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The Relationship between Rheumatic Heart Disease and Coronary Artery Disease and its Implications

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Patients and methods: One hundred and seventy two patients with confirmed Rheumatic heart disease (Group A) were included in the study. All patients underwent coronary angiography. Significant coronary artery disease of any major coronary artery or branch was noted. Between January 2017 and December 2017, 710 patients (Group B) undergoing coronary angiography for suspected/symptomatic coronary artery disease were included as controls and compared to Group A patients. In group A the mean age of patients was 58.17 years. In-group B the mean age of patients was 59.4 years. Risk factors for coronary artery disease were comparable between both the groups. Significant coronary artery disease was observed in 12 (6.98%) patients in group A, and 550 (77.46%) patients in group B. This difference was statistically significant ($p < 0.0001$).

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Conclusion: This study reveals that patients with rheumatic heart disease have a lower incidence of coronary artery disease compared to another group of patients with identical risk factors for coronary artery disease but who do not have rheumatic heart disease. A prospective study in a larger cohort is clearly indicated.

I. INTRODUCTION

Cardiovascular diseases are the leading cause of death worldwide accounting for more than 17 million deaths annually. World Health Organization (WHO) estimates that India accounts for more than 20% of these deaths. In India, cardiovascular deaths amounted to 2.1 million in 2015, out of which 0.9 million (68.4%) were due to Ischemic heart disease.¹ Rheumatic heart disease (RHD) is another major cause of morbidity and mortality in developing countries like India² and it led to 47000 (3.5%) of all deaths in 2015.¹

The non-modifiable risk factors for coronary heart disease are age, gender, family history; and the modifiable factors are smoking or tobacco use in any form, known history of diabetes or hypertension or both, dyslipidemia and lifestyle habits such as obesity and physical inactivity.³ However, due to changing demographics and economics, the risk factors and natural history of subclinical RHD are not well known.²

Comparative studies on the incidence of coronary artery disease (CAD) in patients undergoing surgery for RHD are very few. Although there have been a few studies in which attempts were made to analyze the association of CAD with RHD from India,⁴⁻⁶ Chile,⁷ Nepal,⁸ Rio de Janeiro,⁹ the effect of RHD pathophysiology on the development of CAD has not been clearly understood so far. Many of these studies do not confirm the presence of RHD nor do they compare with the incidence of CAD. This study aims to analyze if and how RHD is related to CAD.

II. PATIENTS AND METHODS

All patients admitted for elective surgery for RHD at our hospital between 1st January 2011 and 31st December 2017 were included and compared with a larger cohort of patients undergoing elective coronary angiography (CAG) for suspected or symptomatic CAD, between 1st January 2017 and 31st December 2017.

a) Inclusion criteria for the study

For the patients to be included in either of the study groups, age more than 40 years and New York Heart Association (NYHA) functional classification stage III or IV with symptoms of angina, breathlessness, palpitations or fatigue were mandatory.

b) Exclusion criteria for the study:

Patients who had:

- Unstable angina.
- Recent myocardial infarction proved by ECG changes or cardiac biomarkers.
- History of previous percutaneous intervention for CAD or who underwent Coronary Artery Bypass Grafting surgery (CABG) in the past.

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- d) Poorly controlled diabetes mellitus with glycosylated hemoglobin (HbA1C) of more than 7%.
- e) Ischemic heart disease patients with severe left ventricular dysfunction and left ventricular ejection fraction (LVEF) less than 30% on transthoracic echocardiography.

Patients with congenital abnormalities like bicuspid aortic valve, those with degenerative valve disease, infective endocarditis, ischemic mitral regurgitation or myxomatous mitral valve were excluded from the study.

Diagnosis of RHD was made on the basis of involvement of mitral valve, with thickening and fusion, which in India is diagnostic of RHD in adult patients. Patients who previously underwent balloon mitral valvotomy (BMV), closed mitral valvotomy (CMV), mitral valve repair for RHD were also included. Patients who underwent Aortic valve surgery were included if surgical findings were suggestive of a tricuspid aortic valve and histopathological examination (HPE) was suggestive of thickening, fibrosis and inflammation of valve leaflets characteristic of RHD.

All patients underwent transthoracic echocardiography (TTE) for assessment of ventricular function and dimensions, valve morphology and function with quantification of gradients or regurgitation across the heart valves and presence/absence of any intra-cardiac lesion including left atrial (LA) or left atrial appendage (LAA) thrombus. Subsequently, all patients underwent elective CAG for screening for CAD before surgery for RHD or for suspected/ symptomatic CAD. Presence of significant CAD (percentage obstruction of luminal diameter more than 50% in any major or branch coronary artery of diameter more than 1.5mm¹⁰) was noted.

Patients were divided into two groups. Group A consisted of patients with RHD undergoing valve surgery and Group B consisted of patients undergoing elective CAG for symptomatic/suspected CAD. Presence of risk factors for CAD in the form of age, gender, history of smoking (more than 10 pack years of smoking history), history of DM, history of hypertension, family history of DM and family history of hypertension were noted for all the patients. All patients were of the same ethnicity.

Out of 318 patients who underwent elective surgery for RHD between the study period, 172 could meet the inclusion criteria of the study. They constituted group A of the study population. The mean age of group A patients was 58.17 ± 9.58 years. 101 (58.72%) were males and 26 (15.12%) had a positive history of smoking. 56 (32.56%) patients had DM, and 67 (38.95%) had hypertension. In group A, 60 (34.88%) patients had a positive family history for DM and 76 (44.19%) patients had a positive family history for hypertension. Mean LVEF for Group A patients was $46.9 \pm 8.4\%$.

Trans Esophageal Echocardiography (TEE) was performed under anesthesia for all patients to re-assess morphology of the valves, quantification of regurgitant lesions, calcification, and presence/absence of LA or LAA thrombus. Surgery was performed under cardiopulmonary bypass (CPB) with normothermic perfusion and cold blood cardioplegia by a single surgeon. The excised valve specimen was sent for HPE. The respective involvement of valves and surgeries done on patients in Group A is as depicted in Table 1.

Table 1: Valve affected and surgical procedures performed on RHD patients

Valve affected	Surgery	Number of patients	Total number of patients for each valve
Mitral valve	Mitral valve replacement	49	81
	Mitral valve repair	15	
	Redo- mitral valve replacement	17	
Aortic valve	Aortic valve replacement	50	51
	Redo- aortic valve replacement	1	
Mitral+ Aortic valve	Double valve replacement	29	39
	Redo-double valve replacement	10	
Mitral + Aortic + Tricuspid valve	Double valve replacement with TV repair	1	1

All patients with significant CAD in-group A underwent concomitant coronary artery revascularization in the form of CABG along with surgery for RHD. Reversed saphenous vein grafts were used for all these patients. Distal anastomoses of grafts to coronary arteries were performed on CPB after delivering cardioplegia. Valve repair and/or replacement were done after distal anastomoses were performed. Proximal anastomoses of vein grafts to ascending aorta were performed on empty beating heart after removal of aortic cross-clamp. Patients were gradually weaned off CPB after valve surgery and coronary revascularization.

Between 1st January 2017 and 31st December 2017, 1054 patients underwent CAG for suspected/symptomatic CAD. Out of those 710 patients met the inclusion criteria. They constituted group B of the study population. The mean age of the study group patients was 59.4 ± 11.02 years. 440 (61.97%) were males and 149 (20.99%) of all the patients had a positive history of smoking. 274 (38.59%) patients had DM, and 314 (44.23%) had hypertension. In group B 297 (41.83%) patients had a positive family history for DM and 348 (49.01%) patients had a positive family history for hypertension. Mean LVEF for Group B patients was $47.57 \pm 9.31\%$.

In-group B, 439 patients underwent percutaneous coronary angioplasty using coronary stent

and 111 patients underwent off-pump CABG surgery. All patients undergoing CABG received Left Internal Mammary Artery graft to Left Anterior Descending (LAD) and reversed saphenous vein grafts to obtuse marginal artery and/or posterior descending artery during the surgery.

Group A patients were further compared with the epidemiological studies on the incidence of coronary artery disease in the general population in India.

c) Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean $\pm$ SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then the non-parametric test was used. Statistical tests applied were:

1. Quantitative variables were compared using the Mann-Whitney Test (as the data sets were not normally distributed) between the two groups.
2. Qualitative variables were correlated using the Chi-Square test. p-value of <0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

III. RESULTS

The risk factors and demographic data between both the groups were comparable (Table 2).

Table 2: Risk factors and demographic comparison of the two groups of patients

	Group A	Group B	p
Mean age	58.21	59.4	0.073
Males	112(59.57%)	440(61.97%)	0.548
Mean LVEF	46.84	47.57	0.077
Smokers	29(15.43%)	149(20.99%)	0.089
DM	60	274	0.092
HTN	71(37.77%)	314(44.23%)	0.112
Family – DM	65(34.57%)	297(41.83%)	0.071
Family – HTN	81(43.09%)	348(49.01%)	0.148

The number of patients with significant coronary artery disease was 12 (6.98%) in Group A and 550 (77.46%) in Group B ($p = 0.0001$). In Group A, 160 (93.02%) patients, and in Group B 160 (22.54%) patients had normal coronary arteries.

Within group A, 81 patients underwent surgery for isolated mitral valve disease and significant CAD was found in 4 patients (4.9%), and 51 patients underwent surgery for isolated aortic valve disease, significant CAD was found in 7 patients (13.7%). Out of 39 patients who

underwent double valve replacement, 1 (2.5%) patient had significant CAD.

The distribution of CAD in arteries in both groups and the statistical comparison is depicted in Table 3.

Table 3: Distribution of significant CAD in both the groups

	LAD	LCx	RCA	LAD +LCx	LAD +RCA	LCx +RCA	TVD	Total patients with CAD	p
Group A	3	0	1	2	3	1	2	12	<.0001
Group B	96	65	82	59	52	36	160	550	

Incidence of coronary artery disease in India as reported by epidemiological studies was compared with the incidence of CAD in group A patients, and the comparison is as depicted in Table 4.

Table 4: Incidence of CAD in Group a patients versus general population in India

Author	Study site	Year reported	Sample size	Known CAD	Known CAD in Group A	p
Chadha SL ¹¹	Delhi	1990	13723	9.67%	6.98%	0.29
Krishnan MN ¹²	Multisite	2016	5167	12.5%	6.98%	0.04

IV. DISCUSSION

It is a retrospective observational study from a single center in India comparing incidence of CAD in symptomatic patients with or without RHD. In our study the incidence of CAD in symptomatic patients of RHD was 6.98%.

We believe it is necessary to have a demographically comparable group as a control in order to remove any bias. It may be argued that the two pathologies may be a coincidence rather than a pathologic relation. As mentioned in our limitations only further studies will throw a light on this, since both RHD and CAD are inflammatory in nature.

Various studies from India have found a similar incidence of CAD amongst RHD patients. Jadhav et al⁴ studied 757 patients undergoing intervention for valvular heart disease (not confirmed RHD) and found the overall incidence of CAD to be 9.1%. Thiyagarajan et al⁵ studied 101 patients undergoing preoperative CAG before undergoing valvular heart surgery for rheumatic mitral and aortic valve disease and found that 4 out of 43 (9.3%) patients undergoing surgery for mitral valve disease had significant CAD. However, they did not compare with the overall incidence of CAD. Jose et al⁶ studied 376 patients with RHD and found an overall incidence of CAD to be 12.2% amongst RHD patients. A few studies published in English literature have also reported similarly. Merchant et al⁷ from Chile studied 100 patients with RHD who underwent CAG and observed significant CAD in 3 patients (6.9%) out of 43 in patients with Rheumatic mitral valve disease. Sahi et

al⁸ from Nepal studied 97 patients with RHD and non-rheumatic valvular heart disease (VHD). They observed the incidence of CAD to be 12.2% in RHD patients and 37.5% in non-rheumatic VHD patients. Kruczan et al⁹ from Rio de Janeiro studied 294 patients and found the incidence of CAD to be 4% in RHD patients versus 33.61% in patients with non-rheumatic VHD (Table 5).

Table 5: Description of various studies published on incidence of CAD in RHD patients

Author	Published year	City/ Country	Study type	Number of patients	Patients with RHD	Incidence of CAD in MV	Incidence in RHD	Incidence in non RHD
Jadhav et al ⁴	2016	Ahmedabad/ India	Retrospective observational	757	757	7/69 (10.1%)	69 (9.1%)	No comparison with Non RHD
Thiyagarajan et al ⁵	2018	India	Cross-sectional observational	101	101	4/43 (9.3%)	23 (22%)	No comparison with non RHD
Jose et al ⁶	2004	Vellore/ India	Prospective observational	376	376	13/96 (13.5%)	46 (12.2%)	No comparison with non RHD
Marchant et al ⁷	1983	Santiago/ Chile	Prospective observational	100	100	3/43 (7%)	14 (14%)	No comparison with non RHD
Sahi R et al ⁸	2018	Kathmandu/ Nepal	Retrospective comparative	97	57	Not checked	7/57 (12.2%)	15/40 (37.5%)
Kruczan et al ⁹	2008	Rio de Janeiro/ Brazil	Cross-sectional	294	175	Not checked	7/175 (4%)	40/119 (33.61%)

It was noted that out of all the above, Jadhav et al⁴ and Kruczan et al⁹ have considered TTE findings of valve morphology as the diagnostic feature of RHD, however none of the other studies have mentioned how they have confirmed RHD in their patients. We have used TTE, TEE as well as HPE findings for the confirmation of RHD.

This is one of the highlights of this study. The results of our study when compared with multicentric epidemiological study in general Indian population by Krishnan et al¹² in which 5167 adults of mean age 51 years were studied, showed a significant difference in the incidence of CAD (6.98% versus 12.5%, $p = 0.04$).

The observation made is that, for reasons not yet known, there is a significant reduction in the incidence of CAD in patients with RHD especially mitral valve disease. Although not conclusive in this small group of RHD patients, this study gives some evidence and it appears that RHD reduces the incidence of CAD. Further prospective study on a larger cohort of patients might be helpful in rewriting the guidelines for preoperative coronary angiography in patients undergoing heart surgery for rheumatic heart disease.

V. LIMITATIONS OF THE STUDY

This is a retrospective study where hospital based population of symptomatic patients have been included and the number of RHD patients is not large. A prospective comparative study with larger number of RHD patients would probably confirm this observation.

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Abbreviations

RHD	Rheumatic Heart Disease
CAD	Coronary Artery Disease
CAG	Coronary Angiography
DM	Diabetes Mellitus Type II
NYHA	New York Heart Association
CABG	Coronary Artery Bypass Grafting
LVEF	Left Ventricular Ejection
TTE	Trans-thoracic Echocardiography
TEE	Trans-esophageal echocardiography
LA	Left Atrium
LAA	Left Atrial Appendage
CPB	Cardiopulmonary bypass
LAD	Left anterior descending coronary artery
LCx	Left circumflex coronary artery
RCA	Right coronary artery
TVD	Triple vessel coronary artery disease
VHD	Valvular heart disease

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