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MORPHOLOGICAL AND HISTOLOGICAL CHARACTERISTICS OF SURGICALLY EXCISED MITRAL VALVE IN PATIENTS WITH RHEUMATIC AND NONRHEUMATIC MITRAL VALVE DISEASE

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ABSTRACT

Background: Among the rheumatic valvular heart disease; Mitral valve is frequently affected. In the past years, the pathology of cardiac valves has been thoroughly studied at autopsy. Now valve specimen obtained during cardiac surgery allow the study of a greater number of valves which affected by different diseases. Thus, the gross morphological study and histological examination of the surgically excised mitral valves will enhance the knowledge about the nature of rheumatic and nonrheumatic valve diseases. An understanding of the abnormal structure of the mitral valve is critical in choosing the optimal therapeutic approach for affected individuals. **Objective:** To see morphological and histological characteristics of surgically excised mitral valve in rheumatic and nonrheumatic mitral valve diseases and compare this characteristic between rheumatic and nonrheumatic mitral valve disease. **Materials and Methods:** This comparative cross sectional study carried out in the department of cardiac surgery, NICVD from first August 2018 to thirteen June 2020. Total 60 patients selected irrespective of age and sex. This patient gone through mitral valve replacement surgery. **Results:** Total sixty patients selected irrespective of age and sex who underwent through routine mitral valve replacement surgery. Based on past history of rheumatic fever patients divided into two group Rheumatic and nonrheumatic mitral valve disease. Among 60 patients 31(51.67%) were male and 29 (48.33%) were female. Among male, 20 (33.33%) male patients in rheumatic group and 11 (18.33%) male patients in nonrheumatic group. Among female, 24 (40%) female patients in rheumatic group and 5 (8.33%) female patients in nonrheumatic group. Morphological study revealed thickening and fibrosis to varying extent present in 48 (80%) cases. Commissural fusion and reduction of valve area present in 36 (60%) patients, Annular dilatation present in 16 (26.67%) cases, Calcium deposition to varying extent present in 39 (65%) patients, sub valvular changes present in 52 (86.66%) patients. The differences of morphological features were statistically significant ($p<0.05$) in *Chi-Square* test (χ^2). Morphological study of valve revealed mitral valve is more distorted and had more features than preoperative echocardiography. Histological study revealed among 60 patient fibrosis found in 48 (80%) slide, calcium deposition found in 42 (70%) cases. Aschoff body found in 32 (53.33%) patients, few specimens revealed multinucleated Aschoff giant cell. Differences between rheumatic and non-rheumatic groups was statistically significant ($p<0.05$). **Conclusion:** In this study, based on morphologic and histologic features of diseased mitral valve following mitral valve replacement procedure, it can be concluded that in national institute of cardiovascular diseases most mitral valve replacement procedure occur due to Rheumatic mitral valve disease than nonrheumatic mitral valve disease.

KEYWORDS: Mitral Stenosis; Mitral Regurgitation; Rheumatic valvular Heart disease; Non Rheumatic Valvular Heart Disease; Mitral Valve Replacement; Morphology; Histopathology.

INTRODUCTION

Mitral valve responsible for modulating blood flow between the left atrium and left ventricle is a complex structure and also known as mitral apparatus. Mitral valve has six components: the posterior wall of the left atrium, an annulus, two asymmetric leaflets, chordae tendineae, papillary muscles and the left ventricular wall. Abnormalities in one or more of these structures may

cause the valve to be incompetent or stenotic.[1] Mitral annulus is ellipsoid, saddle-shaped structure, it's a part of the fibrous skeleton of the heart. The mitral annulus, two leaflets, approximately 1 mm thick. The anterior mitral leaflet (AML) and the posterior mitral leaflet (PML) cover approximately one-third and two-thirds, respectively, of the circumference of the annulus.[2]

Common causes of mitral stenosis are rheumatic heart disease, infective endocarditis, severe mitral annular calcification. However, by far and away, "rheumatic" disease is recognized worldwide as the most common cause of mitral stenosis. Although its incidence is decreasing in western countries, rheumatic mitral stenosis is still frequent in developing countries as well as a major public health problem.[3]

Rheumatic fever is an acute, immunologically mediated multisystem inflammatory disease that occurs after Group A beta hemolytic streptococcus infections. Rheumatic heart disease is the cardiac manifestation of rheumatic fever. It is associated with inflammation of all parts of heart, but valvular inflammation and scarring produces the most important clinical feature. Valve involvement has a chronic sequela that leads to deforming fibrotic valvular disease. Mitral valve lesion is most common. It leads to permanent, severe and sometimes fatal cardiac failure decade's later.[4] In a recent systematic review and meta-analysis including populations in endemic regions around the world, the pooled prevalence of RHD among children and adolescents (≥5 years to <18 years) detected by cardiac auscultation was 2.9 per 1000 people and by echocardiography it was 12.9 per 1000 people.[5]

Common causes of mitral regurgitation are degenerative disease, rheumatic heart disease, mitral annular calcification, infective endocarditis, connective tissue disease, ischaemic Cardiomyopathy, dilated cardiomyopathy, papillary muscle dysfunction/rupture.[6]

Mitral valve replacement is considered when there is severe mitral stenosis with sub valvular changes, severe mitral insufficiency or a combination of the two. Patients with symptomatic isolated mitral stenosis usually treated by mitral commissurotomy but after mitral commissurotomy, restenosis can occur as chronic inflammatory process of rheumatic carditis continues. In such situations mitral valve replacement may remain the treatment of choice for patient's survival as the valve morphology in mitral restenosis may not be amenable for repair in most cases.[5,7]

The morphological findings of chronic rheumatic disease of mitral valve are commissural fusion, the deformity of leaflets caused by thickening and fibrosis and the chordal changes. There are thickening, shortening and fusion of tendinous chordae, fusion of papillary muscle and leaflets are also noted. There may be calcification of valve leaflets and commissures.[8] In infective endocarditis usually the valve leaflets are the primary site of infection, but the mural endocardium may also be involved. It appears that the damage to the endothelium with resulting thrombotic vegetations form the milieu for bacterial colonization. The bacteria and associated inflammation invade and destroy the valve and chordae tissue, usually resulting in valvular regurgitation. Very large vegetations rarely cause stenosis. Healed infective endocarditis often leaves structural change (diffuse fibrosis) mimicking rheumatic disease.[1] Myxomatous degeneration of the mitral valve is characterized by ballooning (hooding) of the mitral leaflets. The affected leaflets are enlarged, redundant, thick, and rubbery; the tendinous cords also tend to be elongated, thinned, and occasionally rupture.[9]

The histological examination of rheumatic mitral valve mainly shows fibrosis, calcification and neovascularization, lymphohistiocytic interstitial infiltrates with or without Aschoff cells.[10] In myxomatous disease histopathology of mitral valve is characterized by architectural changes in the leaflets consisting of fragmentation of collagen with an increase in extracellular proteoglycans and subsequent fibrosis.[11] Feature of Infective endocarditis are presence of colonies of basophilic bacteria within mass of eosinophilic thrombus.[9]

This study was done to see morphological and histological characteristics of surgically excised mitral valve in rheumatic and nonrheumatic mitral valve diseases and compare this characteristic between rheumatic and nonrheumatic mitral valve disease and to observe the number of patients with rheumatic and nonrheumatic mitral valve disease admitted in cardiac surgery department for mitral valve replacement surgery.

MATERIALS AND METHODS

It was a comparative Cross-Sectional Study carried out on patients who underwent elective mitral valve replacement surgery in Department of Cardiac surgery, National institute of cardiovascular diseases during the period of 1st August 2018 to 30 June 2020. Patients who underwent elective mitral valve replacement surgery meeting the selection criteria included in the study. A total number of 60 patients were evaluated in 2 groups, 40 patients in group A (Positive history of rheumatic fever in past) and 20 patients in group B (No history of rheumatic fever in past).

All patients admitted in cardiac surgery department of NICVD for elective mitral valve replacement surgery without exclusion criteria were considered for study population. Patient who fulfilled the inclusion criteria and willing to enroll in the study was included in the study after receiving the proper consent. Detailed history, clinical examination and relevant investigation reports of all patients were recorded in the data collection sheet preoperatively. According to schedule, patients were taken to the operating room. Peripheral venous catheterization and central venous catheterization (in the

internal jugular vein) and arterial line were done aseptically. Standard anesthetic techniques of induction and maintenance were followed for all procedures. All patients were operated through a median sternotomy approach. Cardiopulmonary bypass was established with appropriate aortic, superior & inferior vena caval cannulation. Heart was arrested in diastole by giving antegrade cardioplegia after applying aortic cross clamp. Then heart was opened by giving appropriate incision. Valve excised meticulously approximately 2mm away from the annular ring with intact chorda tendineae and part of papillary muscle if possible, otherwise part of valve was taken. Appropriate prosthetic valve used (mechanical/tissue). After completion of surgery all patients were transferred to intensive care unit (ICU) intubated and ventilated. After surgical excision of mitral valve, it was collected for further study. The shape of the valve orifice was noted. The posterior leaflet then divided at the mid region and spread for examination of leaflet area and commissural tissue. All the resected mitral valves were stored in 10 % buffered formalin solution in a small container within an hour after collection. It was properly labeled & numbered. Subsequently these valves were prepared for histopathological examination. The valves were processed using paraffin impregnation technique and stained by hematoxylin and eosin (H & E). Histopathological study like presence of aschoff bodies, cellular infiltration thickening, fibrosis, hyalinization, neovascularization and calcification was record. Data were analyzed computer based statistical analysis was carried out with appropriate techniques and systems. All data was recorded systematically in preformed data collection form (questionnaire). Quantitative data was expressed as mean and standard deviation and qualitative was expressed as frequency distribution and percentage. Data's were analyzed by the software statistical program for social science (SPSS 26.0). Probability value (p value) <0.05 was considered as level of significance. The association between qualitative variables was measured by Chi-Square test. Student's t test was performed to see the association between quantitative variables.

RESULTS

Out of 60 patients 31 (51.67%) were male and 29 (48.33%) were female. Most of the patients were found in 31-40 years age group. Out of 60 patients 31 (51.67%) were male and 29 (48.33%) were female. According to past history of rheumatic fever study group divided into 2 group rheumatic and nonrheumatic mitral valve disease. Among 60 patients 20 (33.33%) males and 24 (40%) females gave history of rheumatic fever in past. Distribution of patients with their valve pathology. Among 60 valve pathology cases pure mitral stenosis (MS) were 7 (11.67%) in number, mitral stenosis with mitral regurgitation (MS with MR) were 37 (61.67%) in number and mitral regurgitation (MR) were 16 (26.67%) in number. Among 60 valve pathology cases pure mitral stenosis (MS) were 7 (11.67%) in number, mitral stenosis with mitral regurgitation (MS with MR) were 37 (61.67%) in number and mitral regurgitation (MR) were 16 (26.67%) in number. Among 60 patients thickening and fibrosis of leaflet present in 48 (80%) cases, commissural fusion and reduction of valve area present in 42 (70%) patients, annular dilatation present in 16 (26.67%) patient, calcium deposition present in 39 (65%) patients and sub valvular changes in 52 (86.66%) patients. Out of 60 patient fibrosis found in 48 (80%) cases, calcium deposition found in 42 (70%) slide and aschoff body found in 32 (53.33%) patients.

Table I: Distribution of demographic characteristics of patients (n=60)

Characteristics	Rheumatic (n=44)	Nonrheumatic (n=16)	p-value
Age group (Years)			
<20	6(10)	1(1.67)	0.358^{NS}
21- 30	17 (28.33)	5 (8.33)	
31-40	19 (31.67)	7 (11.67)	
>41	2 (3.33)	3 (5)	
Mean ± SD	33.58 ± 7.10	35.56 ± 7.26	
Sex			
Male	20 (33.33)	11 (18.33)	0.120^{NS}
Female	24 (40)	5 (8.33)	0.113^{NS}

Table II: Distribution of patients with mitral valvular disease by history of rheumatic fever (n=60).

Pathology	Rheumatic (n=44)	Non rheumatic (n=16)	Total (n=60)	p-value
MS	6 (10%)	1 (1.67)	7(11.67)	0.154^{NS}
MS with MR	26 (43.33)	11(18.33)	37 (61.67)	0.688^{NS}
MR	12 (20)	4 (6.67)	16 (26.67)	0.751^{NS}

Table III: Distribution of patients by New York Heart Association classification (n=60).

NYHA class	Rheumatic (n=44)	Non-rheumatic (n=16)	p-value
Class I	33(55)	10 (16.67)	0.553^{NS}
Class II	11(18.33)	6(10)	
Class III	0(0)	0(0)	
Class IV	0(0)	0(0)	

Table IV: Distribution of patients by prophylaxis of rheumatic endocarditis (n=60).

Prophylactic treatment	Rheumatic (n=44)	Non-rheumatic (n=16)	p-value
Completed	20 (33.33)	6 (10)	0.395 ^{NS}
Incomplete	14 (23.33)	8 (13.33)	0.789^{NS}
Not received	10 (16.67)	2 (3.33)	0.512 ^{NS}

Table-V: Echocardiographic findings in mitral valvular disease patients

Variables	Rheumatic (n= 44)	Non-rheumatic (n=16)	p-value
Thickening and fibrosis			
Present	40 (66.66)	04 (6.66)	0.001^{S}
Absent	04 (06.66)	12 (20)	
Commissural fusion			
Present	32 (53.33)	04 (6.66)	0.021^{S}
Absent	12 (20)	12 (20)	
Annular dilatation			
Present	12 (20)	12(20)	0.011^{S}
Absent	32 (55.33)	04 (6.66)	
Calcium deposition			
Present	27 (45)	7 (11.67)	0.003^{S}
Absent	17 (28.33)	9 (15)	
Changes in sub valvular apparatus			
Present	38 (63.33)	12 (20)	0.002^{S}
Absent	6 (10)	4 (6.66)	
Left atrial diameter			
Enlarged ≥40mm	40 (66.66)	12 (20)	0.001^{S}
Absent < 40mm	04 (6.66)	4 (6.67)	
Left ventricular end diastolic diameter			
Enlarged ≥5mm	14 (23.33)	04 (6.66)	0.011^{S}
Normal <55mm	30 (50)	12 (20)	

Table VI: Morphological features of excised valves (n=60)

Variables	Rheumatic (n= 44)	Non-rheumatic (n=16)	p-value
Thickening and fibrosis			
Present	42 (70)	6 (10)	0.001^{S}
Absent	02 (3.33)	10 (16.67)	
Commissural fusion and reduction of valve area			
Present	32 (55.33)	04 (6.66)	0.001^{S}
Absent	12 (20)	12 (20)	
Annular dilatation			
Present	12(20)	04(26.67)	0.007^{S}
Absent	32(55.33)	12(20)	
Calcium deposition			
Present	29 (48.33)	10 (16.67)	0.003^{S}
Absent	15 (25)	06 (10)	
Sub valvular changes			
Present	40 (66.66)	12 (20)	

Absent	04 (06.66)	04 (06.66)	0.001[S]

Table VII: Histological features of excised valves (n=60)

Variables	Rheumatic (n= 44)	Non-rheumatic (n=16)	p-value
Fibrosis			
Present	42 (70)	06 (10)	0.001[S]
Absent	02 (03.33)	10 (16.67)	
Aschoff bodies			
Present	23 (38.33)	9 (15)	0.003[S]
Absent	21 (35)	7 (11.67)	
Calcium deposition			
Present	32 (53.33)	10 (16.67)	0.011[S]
Absent	12 (20)	6 (10)	

DISCUSSION

To see evidences of continued rheumatic and nonrheumatic activity, to correlate or to associate different clinical data and laboratory test this study was designed. Rheumatic heart disease (RHD) is the leading cause of mitral valve (MV) disease in the developing world.

This study was carried out in the department of cardiac surgery during the period of 01. 08. 2018 to 30. 06. 2020. Study population was chosen from this institute. Total 60 patients were selected for this study; based on past history of rheumatic fever (RF), they were divided into two groups. Among them, 44 patients had history of RF and 16 didn't give such history. The aim of this study was to study the morphology and histological structure of diseased mitral valve after mitral valve replacement surgery.

The peak incidence MVD found in fourth decade 26 (43.33%), 7 (11.6%) patients were below 20 age group, 22 (11.6%) patients were in 21-30 years age group, 5 (8.3%) patients were > 41 years age. Mean ages were 8.45 ± 0.53, 27.72 ± 5.85, 36.11 ± 5.32, 45.50 ± 5.13 for second, third, fourth and fifth decade respectively. A similar study carried by Sen *et al*., showed more people affected at 21-30 years age.[12] However, data from developed countries contradict with these findings, where juvenile mitral stenosis ranges from 0.5-13%. Maybe because of better socioeconomic condition and carefulness patient diagnosed earlier in the developed countries then developing countries.

There was almost equal sex distribution with male-female ratio, out of 60 patients 31(51.67%) were male and 29(48.33%) were female. Statistical difference between two gender was not significant (p>0.05). a similar study done by Islam et al., showed equal male female ratio.[13]

Patients has distributed by history of rheumatic fever into 2 group to find out pattern of rheumatic involvement of mitral valve in the absence of suggestive history and clinical features of rheumatic fever. Out of 60 patients 44 (73.33%) patients gave history of rheumatic fever where 20 (43.33%) patients were male and 24 (40%) patients were female. Out of 44 patients; 24 (40%) experienced single attack, whereas 22 (36.67%) had recurrent attacks.16 (26.67%) patients didn't give any related history of rheumatic fever. Statistical difference between two group was not significant (p>0.05). Ratnakar et al., found similar finding in his study.[14]

Among 60 valve pathology cases pure MS were 7 (11.66%) in number, MS with MR were 37 (61.66 %) in number and MR were 16(26.67%) in number. Among 44 (73.33%) patients 6 (10%) patients of MS, 26 (43.33%) patients of MS with MR and 12 (20%) patients of MR gave history of rheumatic fever. Among 16 (26.67%) cases 1 (1.67%) patient of MS, 11 (18.33%) patient of MS with MR and 4 (6.67%) patients of MR gave no related history of rheumatic fever. There is no statistical significance in terms of history of rheumatic fever in different pathological group (p >0.05). which corelate to the findings of Fowler *et al*., in their study.[15]

Out of 60 patients, 43(71.67%) in NYHA class I and 17(28.33%) in NYHA class II. Differences was not statistically significant (p>0.05). None of patients was in class III and IV. Salgo *et al*., found almost similar result in his study.[16]

Most of the patient i.e. 26 (43.33%) completed prophylaxis of rheumatic endocarditis, these patients received treatment from the registered medical practitioners or Hospitals. 22 (36.67%) patients didn't complete it, these patients took treatment from both registered medical practitioners and quacks. 12 (20%) patient received treatment from quacks only. So, in total 34 (56.66%) patients either didn't received treatment or handled by the quacks only. Differences was not statistically significant (p>0.05). Similar result was published by Chandra *et al*., in their study.[17]

Echocardiography revealed out of 60 patients thickening and fibrosis of leaflet to varying extent present 44 (73.33) cases, commissural fusion and reduction of valve area present in 36 (60%) patients, annular dilatation present in 16 (26.67%) patients, calcium deposition to varying extent present in 34 (56.67%) patients, sub valvular changes like fibrosis, thickening of

papillary muscles present in 50 (83.33%) patients, left atrium enlarged in 52 (86.66%) patients and left ventricle enlarge in 18 (30%) patients. Mean differences were statistically significant ($p<0.05$). Similar result reported by Sugeng, *et al*., in their study.[18]

Morphological examination is more reliable way of determining the nature of valve disease. Features were recorded include the number of cusps, fibrous thickening, calcific deposits, perforation, indentation of valve edge, tissue excess, commissural fusion, vegetations, chordae tendineae (fused, elongated, shortened, ruptured) and abnormal papillary muscles. Morphological feature of the study revealed thickening and fibrosis to varying extent present in 48 (80%) cases. Commissural fusion and reduction of valve area present in 36 (60%) patients, severe mitral stenosis (valve area < 1 cm^2) present in 7 (11.66%) cases and moderate stenosis (valve area 1 to 1.5 cm^2) found in 29 (48.33%) cases. Annular dilatation present in 16 (26.67%) cases. Calcium deposition to varying extent present in 39 (65%) patients; severe calcification seen in 7 (11.66%) patients whereas mild to moderate calcification was observed in 32 (53.33%). Calcification was found most commonly at valve margins and commissures. sub valvular changes present in 52 (86.66%) patients, among them 40 (66.66%) had history of rheumatic fever. Morphological study of valve revealed mitral valve is more distorted and had more features than preoperative echocardiography. The differences of morphological features were statistically significant ($p<0.05$). Similar result published by Rush *et al*., in their study.[19]

Histological structure of mitral valve has five layers; endothelial covered atrial and ventricular layer with a narrow layer of underlying loose connective tissue, zona spongiosa layer of loose connective tissue, the zona fibrosa, dense fibrous layer which is continuous with the chordae tendineae and annulus. The ventricular aspect of the valve has a narrow fibroelastic layer covered by endothelium.[20] Features were recorded during histological examination include presence of Aschoff body, Fibrosis, Calcification, colonies of basophilic bacteria, mass of eosinophilic thrombus, thinning of fibrosa layer of the valve accompanied by expansion of the middle spongiosa layer, increased deposition of myxomatous (mucoid) material, myocytes exhibit hypertrophy with enlarged nuclei. Features of Rheumatic heart disease are presence of fibrosis, calcification and aschoff body. The aschoff nodule is pathognomonic of rheumatic heart disease. Its presence indicates that an attack of acute rheumatic fever occurred at some time in the past but does not necessarily indicate an ongoing acute attack. Fibrinoid necrosis (acute phase) in the interstitial tissue is the earliest stage, followed by the appearance of histiocytes and giant cells (granulomatous phase). The earliest lesion is found in the heart several weeks after the acute attack, and the granulomatous phase occurs 3-6 months or more after the acute phase.[21] Feature of Infective endocarditis are presence of colonies of basophilic bacteria within mass of eosinophilic thrombus. Features of cardiomyopathy are most myocytes exhibit hypertrophy with enlarged nuclei, but many are attenuated, stretched, and irregular. There is also variable interstitial and endocardial fibrosis, with scattered areas of replacement fibrosis, DCM secondary to iron overload which is demonstrable by staining with Prussian blue.[9]

Histological study revealed among 60 patient fibrosis found in 48 (80%) slide, calcium deposition found in 42 (70%) cases. Aschoff body found in 32 (53.33%) patients where 23 (38.33%) patients had history of rheumatic fever and 9 (15%) patients without any past history of rheumatic fever, few specimens revealed multinucleated Aschoff giant cell. Rest 7 (11.67%) patient of nonrheumatic group include one patient had SLE, two patient had floppy mitral valve, one patint have cardiomyopathy and three patients have chronic annular calcification. Study reveal chronic rheumatic disease is the single major cause nowadays for replacement of the mitral valve. Differences between rheumatic and non-rheumatic groups was statistically significant ($p<0.05$). All p-values were calculated by chi square test. Similar results published by Ratnakar *et al*., in their study.[14]

CONCLUSION

In this study, based on macroscopic and microscopic features of mitral valve study following mitral valve replacement procedure, it can be concluded that mitral valvular heart disease is mostly occur due to rheumatic mitral valve disease.

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