Pathology and Etiology of 154 Mitral Valve Abnormalities Surgically Removed in Siriraj Hospital

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Abstract : *Objectives:* To study the pathology, determine the etiology and prevalence of mitral valve disease from surgically removed mitral valve specimens.
Materials and Methods: All the native surgically excised mitral valves (MV) received during June 1997 to March 1999 (22 months) were studied macroscopically and microscopically. By preoperative echocardiographic and macroscopic studies, they were classified into functional disorders of predominant mitral stenosis (MS), mitral stenosis with regurgitation (MS-MR) and predominant mitral regurgitation (MR). The patients' medical records were reviewed and the clinical information was extracted. The etiology was determined according to the macroscopic, microscopic and clinical findings.
Results: Among 154 MV (120 isolated MV and 34 with concomitant aortic valves from patients aged 7-79 years, mean age 43.98 years) there were 68 MS (44.16%), 30 MS-MR (19.48%) and 56 MR (36.36%) cases. All MS cases (age range 10 – 65 years, mean age 45.37 years, male : female = 1:1.51), all MS-MR cases (age range 20 – 66 years, mean age 40.03 years: male : female = 1:1.31) and 20 of 56 MR cases (35.71% of MR cases, 12.98% of total cases, age range 8 – 63 years, mean age 31.21 years, male : female = 1.22 : 1) were attributable to post-inflammatory disease. Prominent calcification occurred in 76.47% of MS, 70% of MS – MR and 25% of post-inflammatory disease MR cases. Moderate to marked neovascularization was found in 34.32% of MS, 56.66% of MS–MR and 65% of MR cases. Aschoff bodies were found in 1 MS and 4 MR cases. Eight of 39 MS (20.51%), 4 of 16 MS–MR (25%) and 6 of 13 (46.15%) post-inflammatory disease MR cases had past history of rheumatic fever. Other causes of pure MR included floppy valves (18 cases, 32.14% of MR cases, age range 40 - 79 years, mean age 61.72 years, male : female = 3.5 : 1;15 cases with chordal rupture), infective endocarditis (IE) [7 cases including one with post-inflammatory disease MS and one post-IE (age range 20 – 50 years, mean age 34.12 years, male : female = 6 : 1) with gram positive cocci in all IE], papillary muscle necrosis (1 case), ruptured necrotic papillary muscle (1 case), miscellaneous and indeterminate cause (4 cases). In comparison with post-inflammatory MR, posterior leaflet in floppy MR had longer basal-free edge length (mean basal-free edge length of floppy valve = 16.65 mm. $p < .0001$)and more frequent chordal rupture. Among MS and MS–MR post-inflammatory valves, 90.81%

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were completely excised whereas partial specimens were received in 40% of post-inflammatory MR, 61% of floppy valves and 50% of miscellaneous cases.

Conclusion: **Post-inflammatory disease (presumably rheumatic fever associated) of MV is still a main valvular heart disease in Thai patients undergoing valvular operation as it accounted for 75.97% of all MV specimens. In pure MR, the three most common causes were post-inflammatory disease, floppy valve and infective endocarditis. Macroscopic and microscopic examinations together with clinical information, echocardiographic findings and operative details are important in the evaluation of the etiology of valvular disease especially in partial specimens.**

Key words: Mitral valve; postinflammatory disease; floppy valve; chordal rupture; infective endocarditis.

เรื่องย่อ : **พยาธิวิทยาและสาเหตุของความผิดปกติของลิ้นหัวใจไมตรัลที่ได้รับการผ่าตัดในโรงพยาบาลศิริราช จำนวน 154 ราย**

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วัตถุประสงค์ เพื่อศึกษาพยาธิสภาพ สาเหตุของความผิดปกติ และอัตราการเกิดโรคของลิ้นหัวใจไมตรัล จากลิ้นหัวใจที่ได้จากการผ่าตัด

วัตถุและวิธีการ ได้ทำการศึกษาลิ้นหัวใจไมตรัล ที่ได้รับการผ่าตัดในโรงพยาบาลศิริราชในช่วงมิถุนายน 2540 ถึงมีนาคม 2542 (22 เดือน) โดยการตรวจพยาธิสภาพด้วยตาเปล่าและด้วยกล้องจุลทรรศน์, และแบ่งประเภทการทำงานผิดปกติของลิ้นหัวใจ โดยอาศัยการตรวจ echocardiography ก่อนผ่าตัดและลักษณะพยาธิสภาพด้วยตาเปล่าออกเป็น ลิ้นหัวใจไมตรัลตีบ (MS) ลิ้นหัวใจไมตรัลรั่ว (MR) และลิ้นหัวใจไมตรัลตีบและรั่ว (MS-MR)

ข้อมูลทางคลินิกของผู้ป่วยได้จากการซักประวัติ, สืบค้นและรวบรวมจากเวชระเบียน การจำแนกสาเหตุของโรคอาศัยข้อมูลการตรวจทางพยาธิสภาพทั้งด้วยตาเปล่าและด้วยกล้องจุลทรรศน์ ร่วมกับประวัติและการสืบค้นที่สำคัญในทางคลินิก

ผล จากลิ้นหัวใจไมตรัล 154 ราย (120 ราย เฉพาะ ลิ้นหัวใจไมตรัล อย่างเดียว และ 34 รายที่ผ่าตัดพร้อม ลิ้นหัวใจเออร์ติค) เป็นผู้ป่วยอายุตั้งแต่ 7-79 ปี อายุเฉลี่ย 43.98 ปี, พบลิ้นหัวใจไมตรัลตีบ 68 ราย (44.16%), ลิ้นหัวใจไมตรัลรั่ว 56 ราย (36.36%), และลิ้นหัวใจไมตรัลตีบและรั่ว 30 ราย (19.48%)

ลิ้นหัวใจไมตรัลตีบทุกราย (ช่วงอายุตั้งแต่ 10-56 ปี อายุเฉลี่ย 45.37 ปี อัตราชายต่อหญิง = 1:1.51) ลิ้นหัวใจไมตรัลตีบและรั่วทุกราย (ช่วงอายุตั้งแต่ 20-66 ปี อายุเฉลี่ย 40.03 ปี อัตราชายต่อหญิง = 1:1.31) และ 35.71% ของลิ้นหัวใจไมตรัลรั่ว (12.98% ของทั้งหมด, ช่วงอายุตั้งแต่ 8-63 ปี อายุเฉลี่ย 31.21 ปี อัตราชายต่อหญิง = 1.22:1) มีสาเหตุจากโรคหลังการอักเสบ (ส่วนใหญ่จากไข้รูห์มาติค)

พบมีหินปูนเกาะเด่นชัดใน 76.47% ของลิ้นหัวใจไมตรัลตีบ, 70%ของลิ้นหัวใจไมตรัล ตีบและรั่ว, และใน 25%ของลิ้นหัวใจไมตรัลรั่วจากโรคหลังการอักเสบ พบหลอดเลือดเกิดใหม่ระดับปานกลางถึงมากใน 34.32% ของลิ้นหัวใจไมตรัลตีบ, 56.66%ของลิ้นหัวใจไมตรัลตีบและรั่ว, และ 65%ของลิ้นหัวใจไมตรัลรั่ว พบ Aschoff bodies ในลิ้นหัวใจไมตรัลตีบ 1 รายและลิ้นหัวใจไมตรัลรั่ว 4 ราย

ผู้ป่วย 8 ใน 39 รายของลิ้นหัวใจไมตรัลตีบ (20.51%), 4 ใน 16 รายของลิ้นหัวใจไมตรัลตีบและรั่ว (25%) และ 6 ใน 13 ราย (46.15%) ของลิ้นหัวใจไมตรัลรั่วจากโรคหลังการอักเสบ มีประวัติเดิมของไข้รูห์มาติคมาก่อน

สาเหตุอื่นของลิ้นหัวใจไมตรัลรั่วเพียงอย่างเดียวได้แก่ floppy valve (พบ 18 ราย คิดเป็น 32.14% ของลิ้นหัวใจไมตรัลรั่ว, ช่วงอายุตั้งแต่ 40-79 ปี อายุเฉลี่ย 61.72 ปี, อัตราชายต่อหญิง = 3.5:1 และพบ chordal rupture 15 ราย), เยื่อบุหัวใจชั้นในอักเสบจากการติดเชื้อ (7 ราย รวมถึง 1 รายที่เป็นลิ้นหัวใจไมตรัลตีบจากโรคหลังการอักเสบ และ 1 ราย ที่เคยมีเยื่อบุหัวใจชั้นในอักเสบ, พบมีบักเตรีกรัมบวกทั้งหกราย ในกลุ่มนี้มีช่วงอายุตั้งแต่ 20-50 ปี อายุเฉลี่ย 34.12 ปี อัตราชายต่อหญิง = 6:1), papillary muscle necrosis (1 ราย), ruptured necrotic papillary muscle (1 ราย) และไม่สามารถแยกชนิดได้ชัดเจน 4 ราย

เมื่อเปรียบเทียบกับลิ้นหัวใจไมตรัลรั่วจากโรคหลังการอักเสบ พบว่า posterior leaflet ใน floppy MR มี basal-free edge length ที่ยาวกว่าและพบสายลิ้นหัวใจฉีกขาดบ่อยกว่า

90.81% ของลิ้นหัวใจไมตรัลตีบ และลิ้นหัวใจไมตรัลตีบและรั่วจากโรคหลังการอักเสบที่ได้รับเป็นลิ้นหัวใจครบวง แต่ 40% ของลิ้นหัวใจไมตรัลรั่วจากโรคหลังการอักเสบ, 61% ของ floppy valve และ 50% ของลิ้นหัวใจไมตรัลรั่วจากสาเหตุอื่น ๆ นั้นได้รับเป็นบางส่วนของลิ้นหัวใจ

สรุป พบว่า 75.97% ของลิ้นหัวใจไมตรัลเป็นโรคหลังการอักเสบ และ 3 สาเหตุหลักของลิ้นหัวใจไมตรัลรั่วคือ โรคหลังการอักเสบ, floppy valve และเยื่อบุหัวใจชั้นในอักเสบจากการติดเชื้อ การประเมินสาเหตุของโรคลิ้นหัวใจจำเป็นต้องอาศัยข้อมูลการตรวจพยาธิสภาพด้วยตาเปล่าและด้วยกล้องจุลทรรศน์ร่วมกับการตรวจทางคลินิก, ผลการตรวจ echocardiography และลักษณะที่ตรวจพบจากการผ่าตัด โดยเฉพาะอย่างยิ่งในรายที่ผ่าตัดลิ้นหัวใจออกเพียงบางส่วน

INTRODUCTION

Until recent years, most cardiac valvular lesions have been believed to be related to rheumatic heart disease.[1] In the last two to three decades, however, it has been appreciated that rheumatic fever is only one of several causes of valvular heart disease and depending on the socioeconomic status it may not be the most common etiology espécially in mitral regurgitation (MR). Increasing prevalence of floppy MR and infective endocarditis in the surgical valvular specimen has been observed.[2,3]

In Thailand, to our knowledge, the pathology and the etiology of surgically resected cardiac valve specimens and the prevalence of each disease have not been systematically studied. Siriraj Hospital is one of the largest hospitals in Thailand with an average of nearly 90,000 inpatients annually. Cardiac valve surgery was first established at Siriraj Hospital in 1954 and ranged 96-128 cases / year during 1994-1998 (mean-116.4 cases / year).

The current study evaluates the macroscopic and microscopic pathology of 154 surgically excised mitral valves according to functional disorders and etiology, and determines the prevalence of each etiology of mitral abnormalities and the correlation with the clinical findings.

MATERIALS AND METHODS

All native surgically excised mitral valves (MV) during June 1997 through March 1999 (a 22 month period) were examined. Each was photographed and evaluated for diffuse or focal fibrosis, myxomatous change, free edge fibrosis, hooding, perforation or indentation and vegetation. The following measurements were recorded for each leaflet: circumferential length, basal-free edge length and thickness at the closing edge, basal margin and midway between closing edge and basal margin. Commissures were examined for fusion and chordae tendineae were evaluated for fusion, shortening and rupture. Papillary muscles were examined for fibrosis, inflammation and infarction. Site and extent of calcification (mild, moderate, or marked degree) were recorded. The overall extent of calcification was graded according to closing circumference involvement of less than ¼ (**mild** degree), up to ½ (**moderate** degree) and more than ½ (**marked** degree). More than 95% of the specimens were examined and recorded by one pathologist. The valvular tissue was serially cut, decalcified when needed and totally embedded. Microscopically, they were all examined for fibrosis,myxoid change, calcification and neovascularization. The latter was graded arbitrarily in three degrees : **mild**-when not all sections contained vessels, **moderate**-when vessels were found in each section and **severe**-when vessels were found in all low power fields of each section. The extent of chronic inflammatory cell infiltration was assessed using the same criteria as neovascularization. The presence of calcification, Aschoff body, lipid deposit, thrombosis or vegetation, neutrophilic infiltration and bacteria clumps were also determined. Gram stain for bacteria and Gomori methenamine silver stain for fungus were performed in cases with vegetation or acute inflammation. On the basis of both pathologic and clinical information, each mitral valve was classified as : 1) **post-inflammatory disease** when there was a chronic noninfectious fibrosing process (diffuse fibrosis with neovascularization) resulting in valvular distortion indistinguishable or identical to chronic rheumatic valvular disease, 2) **floppy valve (mitral valve prolapse)** when there was leaflet redundancy,and diffuse myxoid change without inflammatory change, 3) **infective endocarditis** when vegetation with a demonstrable microorganism was present, 4) **post-infective endocarditis** when there was clinical evidence of infective endocarditis, previously treated but lacking microorganisms in the specimen. Those with nonspecific changes included **dilatation of valve ring, papillary muscle dysfunction** (mostly infarction) and associated with other **congenital heart disease.** Abnormal valves which could not be classified confidently were considered **indeterminate types** of mitral valve disease.

Functional disorders were determined by clinical information using mainly Doppler echocardiography with or without intraoperative evaluation. Mitral stenosis was diagnosed as mild, moderate, or severe when the mitral valve areas were 1.5-2, 1-(<1.5), and <1 cm^2, respectively. Mitral regurgitation was graded as mild, moderate or severe by using color Doppler echocardiography. All cases were classified into one of three groups-**predominant mitral stenosis (MS), mitral insufficiency (MR)** or **combined mitral stenosis and insufficiency (MS-MR).** For the present study, the mildly regurgitant valves with moderate to severe stenosis were also included in the MS group while those with both stenosis and insufficiency of moderate or severe degree were classified into the MS-MR group.

The medical record of each patient was reviewed with the age, sex, clinical symptoms, past history of acute rheumatic fever, underlying diseases (diabetes mellitus, hypertension, dyslipoproteinemia), echocardiographic diagnosis, the surgeon's description of mitral valve and other related abnormalities, and prior management including closed mitral valvulotomy or percutaneous balloon mitral valvulotomy.

Statistical Analysis

Statistical analysis was performed using ANOVA F test and Chi-square test for comparison of the data of various mitral valvular diseases. Difference with probability (p) values <0.05 were considered significant.

RESULTS

Of 154 mitral valves examined, 120 (77.92%) specimens were isolated cases and 34 (22.08%) with concomitant aortic valves. One hundred and fourteen valves (74.03%) were complete specimens.

Functional classification and etiology: The functional status was MS in 68 cases (44.16%) MS-MR in 30 cases (19.48%) and MR in 56 cases (36.36%) (see Table1). All cases with MS and MS-MR had post-inflammatory disease. One with MS also had infective endocarditis. Of 56 cases with MR, 20 (35.71%) were attributed to post-inflammatory disease, 18 (32.14%) floppy valve, 5 (8.93%) infective endocarditis. Other causes of MR included 1 prior infective endocarditis, 1 ASD, 1 cleft anterior leaflet, 2 post-repairs of ASD, 1 post-repair of chordal rupture. There were 4 cases with indeterminate MR; one was associated with probable post-inflammatory disease, one was probable floppy valve, one had free edge fibrosis without other diagnostic abnormalities, the last one was too small and without specific change.

Post-inflammatory disease

Complete specimens were achieved in most MS and MS-MR (90.81% of overall MS and MS-MR) and in only 40% of MR. Diffuse fibrosis including free edge was commonly found (Table 2). Commissural fusion and calcification were more common in MS and MS-MR than in post-inflammatory MR.

Calcification at both commissures was found in more than half of the patients (anterolateral commissure, 61.13%; posteromedial commissure, 56.07%) and decreased in extent from MS or MS-MR through MR (Table 2).

Prominent neovascularization and chronic inflammatory cell infiltration were significantly found more in MR than in MS (p= .028 for neovascularization and .003 for chronic inflammatory cell infiltration). Also chronic inflammatory cell infiltration was more prominent in MS-MR than in MS (p = .034).

Neutrophilic infiltration without demonstrable bacteria was present in 15% of post-inflammatory MR.

Microscopic amount of fibrinous deposits was observed in ¾ of MS and 1/3 of MS-MR at the calcified commissures. It was found in 5 MR cases one of which contained granulomatous form of Aschoff bodies in the endocardium. The latter were present in 1 MS and 4 MR specimens (4.27% of post-inflammatory diseases). Three of the patients with Aschoff bodies had concurrent aortic valve replacement, two of whom had Aschoff bodies in the aortic valve. Lipid deposits were present in ¼ of both MS and MS-MR specimens. Basal calcification was rarely present in MS or MS-MR. Papillary muscle fibrosis was found commonly.

Measurements in MS, MS-MR and MR. For the anterior leaflet, there was no significant difference in circumferential length, basal-free edge length, closing edge thickness and basal thickness in MS, MS-MR and MR (Table 4).

Midportion thickness was significantly increased in MS versus MS-MR (p = .0003) and MR (p = .034). Of the posterior leaflet, MS had significantly decreased circumferential length versus MR (p =.002).

Chordal fusion was common in all MS, MS-MR. (Table 2)

One post-inflammatory MR case exhibited chordal rupture of the anterior leaflet.

Clinical correlation. Post-inflammatory disease was the most common type of MV disease and accounted for 75.97% of the 154 MV specimens (Table1). Women accounted for 57.26% of all post-inflammatory MV, 61.19% of MS, 56.67% of MS-MR and 45% of MR (Table 5). The mean age at operation of MS was significantly increased versus that of MS-MR and MR (MS = 45.46 ± 10.53, MS-MR = 40.03 ± 12.06 and MR = 31.2 ± 15.08 years). Past history of rheumatic fever (including those with prophylactic treatment) was present in 26.47%. One post-inflammatory MS also had infective endocarditis. Five of 20 post-inflammatory MR had concomitant aortic valve replacements. Four of 18 post-inflammatory MR had prior history or were diagnosed as prolapse leaflets. Ischemic heart disease, diabetes mellitus and hypertension were rarely associated (Table 5). Dyslipoproteinemia was present in 33.75% of overall post-inflammatory MV. Of 115 post-inflammatory disease, 15 MS, 2 MS-MR underwent previous mi-

Table 1. Etiologic Diagnosis of Mitral Valve Diseases

Etiology	Functional disorder			Total (% of total)
	MS	MS-MR	MR	
Post-inflammatory disease	67 (98.53%)	30 (100%)	20 (35.71%)	117 (75.97%)
Floppy valve	-	-	18 (32.14%)	18 (11.69%)
Infective endocarditis	1* (1.47%)	-	5 (8.93%)	6 (3.90%)
Postinfective endocarditis	-	-	1 (1.79%)	1 (0.65%)
Papillary muscle necrosis	-	-	2 (3.57%)	2 (1.30%)
Normal morphology with dilated ring	-	-	1 (1.79%)	1 (0.65%)
Associated with ASD, cleft AL, post-repairs	-	-	5 (8.93%)	5 (3.25%)
Indeterminate	-	-	4 (7.14%)	4 (2.60%)
Total (% of total)	68 (44.16%)	30 (19.48%)	56 (36.36%)	154 (100%)

*Post-inflammatory disease with infective endocarditis

tral valvulotomy, 16 to 40 years prior to MV replacement. Nine patients had failed previous balloon valvulotomy.

MR patients had shorter durations of cardiac symptoms (dyspnea) than MS or MS-MR patients (Table 5).

Two MR patients had prolonged fever without conclusive criteria of acute rheumatic fever: one had Aschoff bodies and the other was associated with marked neovascularization. Four MR and one MS with Aschoff bodies were in the age range 15-29 years except for one MR whose age was 63 years and who also has ruptured chordae. Two MR cases with microscopic verrucous endocarditis were 15 years of age and one also had Aschoff bodies.

Atrial fibrillation was common in nearly 90% of MS, and MS-MR patients and was present in less than 40% of post-inflammatory MR cases. Left atrial clots were present in 48.89% of MS, 20% of MS–MR and uncommon in MR cases (Table 5).

Floppy valve

It was diagnosed in 18 cases, accounting for 11.69% of all MV and 32.14% of all MR cases. There were 7 complete specimens (38.69%) (Table 2). Isolated posterior and anterior leaflets were present in 10 and 3 cases, respectively. All except one showed absence of commissural fusion. Hooding was present in 40% of anterior and 56.25% of posterior leaflets. Minimal chordal fusion was detected in 50% of anterior and 35.29% of posterior leaflets. Chordal ruptures (gross and operative findings) were present in 15 of 18 cases (83.33%). All except one (93.33%) had chordal ruptures of posterior leaflet whereas 46.67% has anterior chordal ruptures and 40% exhibited chordal ruptures of both. Isolated posterior chordal ruptures were present in 8 of 15 cases (53.33%). Diffuse myxoid change overlayered by fibrosis was found commonly. There was no neovascularization (Table 3). Minimal chronic inflammatory cell infiltration was infrequently present (11.11%). Rare microcalcification was observed in 27.78% and lipid deposits in 16.67% of cases.

Comparison between measurements of leaflets in floppy valve and post-inflammatory MR. (Table 4) Although the mean lengths and the closing edge thickness of both anterior and posterior leaflets of the floppy valve were more than those of the post-

Table 2. Macroscopic Morphologic Assessment of Various Mitral Valve Diseases

Macroscopic features	Post-inflammatory disease						Floppy valve		IE + Post IE	
	MS		MS-MR		MR					
	No.	%	No.	%	No.	%	No.	%	No.	%
Complete specimen	63/66	94.02•	26/30	86.67•	8/20	40.00•*	7/18	38.69	4/7	57.14
Diffuse fibrosis	63/66	95.45	29/30	96.66	17/20	65.00	6/10	60	3/5	40
Free edge fibrosis	66/66	100	30/30	100	20/20	100•	6/10	60•	5/6	83.33
Myxoid change	8/67	11.94•	4/30	13.33•	9/20	45.00•*	10/10	100•	2/5	40
ALC fusion	50/54	92.59•	22/27	81.48•	4/15	26.67•*	0/8	0	3/5	60
PMC fusion	63/67	94.02•	11/23	47.83•	7/14	50.00•	1/8	12.50	1/4	25
Hooding	0	0	0	0	AL 3/18	16.67	AL 4/10	40	1/7	14.29
					PL 5/14	35.71	PL 9/16	56.25		
Vegetation	0	0	0	0	1/18	5.56	0	0	5/6	83.33
AL calcification	48/65	73.84•	19/30	63.33•	4/20	20•*	0	0	3/6	50
PL calcification	52/64	81.25•*	6/30	20.00•	4/13	30.77•	0	0	3/6	50
ALC calcification	52/65	80.00•*	17/30	56.67•*	2/14	14.29•*	0	0	1/4	25
PMC calcification	44/65	67.69•	15/29	51.72•	1/13	7.69•*	0	0	0	0
AL chordal fusion	64/67	95.52•	27/30	90•	14/20	70•*	5/10	50	3/6	50
PL chordal fusion	56/65	86.15	21/29	72.41	8/13	61.54	6/17	35.29	5/6	83.33
ALC chordal fusion	57/61	93.44•	29/30	96.67•	2/10	20.00•*	1/7	14.29	2/3	66.67
PMC chordal fusion	63/65	96.92•	22/29	75.86•	6/14	42.86•*	0	0	1/4	25
ALC chordal shortening	55/60	91.66•	25/29	86.20	6/11	54.55•*	0	0	1/4	25
PMC chordal shortening	62/66	93.93•	23/30	76.67•	3/14	21.43•*	0	0	1/4	25
Isolated AL chordal rupture	0	0	0	0	1/20	5	1/15	6.67	2/5	40
Isolated PL chordal rupture	0	0	0	0	0	0	8/15	53.33	2/5	40
Both AL+PL chordal ruptures	0	0	0	0	0	0	6/15	40.00	0	0
Tissue loss	0	0	0	0	0	0	0	0	1/5	20

AL = anterior leaflet
ALC = anterolateral commissure
PL = posterior leaflet
PMC = posteromedial commissure

Symbols • † * denote comparison between pairs of post-inflammatory MS, MS-MR, MR and floppy valve with $p<.05$.

Table 3. Microscopic Morphologic Assessment of Various Mitral Valve Diseases

Microscopic features	Post-inflammatory disease						Floppy valve		IE + Post IE	
	MS		MS-MR		MR					
	n=67	%	n = 30	%	n = 20	%	n=18	%	n=6+1	%
Fibrosis	66	98.15	29	96.67	18	90.00•	5	27.78•	2	28.57
Myxoid change	11	16.42	5	16.67	6	30.0•	16	88.89•	2	28.57
Neovascularization										
- prominent (2+, 3+)	23	34.33•	17	56.67	13	65.00•	0	0	6	85.71
- minimal (1+)	44	65.57•	13	43.33	7	35.00•	0	0	1	14.29
- absent	0	0	0	0	0	0	18	100	0	0
Chronic inflammatory infiltration										
- prominent (2+, 3+)	4	5.97•	7	23.33•	7	35•	0	0	4	57.00
- minimal (1+)	59	88.06	23	76.67	13	65•	2	11.11•	3	43.00
- absent	4	5.97	0	0	0	0	16	88.89	0	0
Calcification										
- prominent (2+, 3+)	53	79.10•	21	70.00•	5	25.00•	0	0	0	0
- minimal (1+)	12	17.91	8	26.67	4	20.00	5	27.78	6	85.71
- absent	2	2.99	1	3.33	11	55	13	72.22	1	14.29
Lipid deposit	17	25.37	7	23.33	2	10	3	16.67	1	14.29
Thrombosis	52	77.61•	10	33.33•	5	25•	0	0•	7	100.0
PMN infiltration	6	8.96	2	6.67	3	15	0	0	6	86.00
Basal calcification	3/46	6.52	1/26	3.84	0/15	0	3	16.67	0	0
Papillary fibrosis	44/52	84.62	19/21	90.48	11/15	73.33	4/6	66.67	2/2	100
Aschoff body	1/67	1.50•	0	0	4/20	20	0	0	0	0

Symbols • + ▪ □ denote comparison between pairs of post-inflammatory MS, MS-MR, MR and floppy valve with $p<.05$.

Table 4. Measurements in MS, MS-MR and MR Post-inflammatory Diseases & MR Floppy Valve

	MS			MS-MR			MR			Floppy valve		
	range (mm)	mean (mm)	SD (mm)	range (mm)	mean (mm)	SD (mm)	range (mm)	mean (mm)	SD (mm)	range (mm)	mean (mm)	SD (mm)
Anterior leaflet												
Length	25-45 n=67	32.63	4.21	25-37 n=30	31.63	3.11	25-45 n=19	34.3	5.57	28-48 n=10	37.5	5.8
BFE length	11-30 n=66	21.57	3.53	13-26 n=30	20.33	3.75	15-35 n=19	20.50	4.68	13-27 n=10	21.2	4.0
CE thickness	.9-5.3 n=67	2.15	0.92	1-4 n=29	2.19	.78	.5-4 n=18	1.96	.99	.2-3 n=10	1.31	.7
Midportion thickness	.1-5.5 n=64	1.9	1.07	.7-3.1 n=27	1.62	.67	.5-3 n=14	1.26	.8	.5-3.1 n=8	1.6	.9
Basal thickness	.1-3.9 n=56	.95	.62	.3-2.2 n=26	.95	.5	.4-1.9 n=13	1.01	.47	.3-1 n=7	.6	.2
Interval of strut chordal insertions	5-17 n=51	10.55	2.72	7-17 n=26	10.77	2.14	8-15 n=13	11.46	2.02	12-15 n=6	13.16	1.4
Posterior leaflet												
Length	25-60 n=64	40.9•	6.93	23-53 n=26	41.46	8.6	25-85 n=12	52.58•	17.5	55-92 n=7	70.85	11.8
BFE length	5-22 n=65	11.25	3.01	4-16 n=29	10.27	3.2	4-13 n=15	9.26•	2.81	10-23 n=17	16.65•	3.9
CE thickness	.7-5 n=64	1.96	.79	1.2-3.5 n=29	2.02	.6	.4-5 n=14	1.5	1.16	.4-2 n=17	1.24	.5
Midportion thickness	7-5 n=53	1.86•	.88	.6-3.3 n=24	1.05•	.81	.4-3 n=11	1.53•	1.08	.5-5 n=15	1.81	1.2
Basal thickness	3-3 n=52	1.14	.68	.2-3.5 n=24	1.36	.86	.3-2.2 n=11	1.07	.62	.2-5 n=14	1.47	1.3

BFE = basal-free edge CE = closing edge

Symbols • † denote comparison between pairs of post-inflammatory MS, MS-MR, MR and floppy valve with $p<.05$.

Table 5. Demographics and Clinical Study of Mitral Valve Diseases

		Post-inflammatory disease					
		MS (67)	MS-MR (30)	MR (20)	Floppy valve (18)	IE-post IE (7)	Post-repair (4)
Sex Male : Female		1:1.51	1:1.31	1:0.82 (1.22:1)	1:0.29 (3.5:1)	1:0.17 (6:1)	1:0.33 (3:1)
Age	range	10-65	20-66	8-63	40-79	20-50	38-63
	mean	45.46[a]	40.03[b]	31.2[a,b]	61.72[a]	34.12	47.00
	SD	10.53	12.06	15.08	11.33	10.49	11.05
Rheumatic fever history	No./total	8/39	4/16	6/13	0/16	0/7	0/4
	%	20.51	25	46.15			
Endocarditis	No./total	0/65	0/29	0/16	0/18	4	1
	%					57.14	25
Prolapse valve	No./total	0/65	0/29	4/18	16	2	3
	%	-	-	22.22	88.89	28.57	75
Congenital heart disease	No./total	0/65	0/28	0/19	0/18	1	2
	%					14.29	20
Ischemic heart disease	No./total	1/65	0	0	0	0	0
	%	1.54					
Diabetes	No./total	3/65	0	1/19	0	0	0
	%	4.62		5.26			
Hypertension	No./total	2/65	1	1/19	4	0 -	0
	%	3.08	3.33	5.26	22.22		
Dyslipoproteinemia	No./total	12/47	12/22	3/11	7/13	1	0
	%	25.53	54.55	27.58	53.85	14.29	
Smoking	No./total	6/31	2/13	1/12	2/8	2	0
	%	19.35	15.38	8.33	25	28.57	
Alcohol consumption	No./total	2/28	1/11	1/10	1/6	2	1/4
	%	7.14	9.09	10.00	16.67	28.57	25.00
Dyspnea	< 1 yr (%)	11.11	10	44.44	29.41	71.43	75.00
	1-5 yr (%)	41.27	50	44.44	52.94	14.29	25.00
	>5 yr (%)	47.62	40	11.11	17.65	14.29	
Fever		0	1/29	2/18	0	4/7(57.14%)	0
AF	No./total	25/28	15/17	7/17	3/17	1	0
	%	89.29[a]	88.24[b]	36.84[a,b]	17.65	14.29	
LA clot	No./total	22/45	4/20	1/18	1/15	0	0
	%	48.89[a]	20[b]	5.56[a,b]	6.67		

Symbols a + a, b denote comparison between pairs of post-inflammatory MS, MS-MR, MR and floppy valve with $p<.05$.

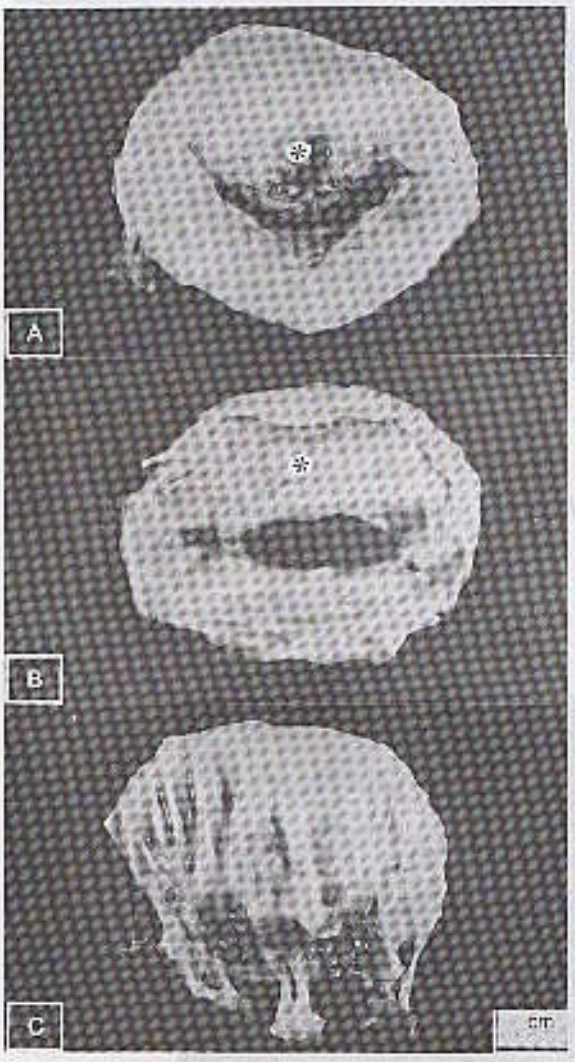

Figure 1. Complete specimen of post-inflammatory mitral valve showing diffuse fibrosis and commissural fusions with A) MS showing calcification of leaflets and posteromedial commissure B) MS-MR functional disorders and C) chordal fusion and shortening. * = anterior leaflet

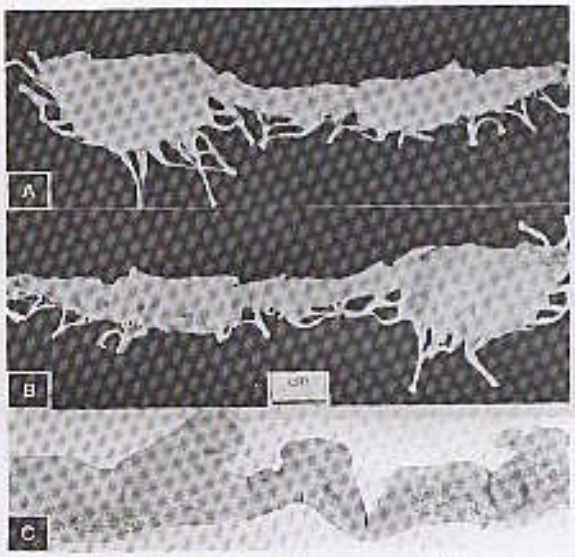

Figure 2. Post-inflammatory MR in an 8-year-old girl with clinical mitral valve prolapse. A) atrial surface showing diffuse fibromyxoid change B) ventricular surface showing distorted strut chordal insertions and minimal chordal fusion C) prominent neovascularization and some chronic inflammatory cell infiltration. (H&E x 20)

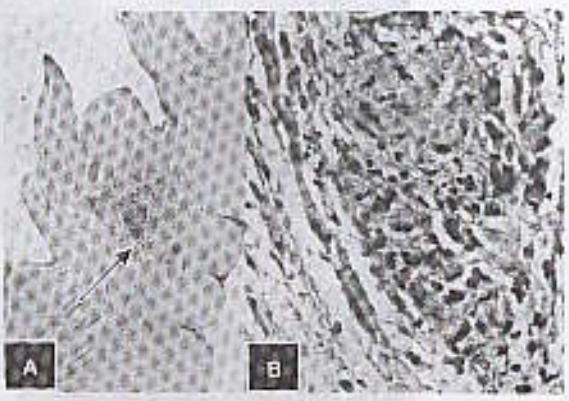

Figure 3. Granulomatous form of Aschoff body in leaflet with fibrosis and neovascularization. [H&E, A) x 20, B) x 200]

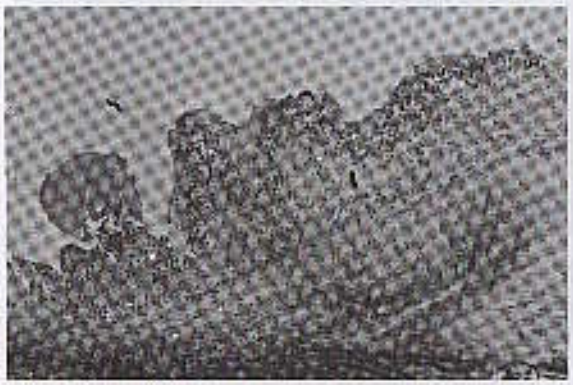

Figure 4. Fibrinous deposit overlayering histiocytic reaction (microscopic noninfective verrucous endocarditis) in some post-inflammatory MR. (H&E x 40)

Figure 5. Fibrinous deposit with underlying neovascularization and calcification. (H&E x 20)

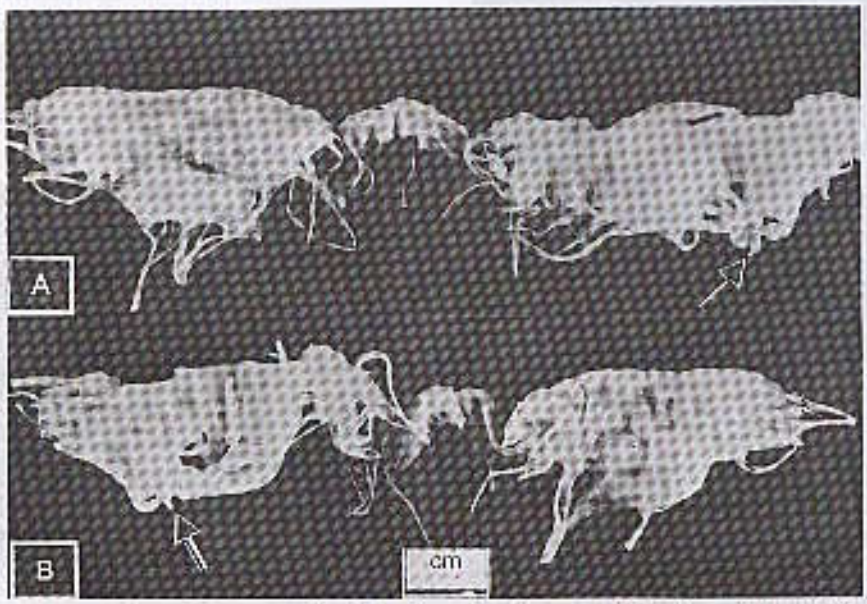

Figure 6. Complete specimen of floppy valve showing redundancy and hooding of both leaflets and rupture of posterior chordae (arrow). A) atrial surface B) ventricular surface.

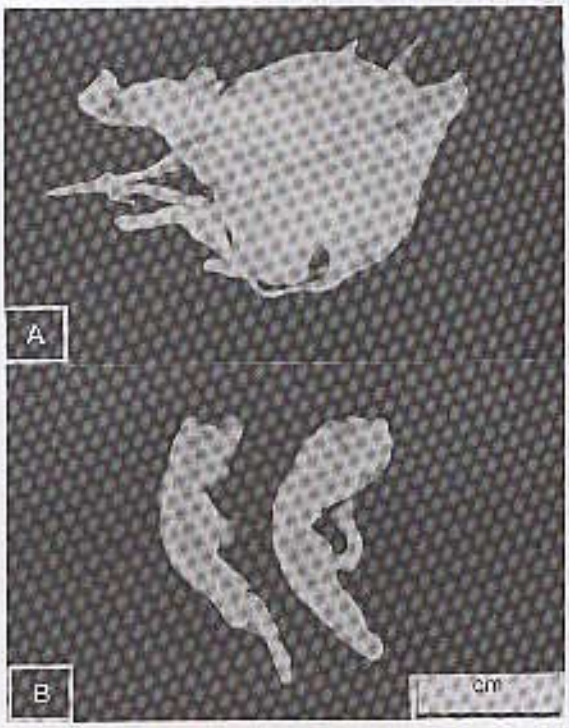

Figure 7. Floppy valve. A) partial specimen of posterior leaflet B) cut surface showing diffuse myxoid change.

inflammatory MR , only the basal- free edge length of the posterior leaflet was significantly longer ($p < .0001$). The mean of the floppy valve' s basal- free edge length was 16.65 mm.

Clinical correlation. Men outnumbered women at a ratio of 3.5:1. Most patients were old aged (age range 40-79, mean 61.72 ± 10.53 years) (Table 5). The mean age of the patients was significantly increased in floppy valve versus post-inflammatory MR. There was no history of endocarditis, other associated congenital heart disease, ischemic heart disease and diabetes mellitus. Four of 18 cases and 7 of 13 cases had hypertension and dyslipoproteinemia, respectively. Nearly 30% of patients had dyspnea for less than one year and 18% for more than 5 years. Atrial fibrillation was present in 3 of 17 cases and

Figure 8. Vegetations on both leaflets (arrows) and chordae causing chordal rupture (arrow head) in a case of infective endocarditis.

left atrial clot was found in only one.

Infective endocarditis

There were five which presented with MR, and one with preexisting MS. The only one with post-IE-MR has endocarditis without microbial existing in surgical specimen. Of 6 IE specimens three were identified as complete specimens with portion of leaflets sent for microbial culture. Diffuse fibrosis and free edge fibrosis were present in 2 and 5 cases, respectively. Diffuse myxoid change and hooding were present in 2 and 1 case, respectively. Commissural fusions were present in 3 and chordal fusion in 5. Four specimens also showed ruptured chordae (2 ruptured anterior leaflet chordae, 2 ruptured posterior leaflet chordae). Calcification was found in 50% of anterior and posterior leaflets (Table 2). Vegetations were present in 5 of 6 patients (83.33%).

Prominent neovascularization, minimal calcification and neutrophilic infiltration were found in most patients. All 6 patients with active infective endocarditis exhibited numerous gram positive cocci from gram stain of surgical specimen except for one MS which displayed only a small amount of microorganism. Two of six cases of active infective en-

docarditis had concomitant aortic valve involvement.

Clinical correlation. Six of 7 patients were male. The mean age was 34.12 ± 10.49 (range 20-50) years. There were no prior histories of rheumatic fever or intravenous drug abuse. Four and two had prior history of infective endocarditis and prolapse valve, respectively. One patient had ASD. There were no histories of diabetes mellitus, hypertension and ischemic heart disease. Dyslipoproteinemia was present in one. Two were smokers and alcohol consumers. There were no prior minor surgical or instrumental procedures. Short duration of dyspnea was the common presenting symptom. Fever was present in 57.14%. Three patients had prior history of positive hemoculture for Streptococcus viridans. The only one post-IE had prior positive hemoculture for Staphylococcus aureus. Of six cases, fresh samples of cardiac valve were sent for microbial culture and all yielded no microbial organism.

Miscellaneous causes (Table 1)

One patient had papillary muscle necrosis, normal mitral morphology but with post-infective endocarditis of aortic valve, ischemic heart disease and hypertension.

One patient who had ruptured necrotic anterolateral papillary muscle at the head, was a 59-year-old man with prior history of myocardial infarct.

Four patients with MR were associated with ASD two of which had prior ASD repair.

One patient had dilated ring without abnormal morphology of mitral valve.

DISCUSSION

Post-inflammatory disease

Post-inflammatory disease (presumably rheumatic fever associated) is the most common cause of MS or MS-MR in those who required mitral valve replacement, as it accounted for 99% to 100% of these mitral valve dysfunctions in most studies[3,4,6] and 100% of MS and MS-MR in the present study. Rare cases of these dysfunctions are congenital lesion, massive annular calcium and metabolic disorder.[7,8] Dare et al reported in their 24 MS-MR patients one case of type VI mucopolysaccharidosis and one case of ergotamine-induced.[9]

MS and MS-MR are the predominant dysfunction in post-inflammatory disease in surgical cardiac valve specimen as it accounted for 83.05% in our study, 74,[10] 85,[4] 87[1] and 93.89%[11] in others. Except for the more incompetent orifice and less posteromedial commissural fusion and calcification in MS-MR, MS and MS-MR had no distinctive gross morphology. In post-inflammatory MR, commissural fusion, chordal shortening and calcification were lessly observed. Prominent neovascularization, prominent chronic inflammatory cell infiltration and even Aschoff bodies were more frequent. Agozzino et al found lymphocytic infiltrates together with papillary muscle myocarditis in 4.41% of their 1,179 post-rheumatic specimens (1.81% of MS and MS-MR, and 44.44% of post-rheumatic pure MR).[11] Granulomatous forms of Aschoff bodies were present in three cases all of whom were negative for blood tests and clinical symptoms of rheumatic fever. The presence of Aschoff bodies in our cases and Agozzino et al's cases might reflect the attack of rheumatic fever at sometime before the excision of the cardiac valves.

The high percentage of prominent calcification in MS, MS-MR specimens did not indicate that the whole population had prominent calcification in this mitral dysfunction. It just indicated that these patients were selected for surgery rather than for balloon mitral valvulotomy. Patients with post-inflammatory MR who required operation were found in younger age group and some might have been diagnosed as floppy valve due to the mitral valve prolapse presentation. There is no explanation why some mitral valves become stenotic and others purely regurgitant.

In most MS, frequent fibrinous deposits were found most commonly in association with disrupted endocardium with calcific deposits underneath. It could be a source for verrucous calcification at the atrial side. However, when they were present with histiocytic reaction underneath without underlying calcification, endocardial injuries including recurrent rheumatic fever episode should also be considered as two of four MR cases with fibrinous deposits but without calcification had Aschoff bodies in

the specimens.

In this study females (57.26%) prevailed males in the overall incidence of surgical cases of mitral valve disease as also noted by others ranging from 68-72%.[1,11,12] Increasing incidence in males was observed in MR (50% of MR reviewed by Olson et al[4] and 55% in the present study). In this study, the age at the time of operation for post-inflammatory MR was younger than for MS or MS-MR while in other studies[5,6] it was not different.

Floppy valve

Morphologically, the floppy valve is characterized by diffuse myxomatous leaflet thickening, redundancy, and annular dilatation. Focal chordal thickening, fusion, abnormal insertion or hooding may be found. Patients may present with chordal rupture as a sudden and serious complication.[13,14] Chordal rupture was present in 22-74% of the excised regurgitant floppy valves from many reports.[3,4,12,14,15] In our study it was found in 83.33% of the floppy valves and occurred at the posterior leaflets two times more often than at the anterior leaflets. Also the redundancy of the valve leaflet was indirectly supported by the present study that the basal-free edge length of the posterior leaflet was significantly longer than that of the post-inflammatory MR. The widening of the basal free edge length of the posterior leaflet could be used grossly to distinguish the floppy valve from the post-inflammatory MR.Coexistent floppy and post-inflammatory changes have been observed in one case by Hanson et al[12] and three cases by Olson et al[4]. We found no such case, although an indeterminate case of probably post-inflammatory MR with redundant posterior leaflet was observed. There was no clinical evidence of prior mitral valve prolapse in this patient.

The floppy valve may occur as an isolated disorder or, less frequently may be associated with other diseases including Marfan syndrome, Ehlers-Danlos syndrome, von Willebrand syndrome and several types of congenital heart disease. In our study, there was no associated disease. The patient's age at the time of operation was much older than that of the post-inflammatory MR cases. The mean ages were 61 years in the present study, 46±17.1,[6] 60,[4] 55,[1] 62.5±13.6,[17] and 49 years[11] in others. It was interesting that post-inflammatory MR in young patients with clinical mitral valve prolapse could have macroscopic appearance indistinguishable from floppy mitral valve. However, microscopic evidence of inflammatory changes including neovascularization and chronic inflammatory infiltrates could help provided that there was no superimposing infective endocarditis which could create some inflammatory change. Due to the declining incidence of rheumatic heart disease in some well developed countries, floppy valve has become a more common underlying disorder in pure MR, occurring in 29% of the 76 cases of Allen et al[16], 32.14% of the 56 cases in the present study, 38% of the 260 cases of Olson et al[4], 46.4% of the 181 cases in 8 years duration of Agozzino et al,[11] 52% of the 61 cases of Hanson et al,[12] and 62% of 97 isolated cases reported by Waller and colleagues.[2]

Contrary to the prevalence of females in general population,[18] the floppy valve with extensive dysfunction by dilatation or flail leaflet from ruptured chordae requiring surgery occurred in more males than females (male : female = 3.5:1 in this study, 3.2:1 in excised and 3.5:1 in repaired specimen by Olson et al,[4] 1.54:1 by Agozzino et al[11] and 2.83:1 by Virmani et al[17]). However, others have reported a prevalence of females (male : female = 0.92:1 in the study of Waller et al[2] and 0.44:1 in the study of Rose).[5]

Infective endocarditis

Similar to other studies, this mitral valve disease was one of the most common causes of MR ranging from 5.15-14.37% of MR group[2,6,11,14] including 10.71% in this study. Males predominated.[2,6,11,14] The preexisting mitral valve diseases included chronic rheumatic disease, floppy valve[11], asymmetrical septal hypertrophy and mitral annular calcification.[19] Our seven cases included 1 post-inflammatory MS without clinical suspicion of IE and one with probably underlying post-inflammatory MR . All cases presented gram positive cocci without positive culture of tissue from cardiac valve. History of endocarditis was present in less than 60%. Prolapsed valve occurred due to destruction of chordae. Histologic diagnosis was the most reliable method if adequate tissue was received.

Papillary muscle dysfunction causing severe MR was rather rare in our study in comparison with 11-30 % of other reports.[2,4,12]

CONCLUSION

Postinflammatory disease (presumably rheumatic fever associated) was the most common surgical mitral valve disease with stenotic and combined stenotic-regurgitation as the most prevalent form. The incidence of floppy valves and infective endocarditis is expected to rise as the incidence of rheumatic fever in this country declines. To study the etiology of the mitral valve disease, the clinical history including associated diseases and previous operation, physical examination, echocardiographic study, operative findings including information about dilatation of valve ring, chordal rupture and concomitant valvular pathology are needed especially in the regurgitant group for which partial resection of the valve may be performed.

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