valve Replacement
BMV	-	Balloon mitral valvotomy
CMRI	-	Cardiac MRI
CVA	-	Cerebrovascular events
CI	-	Confidence interval
CAD	-	Coronary Artery disease
CMV	-	Closed mitral valvotomy
CTR	-	Cardiothoracic ratio
DE	–	Delayed enhancement
DE-MRI	–	Delayed enhancement MRI
Edt	–	E deceleration time
EF	-	Ejection fraction
FC	–	Functional class
FS	-	Fractional Shortening
HR	-	Hazard ratio
IAS	–	Interatrial septum LA – Left Atrium
LVEF	-	Left Ventricular Ejection Fraction
LGE	-	Late Gadolinium enhancement
LLPV	-	Left lower pulmonary vein

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
PAH	-	Pulmonary arterial hypertension
PWs	-	Posterior wall thickness in diastole
RHD	–	Rheumatic heart disease
RUPV	-	Right upper pulmonary vein
RVEMF	-	Right ventricular endomyocardial fibrosis
RVSP	-	Right ventricular systolic pressure
RWMA	-	Regional wall motion abnormalities
RVOT	-	Right ventricular outflow tract
Sd	–	Septal thickness in diastole
SR	-	Sinus rhythm
Ss	-	Septal thickness in systole
TAVR	–	Trans catheter aortic valve replacement
TGF- β	–	Transforming growth factor- β
TR	-	Tricuspid regurgitation
VHD	-	Valvular heart disease
VPC	-	Ventricular premature contraction

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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013)

SCT/IEC/877/APRIL-2016 27.05.2016

Dr. Hitesh Yadav
Senior Resident
Department of Cardiology
SCTIMST, Thiruvananthapuram

Dear Dr. Hitesh Yadav,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "ATRIAL FIBROSIS BY CMR (CARDIAC MAGNETIC RESONANACE) IN RHD (RHEUMATIC HEART DISEASE) PATIENTS WITH MITRAL AND AORTIC VALVE INVOLVEMENT AND IT'S CORRELATION WITH ATRIAL FIBRILLATION" (IEC/877) on 16th April, 2016.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST, dated 21.03.2016 with check list*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Response to TAC queries and consent waiver*
6. *Proforma*
7. *Consent Forms in English and Malayalam*
8. *Declaration*
9. *CV of Principal Investigator and Co- Investigators*

Revised submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 10.05.2016 with check list*
2. *IEC Recommendation Letter dated 03.05.2016*
3. *TAC Approval Letter*
4. *IEC Application Form*
5. *Project Proposal*
6. *Response to TAC queries and consent waiver*
7. *Proforma*
8. *Consent Forms in English and Malayalam*
9. *Declaration*
10. *CV of Principal Investigator and Co- Investigators*
11. *Abbreviations*

The following members of the Ethics Committee were present at the meeting held on 16th April, 2016 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Justice Gopinathan. P.S	BSc. LLB	Male	Legal Expert (Chairperson)	No
2.	Dr. Asha Kishore	MD, DM	Female	Clinician (Neurologist)	Yes
3.	Shri. O.S. Neelakantan Nair	BE	Male	Engineer	Yes
4.	Dr. Meenu Hariharan	DM	Female	Clinician (Gastro-Enterologist)	No
5	Dr. Rema M. N	MD	Female	Pharmacologist	No
6.	Dr. V. Raman Kutty	MPH(Harvard) MPhil, MD	Male	Public Health	Yes
7.	Dr. K R S Krishnan	ME, PhD	Male	Biomedical Scientist/Engineer	No
8.	Dr. Kala Kesavan. P	MD	Female	Pharmacologist	No
9.	Smt. Sathi Nair	MA	Female	Lay Person	No
10.	Dr. Christina George	MD	Female	Psychiatrist	No
11.	Dr. Mala Ramanathan	MSc, PhD, MA	Female	Ethicist/Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Hitesh_Thesis.docx

ORIGINALITY REPORT

2%

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