Pathology and Etiology of 110 Consecutively Removed Aortic Valves

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Objectives : *To study the pathology and determine the etiology and prevalence of aortic valve disease from surgically removed aortic valve specimens.*
Material and Method : *All the native surgically excised aortic valves (AV) received from June 1997 to March 1999 (22 months) were studied macroscopically including cuspal measurements and microscopically. By preoperative echocardiographic and macroscopic studies, they were classified into functional disorders of predominant aortic stenosis (AS), aortic stenosis with regurgitation (AS-AR) and predominant aortic regurgitation (AR). 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 110 AV (76 isolated AV and 34 with concomitant mitral valves from patients aged 15-96 years, mean age 47.54 years; male:female = 1.39:1) there were 25 AS (22.73%), 34 AS-AR (30.91%) and 51 AR (46.36%) cases. Eighty four (76.36%) were tricuspid, 16(14.54%) were bicuspid and 10 were undetermined. Cuspal measurements of each disease were provided and compared. All AS specimens were related to moderate to severe calcification and causes included postinflammatory disease (14 cases, 56%; age range 38-67 years, mean age 53.29years, male:female = 0.56:1), degenerative calcific change (11 cases, 44%, age range 56-76 years, male:female = 1.2:1; mean age 69 years of 5 tricuspid AV and 60.83 years of 6 bicuspid AV). In AS-AR, 29 cases (85.29%; mean age 47.10 years; male:female = 1.23:1) were attributable to postinflammatory disease and 5 cases (mean age 70.20 years; male:female = 1.5:1) to degenerative calcific change. In pure AR, there were 21 cases (age range 15-65 years, mean age 29.76 years) of postinflammatory disease, 14 cases of infective endocarditis(IE) and post IE (age range 20-63 years, mean age 42.21 years; all 10 IE cases contained gram positive cocci), 1 case (age 55 years) of bicuspid calcific change, 8 cases of AV with dilated valve ring, 5 cases of miscellaneous causes and 2 cases of indeterminate etiology. Aschoff bodies were found in 3 AR cases. Four of 18 postinflammatory AS-AR and 4 of 14 postinflammatory disease AR cases had past history of rheumatic fever. One postinflammatory AS also had infective endocarditis from gram positive cocci without clinical sign. Severe degenerative calcific change had a higher incidence of underlying diabetes (3 of 15 cases, 20%), hypertension (8 of 14 cases, 57.14%) and dyslipoproteinemia (9 of 13 cases, 69.23%) in comparison with 3.37% (3/89) for diabetes, 9.09% (8/88) for hypertension and 30.99% (22/71) for dyslipoproteinemia in other AV diseases in combination.*
Conclusion : *The three common causes of severe AV functional disorders were postinflammatory disease (58.18%), degenerative calcific change (15.45%) and IE-postIE (12.72%). Underlying diseases of severe degenerative calcific change included hypertension, dyslipoproteinemia and diabetes.*

Macroscopic and microscopic examinations together with clinical information, echocardiographic findings and operative details are important in evaluating the etiology of valvular diseases especially in severely calcified specimens.

Keywords : *Aortic valve, Cuspal measurements, Postinflammatory disease, Degenerative calcific change, Infective endocarditis.*

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Among the excised native cardiac valves of developed countries, the aortic valves were frequently excised ranging from 63-66% of the whole specimens [1,2]. The prevalence of the etiology of the excised cardiac valves varied according to series[1-8]. 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 socio-economic status it may not be the most common etiology especially in aortic stenosis[2,6,8-10]. Increasing prevalence of degenerative calcific change, infective endocarditis, and diseases causing aortic root dilatation has been observed[5,9].

The authors studied the pathology and the etiology of surgically resected cardiac valve specimens from Siriraj Hospital which is one of the largest hospitals in Thailand with an average of nearly 90,000 inpatients annually. The present study is a part of the native valvular study from surgical specimens of which the simultaneous study of 154 mitral valves has been previously reported[11].

The current study evaluates the macroscopic and microscopic pathology of 110 surgically excised aortic valves according to functional disorders and etiology, and determines the prevalence of each etiology of aortic abnormalities and the correlation with the clinical findings.

Material and Method

All native surgically excised aortic valves (AV) from June 1997 to March 1999 (a 22 month period) were examined. Each was photographed and evaluated for diffuse or focal fibrosis, myxomatous change, free-edge fibrosis, lipid deposit, perforation, indentation and vegetation. The following measurements were recorded for each cusp: 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 calcification. 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 (mild degree), up to (moderate degree) and more than (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 (acute or chronic stage), 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 aortic valve was classified as: 1) postinflammatory disease when there was a chronic noninfectious fibrosing process (diffuse fibrosis with neovascularization) with or without fused commissure(s) resulting in valvular distortion indistinguishable or identical to chronic rheumatic valvular disease, 2) degenerative calcific change when there was increased fibrosis, lipid deposits and calcification predominantly at the cuspal body and basal part without fused commissure(s), 3) infective endocarditis when vegetation with a demonstrable microorganism was present, 4) postinfective endocarditis when there was clinical evidence of infective endocarditis, previously treated but lacking micro-organisms in the specimen, 5) prolapse valve when the cusps showed some degree of myxoid change with redundancy. Those with nonspecific valvular changes included cusps with free edge cord-like thickening or dilated valve ring without diffuse fibrosis or diffuse myxomatous change. Abnormal valves which could not be classified confidently were considered indeterminate types of aortic valve disease.

Functional disorders were determined by clinical information using mainly Doppler echocardiography with or without intraoperative evaluation. Aortic stenosis was diagnosed as mild, moderate, or severe when the aortic valve orifice areas were > 1.5, between 0.8 and 1.5 and < 1.5cm^2, respectively. Aortic regurgitation was graded as mild, moderate or severe by using color Doppler echocardiography. All cases were classified into one of three groups- predominant aortic stenosis(AS), aortic regurgitation(AR) or combined aortic stenosis and regurgitation (AS-AR). For the present study, the mildly regurgitant valves with moderate to severe stenosis were also included in the AS group while those with both stenosis and regurgitation of moderate or severe degree were classified into the AS-AR 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 aortic valve and other related abnormalities, and prior management including cardiac valve surgery.

Statistical Analysis

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

Results

Of 110 aortic valves examined, 76 (69.09%) specimens were isolated cases and 34 (30.91%) had concomitant mitral valves. Twenty nine valves from those with severe calcification or infective endocarditis were received as multiple fragments or incomplete specimens.

Functional classification and etiology

The functional status was AS in 25 cases (22.73%), AS-AR in 34 cases (30.91%) and AR in 51 cases (46.36%) (Table 1).

The etiology of AS was related predominantly to postinflammatory disease (56%) and degenerative calcific change. One postinflammatory AS also had infective endocarditis. Most cases of the AS-AR group were attributed to postinflammatory disease (85.29%) with the remainder related to degenerative calcific change. In the AR group, postinflammatory disease was the most common etiology (41.18%) with the IE and post IE as the next common cause, followed by normal valve with aortic root dilatation.

Postinflammatory disease

This disease accounted for 58.18% of surgically excised aortic valves. The most common functional disorder was AS-AR(29/64, 57.2%) (Table 1). Diffuse fibrosis was found in 85.94 % (55/64) with the free edge fibrosis in all (Table 2). Commissural fusion and prominent calcification were the major findings in postinflammatory AS and postinflammatory AS-AR in comparison with the postinflammatory AR group (97.37% for commissural fusion in postinflammatory AS & AS-AR and 47.05% in postinflammatory AR, $p < .0001$; 79.07% for prominent calcification in postinflammatory AS & AS-AR and 9.52% in postinflammatory AR, $p < .0001$). Neovascularization was found in nearly all cases one third of which exhibited prominent vascularization (Table 3). Chronic inflammatory infiltration was prominent in only 6.25%, absent in 9.38% and focally found in the remainder. Aschoff body of chronic stage was found only in 3 postinflammatory AR (4.69% of all postinflammatory disease). Lipid deposits and basal calcification were rarely found in postinflammatory AR but rather common in postinflammatory AS ($p < .001$). Thrombosis on the surface of the valve or within the calcification areas was found only in postinflammatory AS and postinflammatory AS-AR.

Table 1. Etiologic Diagnosis of Aortic Valve Diseases

Etiology	Functional disorder			Total (% of total)
	AS	AS-AR	AR	
Postinflammatory disease	14 (56%) #	29 (85.29%) *	21 (41.18%) *	64 (58.18%) #
Infective endocarditis		-	10 (19.61%) **	10 (9.09%)[0]
Postinfective endocarditis	-	-	4 (7.84%)	4 (3.64%)
Degenerative calcific change (tricuspid)	5 (20%)	3 (8.82%)	-	8 (7.27%)
Congenital bicuspid	6 (24%) +	2 (5.88%) +	1 (1.96%)	9 (8.18%)
Normal morphology with dilated ring	-	-	8 (15.67%)	8 (7.27%)
Indeterminate	-	-	2 (3.92%)	2 (1.82%)
Miscellaneous	-	-	5 (9.8%)	5 (4.55%)
Total (% of total)	25 (22.73%)	34 (30.91%)	51 (46.36%)	110 (100%)

* including three bicuspids ** including one bicuspid + bicuspids with degenerative change

\# including one case of postinflammatory disease with infective endocarditis

0 excluding the case of postinflammatory disease with infective endocarditis

Table 2. Macroscopic Morphologic Assessment of Various Aortic Valve Diseases

Macroscopic features	Postinflammatory disease						IE		Post IE		Degenerative calcific change						b-AR		Dilated ring AR	
	AS		AS-AR		AR						t-AS & AS-AR			b-AS & AS-AR						
	No/ total	%	No/ total	%	No/ total	%	No/ total	%	No/ total	%	t-AS No/ total	t-AS-AR No/ total	total %	b-AS No/ total	b-AS-AR	total %	No/ total	%	No/ total	%
Complete specimen	11/14	78.57	27/29	93.10	18/21	85.17	4/10	40	2/4	50	2/5	2/3	50	1/6	0/2	12.5	1/1	100	7/8	87.50
Tricuspid	12/14	85.17	25/29	86.21	18/21	85.71	6/10	60	3/4	75	5/5	3/3	100	-	-	-	-	-	7/7	100
Bicuspid	-	-	3/29	10.34	3/21	14.29	-	-	1/4	25	-	-	-	6/6	2/2	100	1/1	100	0/7	-
Undetermined	2/14	14.29	1/29	3.45	-	-	4/10	40	-	-	-	-	-	-	-	-	-	-	1/8	12.50
Free edge calcification	10/14	71.43	11/29	37.93	3/21	14.29	3/10	30	1/4	25	4/5	1/3	62.5	3/6	1/2	50	-	-	3/8	37.50
Cuspal body calcification	14/14	100	20/29	68.97	2/21	9.52	4/10	40	2/4	50	5/5	3/3	100	6/6	2/2	100	1/1	100	2/8	25
Basal calcification	12/14	85.71	11/29	37.93	1/21	4.76	2/10	20	1/4	25	4/5	3/3	87.5	6/6	1/2	87.5	-	-	1/8	12.50
Vegetation	1/14	7.14	-	-	-	-	10/10	100	3/4	75	-	-	-	-	-	-	-	-	-	-
Diffuse fibrosis	11/14	78.57	28/29	96.55	16/21	76.19	3/10	30	1/4	25	2/5	2/3	50	6/6	2/2	100	1/1	100	-	-
Free edge fibrosis	14/14	100	29/29	100	21/21	100	7/10	70	4/4	100	4/5	3/3	87.5	6/6	2/2	100	1/1	100	8/8	100
Myxoid change	-	-	1/29	3.45	5/21	23.81	3/10	30	1/4	25	-	-	-	-	-	-	-	-	4/8	100
Commissural fusion	12/12	100 *	25/26	96.15 •	8/17	47.05 *•	1/2	50	1/2	50	1/5	-	20	0/1	-	-	-	-	1/5	20

t = tricuspid b = bicuspid Symbols • * denote comparison between pairs of diseases with $p < 0.05$

Table 3. Microscopic Morphologic Assessment of Various Aortic Valve Diseases

		Postinflammatory disease						IE		Post IE		Degenerative calcific change			Bicuspid			Dilated ring AR	
		AS		AS-AR		AR													
		No/ total	%	No/ total	%	No/ total	%	No/ total	%	No/ total	%	t-AS	t-AS-AR	Total %	AS	AS-AR	Total %	No/ total	%
Neovascularization	2-3 (+)	5/14	35.71	8/29	27.59	5/21	23.81	1/10	10	-	-	-	-	-	-	-	-	-	-
	rare-1 (+)	9/14	64.29	20/29	68.96	16/21	76.19	8/10	80	4/4	100	2/5	2/3	50	4/6	1/2	62.5	1/8	12.50
	0	-	-	1/29	3.45	-	-	1/10	10	-	-	3/5	1/3	50	2/6	1/2	37.5	7/8	87.50
Chronic	2-3 (+)	2/14	14.29	2/29	6.90	-	-	-	-	1/4	25	-	-	-	-	-	-	-	-
inflammatory	rare-1 (+)	11/14	78.57	24/29	82.76	19/21	90.48	10/10	100	2/4	50	4/5	1/3	62.5	4/6	2/2	75	2/8	25
infiltration	0	1/14	7.14	3/29	10.34	2/21	9.52	-	-	1/4	25	1/5	2/3	37.5	2/6	0/2	25	6/8	75
Aschoff body (chronic stage)		-	-	-	-	3/21	14.29	-	-	-	-	-	-	-	-	-	-	-	-
Calcification	2-3 (+)	14/14	100 •	19/29	65.5 •	2/21	9.52 •	5/10	50	1/4	25	5/5	3/3	100	6/6	2/2	100	-	-
	rare-1 (+)	-	-	10/29	34.48	5/21	23.81	4/10	40	1/4	25	-	-	-	-	-	-	4/8	50
	0	-	-	-	-	14/21	66.67	1/10	10	2/4	50	-	-	-	-	-	-	4/8	50
Lipid deposit		11/14	78.57 *	15/29	55.72	2/21	9.52 *	2/10	20	-	-	5/5	3/3	100	6/6	2/2	100	3/8	37.50
Basal calcification		12/14	85.71 ▲	12/29	41.38	1/21	4.76 ▲	2/10	20	1/4	25	4/4	3/3	100	6/6	2/2	100	3/8	37.50
Thrombosis		5/14	35.71	13/29	44.83	-	-	8/10	80	3/4	75	-	-	-	1/6	0/2	12.5	-	-
PMN infiltration		2/14	14.28	1/29	3.45	-	-	8/10	80	3/4	75	-	-	-	-	-	-	-	-
Bacteria		1/14	7.14	-	-	-	-	10/10	100	0/4	0	-	-	-	-	-	-	-	-

Symbols • * ▲ denote comparison between pairs of postinflammatory AS, AS-AR, AR with $p < 0.05$

Table 4. Measurement of Aortic Cusps in Various Aortic Valve Diseases

		Postinflammatory disease			IE& Post.IE	Degenerative calcific change		Dilated ring AR	Miscellaneous AR
		AS	AS-AR	AR		t-AS	t -AS & AS-AR		
Cuspal length	Range (mm)	13-28	12-28	12-37	15-33	18-28	18-28	18-36	15-40
	Mean (mm)	19.66 + *	19.81 • ◊	24.00 + •	22.77	22.73	22.00	26.48 *◊	25.09
	No.of Cusps	N=37	N=82	N=58	N=26	N=11	N=14	N=22	N=17
	SD (mm)	3.08	34.01	5.03	4.26	3.66	3.64	4.39	6.17
Basal-free edge length	Range (mm)	8-20	5-18	3-15	8-25	7-17	7-17	8-21.7	4-16
	Mean (mm)	13.34 • □	11.13 ◀ □▼	8.70 •◀▲*	14.0 ▲▼	11.75	11.94	12.67 *	11.59
	No.of Cusps	N=39	N=85	N=57	N=26	N=12	N=17	N=22	N=17
	SD (mm)	2.51	3.05	2.85	3.53	3.08	2.61	3.46	3.45
Closing edge thickness	Range (mm)	0.3-7	0.5-8	0.4-7	0.4-5	0.3-4	0.3-4	0.8-2.5	0.3-4.0
	Mean (mm)	2.01 *	2.18 +▲✦	1.80 •	1.29 ▲	1.23	1.72	1.36 +	1.01 • * ✦
	No.of Cusps	N=39	N=81	N=57	N=27	N=13	N=18	N=22	N=18
	SD (mm)	1.61	1.17	1.10	0.92	0.97	2.23	0.49	0.42
Midway thickness	Range (mm)	0.4-8.8	0.5-6	0.3-8	0.5-5	0.6-3	0.6-6.9	0.3-1.2	0.3-3
	Mean (mm)	2.93 ■▶	2.63 ▲▼	2.05 •	1.60 □	1.83	2.88	0.5 ■ • □▼	1.14 ▲ ▶
	No.of Cusps	N=33	N=50	N=38	N=20	N=9	N=13	N=19	N=9
	SD (mm)	2.07	1.25	1.78	1.17	0.89	2.14	0.28	0.93
Basal thickness	Range (mm)	0.3-3.2	0.3-5.0	0.3-2.2	0.3-3	0.3-4.5	0.3-4.5	0.3-2.9	0.2-1.0
	Mean (mm)	1.22 •	1.07	0.97	1.01	1.06	1.0	0.63	0.49 •
	No.of Cusps	N=30	N=48	N=23	N=12	N=9	N=10	N=19	N=7
	SD (mm)	0.92	0.96	0.52	0.91	1.40	1.33	0.67	0.26

Symbols • * ▶ ◀ ▼▲ ■ ✦ + □ denote comparison between pairs of diseases with $p < 0.05$

Measurements of cusps

The mean cuspal circumferential length of each disease is provided in Table 4. The mean cuspal circumferential length of postinflammatory AR was significantly longer than that of postinflammatory AS and postinflammatory AS-AR while its mean basal free edge length was shorter than that of post-inflammatory AS and postinflammatory AS-AR ($p < .000$, each) (Table 4). The postinflammatory AS's and postinflammatory AS-AR's mean cuspal lengths were significantly shorter than that of the AR with dilated ring and postinflammatory AR ($p < .0001$).

The basal-free edge length was significantly longer in postinflammatory AS versus postinflammatory AS-AR ($p = .002$), shorter in postinflammatory AS-AR versus IE-AR ($p = .028$) and shorter in postinflammatory AR versus AR with dilated ring ($p = .002$), IE ($p < .0001$), bicuspid degenerative AS ($p = .010$), and degenerativeAS-AR ($p < .0001$).

There was no significant difference in thickness at various levels between each of the three functional disorders with postinflammatory disease.

The closing edge thickness was significantly increased in postinflammatory AS, postinflammatory AS-AR or postinflammatory AR versus miscellaneous AR ($p = .032$, $p < .0001$, and $p = .0001$, respectively), postinflammatory AS-AR versus AR with dilated ring, and postinflammatory AS-AR versus IE.

The midway thickness was significantly increased in all postinflammatory AV versus AR with dilated ring: postinflammatory AV versus AR with dilated ring ($p < .0001$), postinflammatory AS-AR versus AR with dilated ring ($p < .0001$), versus miscellaneous AR ($p = .034$), postinflammatory AS versus AR with dilated ring ($p < .0001$), versus miscellaneous AR ($p = .025$).

The basal thickness was significantly increased in postinflammatory AS versus miscellaneous AR ($p = .023$).

Clinical correlation

There were equal numbers of males and females with postinflammatory disease. However, females predominated in postinflammatory AS (male:female = 0.56:1) (Table 5). The youngest age at operation was 15 years in AR and the oldest age was 96 in a postinflammatory AS-AR. The mean age at operation of postinflammatory AR was significantly decreased versus that of postinflammatory AS, AS-AR, and AR with dilated ring ($p < .0001$, each), and miscellaneous AR ($p = .016$). Thirty one of 64 postinflammatory cases had concomitant mitral valve replacements. One postinflammatory AS-AR and one postinflammatory AR had prior diagnosis of mitral prolapse. Nearly half of postinflammatory AR had shorter duration of dyspnea (less than 1 year) (Table 5). Past history of rheumatic fever (including those with prophylactic treatment) was present in

Table 5. Demographics and Clinical Study of Aortic Valve Diseases

		Postinflammatory disease			IE & post IE (14)	Degenerative calcific change		Bicuspid AR (1)	Dilated ring AR (8)
		AS (14)	AS-AR (29)	AR (21)		AS (t = 5, b = 6)	AS-AR (t=3, b=2)		
Sex, Male:Female		1:1.8	1:0.81	1:0.91	1:0.27	1:0.83	1:0.67	Male	1:0.6
		0.56:1	(1.23:1)	(1.1:1)	(3.66:1)	(1.2:1)	(1.5:1)		(1.67:1)
Age (years)	range	38-67	22-96	15-65	20-63	t 64-76 b 56-73	64-82	55	28-69
	mean	53.29●	47.10*■✦ □	29.76● *▼▲◇◀	42.21■▼	69.00 ✦ ◇ 60.83	70.20 □◀	-	54.50 ▲
	SD	8.53	13.65	12.09	13.93	4.69 6.31	7.69	-	14.11
Dyspnea	< 1 yr (%)	28.57	18.52	44.44	69.23	36.36	50	-	50
	1-5 yr (%)	42.86	44.44	33.33	30.77	36.36	50	-	37.50
	>5 yr (%)	28.57	37.04	22.22	-	18.18	-	-	12.50
Angina	No/total	1/14	3/29	1/21	-	2/11	0/5	0/1	3/8
	(%)	7.14	10.34	4.76		18.18	0	0	37.5
Fever	No/total	0/14	0/29	2/20	7/14	0/11	0/5	0/1	0/8
	(%)	0	0	10	50	0	0	0	0
Ischemic heart disease	No/total	3/14	2/29	1/21	1/13	5/11	3/5	1/1	1/8
	(%)	21.43	6.89	4.76	7.69	45.45	60	100	12.50
Diabetes	No/total	0/13	2/28	0/20	0/13	3/11	0/4	0/1	0/8
	(%)	0	7.14	0	0	27.27	0	0	0
Hypertension	No/total	1/13	0/28	1/20	1/13	7/10	1/4	1/1	3/8
	(%)	7.69	0	5	7.69	70	25	100	37.5
Dyslipoproteinemia	No/total	3/11	7/23	4/13	3/12	7/9	2/4	1/1	4/7
	(%)	27.27	30.43	30.77	25	77.78	50	100	57.14
Smoking	No/total	2/8	5/14	3/10	4/10	3/6	1/3	0/1	0/6
	(%)	25	35.71	30	40	50	33.3	0	0
Alcohol consumption	No/total	1/7	1/8	3/8	5/8	1/3	0/1	-	4/7
	(%)	14.29	12.50	37.50	62.50	33.33	0		57.14
Vegetation by echocardiogram	No/total	0/14	0/29	0/21	12/14	0/11	0/5	0/1	0/8
	(%)	0	0	0	85.71	0	0	0	0

Symbols ● * ▼ ◀ ▲ ■ ◇ ✦ □ denote comparison between pairs of diseases with $p < 0.05$

25% (4 of 18 postinflammatory AS-AR and 4 of 14 postinflammatory AR) including one AR with Aschoff bodies. All three cases (aged 19, 15, 23 years) with Aschoff bodies had concurrent mitral valve replacement one of which did not have Aschoff body in the mitral specimen. One postinflammatory AS also had infective endocarditis without clinical sign.

Ischemic heart disease, diabetes mellitus and hypertension were rarely associated (9.38%, 3.28% and 3.28%, respectively). Dyslipoproteinemia was present in 29.79% of overall postinflammatory cases.

Atrial fibrillation was found in 15 cases (23.44%), 14 of which were associated with concurrent surgically resected mitral valve diseases (7 mitral stenosis and 6 mitral stenosis with requrgitation). Left atrial clot was present in only 3 cases all of which had concurrent mitral valve abnormalities (1 mitral stenosis and 2 mitral stenosis with regurgitation).

Congenital bicuspid aortic valve

It was present in 16 cases (14.55%) including 6 with postinflammatory disease. Eight presented with degenerative calcific change (6 AS, 2 AS-AR) and the other one with IE. Unequal cusps were present in 7 out of 16 cases with a 0.6-1.6 cm difference in circumferential length. Male predominated in overall bicuspid (2.2:1). Of 8 bicuspid degenerative calcific change, female predominated at a ratio of 1.6:1. The mean age was 62 years (range 56-73, SD = 5.78 years). It was significantly younger than that of tricuspid degenerative calcific change (p = .008). The only one AR case, aged 55 years, had minimal degenerative change with an underlying disease of ischemic heart disease, hypertension and dyslipoproteinemia.

Degenerative calcific change

Tricuspid degenerative calcific change occurred in 7.27% of all specimens (Table 1). For all degenerative disease including bicuspid, complete specimen was achieved in 37.5%; free edge fibrosis was found in 75%. Commissural fusion could be identified in only one out of 5 degenerative tricuspid AS. Neovascularization was present in 50% of all tricuspid degenerative change(Table 3). It was significantly decreased in degenerative AS compared with postinflammatory AS (p < 0.008). Chronic inflammatory cell infiltration was present in 62.5% of tricuspid degenerative change. Lipid deposits were found in all degenerative AS. Prominent calcification was found in all.

Measurements of cusps

There were no significant differences in cuspal length, basal free edge length and thickness at various levels between postinflammatory AS and tricuspid degenerative AS and between postinflammatory AS-AR and degenerative AS-AR.

Clinical correlation

For tricuspid degenerative AS & AS-AR, men outnumbered women at a ratio of 3:1; most patients were old (age range 64-82; mean age = 70.63, SD = 6.39 years).The mean ages were significantly increased in tricuspid degenerative AS, bicuspid degenerative AS, degenerative AS-AR versus posinflammatory AR (p < .0001); tricuspid degenerative AS, degenerative AS-AR versus posinflammatory AS-AR (p = .009 and .004). Most of the patients had dyspnea within less than one year to 5 years.

For all degenerative calcific change, angina was found in only two cases but ischemic heart disease was found in 8 out of 16 degenerative AS & AS-AR (Table 5). The incidence of various underlying diseases was significantly increased in this group versus other non degenerative aortic valve diseases (p = .0006 for ischemic heart disease, p=.024 for diabetes mellitus, p = .0009 for hypertension and p =.002 for dyslipoproteinemia), and also increased when compared with postinflammatory AS & AS-AR (p = .0003 for ischemic heart disease, p = .0001 for hypertension and p = .031 for dyslipoproteinemia).

Infective and postinfective endocarditis

There were 10 IE and 4 post IE presented with AR and one postinflammatory AS with bacteria without clinical sign (overall IE and post IE = 13.64% of AV disease) (Table 1). Of 15 specimens including 1 postinflammatory AS, 7 were identified as complete with portion of leaflets sent for microbial culture. One was bicuspid and six were tricuspid. Free edge fibrosis was present in 80% of cases while diffuse fibrosis was found in one third of specimens (Table 2). Calcification was present at the cuspal body and basal part in 42.86% and 21.43%, respectively. Commissural fusion was present in 3 specimens including one postinflammatory AS. Neovascularization and chronic inflammatory cell infiltration were found in 14 out of 15. Vegetation was present in 13 of 15 cases. Neutrophilic infiltration and fibrin deposits (thrombosis) were present in 60% and 73.33%, respectively. Only 20% of cases did not contain calcification. All the infectious agents

identified in active infective endocarditis were gram positive cocci.

Measurements of cusps

There was no significant difference in circumferential length of this disease versus other AV diseases. Its basal-free edge length was longer than that of postinflammatory AS-AR and post-inflammatory AR ($p = .028$, $p < .0001$). The closing edge thickness was thinner when compared with AS-AR ($p = .007$) and the midway thickness was thicker than that of AR with dilated ring ($p = .019$).

Clinical correlation

Men predominated in this disease (male: female = 3.66:1) (Table 5). The mean age was 42 years and was decreased significantly in IE versus degenerative AS-AR and tricuspid degenerative AS ($p = .001$, $p = .001$). Three patients had concomitant mitral valve resection (21.43%) and one with tricuspid valve resection for the same disease. Fever was present in 7 of 15 patients. There were no prior histories of rheumatic fever or intravenous drug abuse. Nine of 15 patients had a prior history of infective endocarditis. The associated micro-organisms yielded were Streptococcus viridans in 2 patients, others were enterococci, Staphylococcus aureus and coagulase-negative staphylococcus. A small number of patients had dyslipoproteinemia, hypertension and ischemic heart disease (Table 5). No patients had diabetes. There were no prior surgical or instrumental procedures. Vegetation had been demonstrated by echocardiogram in 85.71% of patients while it was noted in 14 out of 15 patients on macroscopic examination. Of 12 fresh samples of cardiac valve sent for microbial cultures, all yielded no microbial growth. The ASO titer was performed from 4 patients, only one from post IE was positive (> 800 IU/L).

Normal valve with aortic root dilatation

There were 8 cases, three of which displayed a mild degree of degenerative calcific change. All cases had free edge fibrosis (cord - like thickening). Mild myxoid change was found in half of the specimens. Five patients were male.The mean age was 51.73 years. Neovascularization was almost absent, only rarely found in one case. The associated diseases included one Marfan's syndrome and one VSD status postrepair. One patient had prior mitral valve replacement and one with AV plasty.

Miscellaneous etiology associated with AR

Four cases showed fibromyxoid change of the cusps. The associated diseases were hypertension, cardiomyopathy, and Marfan's syndrome status post mitral valve replacement. One case had AR due to prolapse cusp with dilated aorta. Non-bacterial thrombotic endocarditis was diagnosed in one case. The two indeterminate cases included one case aged 39 years status post AV repair, with prior history of endocarditis and rheumatic fever but the excised valve revealed only focal fibrosis and myxoid change without any postinflammatory reaction. The other case aged 55 years had indentation of one cusp without inflammatory change but also had a dilated ring.

Discussion

This study required macroscopic morphologic study including measurements of cusps and microscopic examination of the entire specimen to identify histologic features essential for diagnosis of some diseases. Other studies have not used such an intensive examination protocol to examine these specimens. The measurement data could be used as a rough guideline for determining certain dysfunctions and/ or diseases.

The incidence of the three functional disorders of the aortic valves varied. Of 1,221 aortic valves excised at the Mayo Clinic Rochester during 1965-1990, 52% were stenotic, 26% were regurgitant and 21% were both stenotic and regurgitant[6], while in a series of 1,973 excised aortic valves reported by Waller et al, 91% were classified as stenotic (with or without regurgitation) and 19% were purely regurgitant[1]. In the present study, 22.73%, 30.91% and 46.36% of the specimen had AS, AS-AR and AR, respectively. The difference in the incidence of the functional disorders might reflect the more prevalence of some diseases in some countries.

The common etiologies of the AS are post-inflammatory disease, congenital anomalies of cusps (predominantly bicuspid) and degenerative change [1-3,5,9,10]. Other rare causes constituting less than 1% of operatively excised AV include active infective endocarditis[12], homozygous type II hyperlipoproteinemia[13], systemic lupus erythematosus[14], metabolic disease (MPS type I - S[15]), Fabry's disease, ochronosis[16,17] and post-therapeutic[6]. Causes of AS-AR are nearly the same as AS and some reports included the AS-AR to the AS group[18]. Postinflammatory diseases accounted for 16.57-34.75% of excised stenotic aortic valves[2,3,9,10] and 69.48% of

Fig. 1 Fragmented specimen due to heavy calcific deposits precludes definite morphological diagnosis

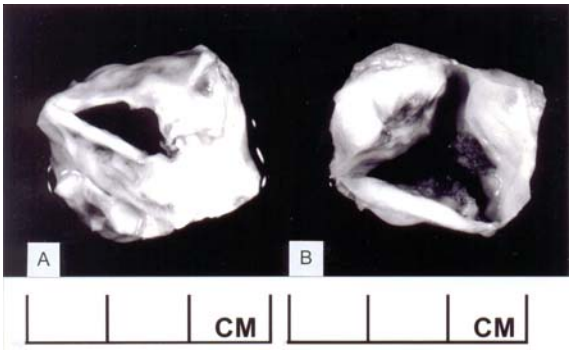

Fig. 2 Diffuse fibrosis, commissural fusion and calcification in postinflammatory AS-AR:
A) Aortic view; B) Ventricular view

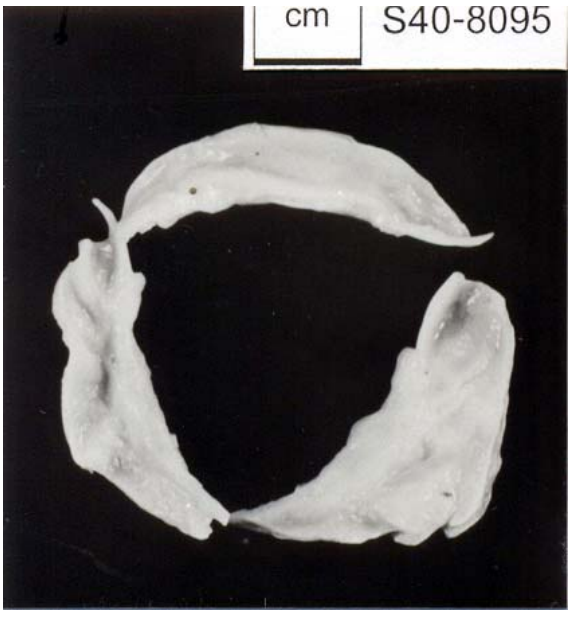

Fig. 3 Tricuspid aortic valve with retracted and diffusely fibrotic cusps from a 38-year-old female with postinflammatory AR

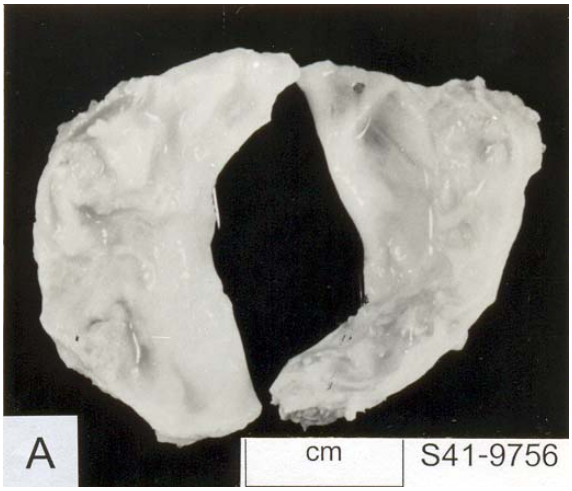

Fig. 4 Bicuspid valves with lipid deposit and calcification:
A) Equal cusps of a 65-year-old female with AS-AR
B) Unequal cusps of a 73-year-old male with AS

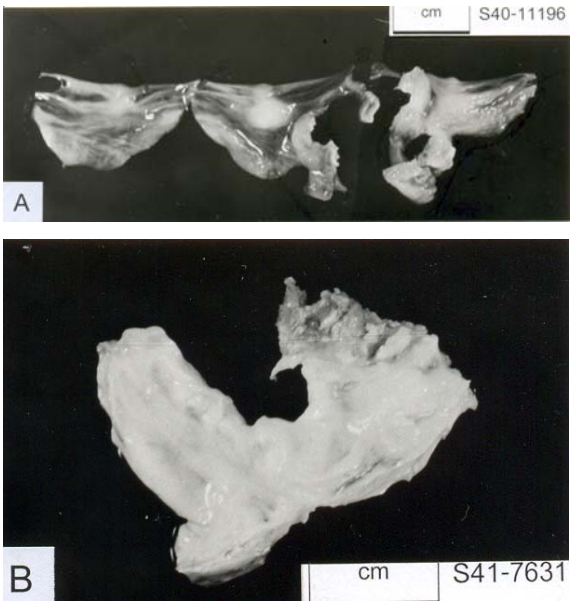

Fig. 5 A) Vegetation with perforation involving adjacent cusps in an apparently normal valve of a 23-year-old man with IE; B) An IE with underlying fibrotic cusp

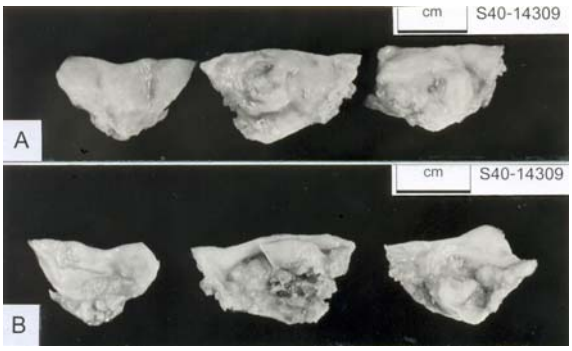

Fig. 6 Heavy calcification with lipid deposits at the cuspal body and basal parts of the aortic valve from an 82-year-old male with degenerative calcific change: A) Ventricular surface; B) Aortic surface

Fig. 7 Apparently normal cusps with free edge cord-like thickening from a 47-year-old female with dilated aortic root from Marfan's syndrome

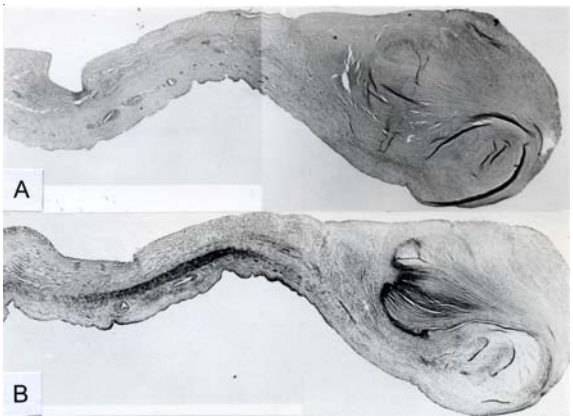

Fig. 8 Diffuse fibrotic thickening and neovascularization in postinflammatory disease A) H&Ex20; B) Elastic stain x 20

AS-AR and 42.34% of excised AS & AS-AR[1]. In the present study, postinflammatory disease (presumably rheumatic fever associated) was the most common etiology in AS (56%) with congenital bicuspid (24%) and degenerative tricuspid (20%) as the remainder. However, in a study of 465 consecutively excised adult aortic valves, Davies et al[8] found that 63.7% of patients had calcific bicuspid valves, 26.9% tricuspid calcifc valves, 5.4% rheumatic, 2.6% mixed pathology and 1.5% unicommissural valves.

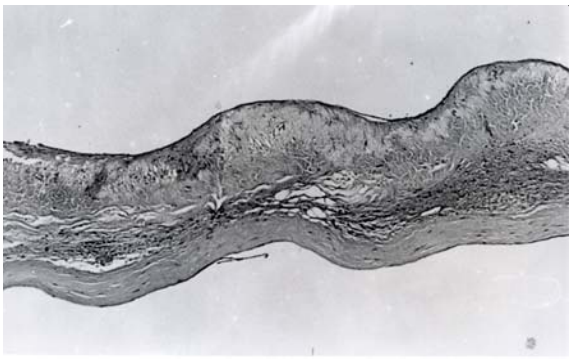

Fig. 9 Early degenerative calcific change: lipid deposit of fibrosa indistinguishable from lipid deposit of vascular wall (H&Ex20)

The etiology of AR is multiple and can be categorized into diseases affecting the valve (post-inflammatory disease, infective endocarditis, congenital bicuspid, floppy valve), diseases affecting the wall of aorta with normal valve (syphilis, Marfan's syndrome aortic dissection, Ehler- Danlos syndrome), diseases affecting both aorta and valve (ankylosing spondylitis) and diseases affecting neither aorta nor valve (ventricular septal defect, systemic hypertension, trauma, subaortic stenosis)[2]. Postinflammatory disease is the most common cause as it accounted for 20-50.26% of excised regurgitant aortic valves in some studies[13,19-21] including 41.18% in the present study. Other common causes were infective endocarditis (9-37%)[1,2,19-23] including 27.45% in the present study, and aortic root dilatation (10.8-31%)[2,19-23] including 15.67% in the present study. The causes of aortic root dilatation were mostly idiopathic and Marfan's syndrome[19-23].

Postinflammatory disease

Postinflammatory disease was the most common cause of AS,AS-AR, and AR in this study leading to an overall prevalence of 58.18% from110 aortic valves, and in Dare et al (36% of 1,221 cases of excised aortic valves)[6]. As also addressed in other studies[6,18,24,25], diffuse leaflet thickening (confirmed by the measurements of cuspal thickness at three levels in this study), free edge fibrotic thickening, commissural fusion and neovascularization are the main pathology in this disease. It was also confirmed by the present study that neovascularization was present in 98.44% of the postinflammatory aortic valve. In addition to the anatomically concomitant involvement of the mitral valve, the presence of commissural fusion is helpful in distinguishing

postinflammatory AS and AS-AR from degenerative AS or AS-AR since vascular channels are also frequently present in the calcified area of degenerative calcific stenosis and may be interpreted as neovascularization. Limitation may have occurred in a case with prominent calcification that the aortic valve cannot be excised as a whole piece but in multiple fragments from which the commissure cannot be identified.

Similar to Dare et al's study[6], there was no sex predilection in the postinflammatory group and the mean age of the postinflammatory AR was younger than any of other dysfunctions. The presence of Aschoff body found only in 3 AR might reflect a rather increased incidence of acute rheumatic attack in younger age group.

Degenerative calcific change

This etiology on tricuspid aortic valve was the third most common cause of excised stenotic aortic valves ranging from 10.16-33.43%[1-3,9,11] including 20% in the present study. Due to marked calcification, only less than half of the specimens could be completely reconstructed. Neovascularization was less frequent in degenerative aortic stenosis compared with postinflammatory AS and commissural fusion may be used to differentiate postinflammatory AS from degenerative AS.

Bicuspid aortic valve is the most frequent malformation of the aortic valve, occurring in 0.4-2% of the population [28,29]. It may have equal or unequal cusps and may exist in two major forms: a right-left and an anterior-posterior position of the two cusps. In a large study of 542 excised bicuspid cases, unequal cusps were present in 95% and a raphe was present in 76% occurring more often in valves with equal-sized cusps[30]. Of those patients undergoing aortic valve surgery, bicuspid aortic valves accounted as underlying malformed valves in 31.52-41.82%in some series [2-4,6,20] and varied from 18.77-55.6% in reported AS or AS & AS-AR[1-4,6,9,10] and 2.70-20% in AR[2,19-23]. The most common pathology of bicuspid valve is calcific stenosis either isolated or in combination with regurgitation (68-85% of cases reported from Mayo Clinic Rochester, Davies and Roberts)[27,29,30]. Moderate to severe calcification affected valves with AS more often than AR while annular dilatation was associated with AR more often than AS. Acquired commissural fusion involved valves with AS-AR more often than the other functional states[30]. Other associated conditions are the frequent occurrence in infective endocarditis and aortic dissection. Bicuspid was present in 12.3% of 408 cases with infective endocarditis reported by Lamas and Eykyn[31] and 42% of 31 cases by Dare et al[6]. The incidence of bicuspid aortic valve in aortic dissection ranged from 7.5-13%[32-34].

The prevalence of overall bicuspid valves in the present study (14.55%) seems to be low with half of the valves related to degenerative calcific change.

Men outnumbered women in degenerative calcific stenosis ranging from 1.6:1 to 1.9:1[6,35] except in one series of 0.76:1[8] and in bicuspid stenosis ranging from 1.4:1 to 3.66:1[6,8,35]. In the present study, males predominated in overall degenerative disorders (tricuspid and bicuspid). Patients of this group were rather old with the mean age at operation in degenerative bicuspid AS lower than in degenerative tricuspid AS[6,35]. It was also confirmed in the present study, that the mean age at operation of the bicuspid degenerative AV was significantly younger than that of the tricuspid degenerative AV.

The incidence of ischemic heart disease, diabetes mellitus, hypertension and dyslipoproteinemia was significantly increased in degenerative aortic valve in comparison with overall nondegenerative aortic valve diseases. Recently, there have been some epidemiological clinical studies showing that the risk factors for arterial atherosclerosis - male sex, smoking and raised serum cholesterol are similar to the risk factors associated with the development of calcific aortic stenosis and experimental studies have supported the hypothesis that the development of aortic valve calcification is similar to that of vascular calcification[36-38].

Infective and postinfective endocarditis

The aortic valve is the valve most commonly affected by fatal infective endocarditis[39]. In the present study, the incidence of aortic valve with IE was rather high in comparison with mitral valve with IE studied in the same period (13.64% versus 4.54%)[11]. It rarely presented with aortic stenosis. The incidence of IE in AR varied from 9.33 - 33.52%[2,19-23,26,35]. Males predominated as in other studies[20,40]. The mean age varied from 39-48 years[20,40]. The incidence of aortic valves with concomitant mitral valves involved by IE was 18.64-25.74%[26, 40] including 21.43% in the present study. Streptococci and staphylococci were the most frequently cultivated microorganisms as in other reports[31,40] and not associated with drug abuse. The preexisting aortic valve diseases included aortic valve prolapse, bicuspid aortic valve, annuloaortic ectasia and postinflammatory disease[20,41].

Conclusion

Similar to the concurrent study of excised mitral valve disease, postinflammatory disease (presumably rheumatic) was also the most common cause of the excised aortic valves. The incidence of degenerative calcific change (including congenital bicuspid anomaly), infective endocarditis and aortic root dilatation is expected to rise as the incidence of rheumatic fever in this country declines. To determine the etiology of an excised cardiac valve, careful examination of the excised valves, the preoperative diagnosis including clinical symptoms, associated diseases, prior history of treatment and operation, echocardiographic study, operative findings including information about number of cusps, commissural fusion, dilatation of valve ring, and concomitant abnormality of mitral valve and aorta are needed especially in the severely calcified aortic valve.

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พยาธิวิทยาและสาเหตุของความผิดปกติของลิ้นหัวใจเอออร์ติก ที่ได้รับการผ่าตัด จำนวน 110 ราย

เตือนใจ ช่วงสุวนิช, มาลี วรรณิสสร, พ.ต.ต.(หญิง) ปิยะวดี เล็กศรีสกุล, พันธุ์ศักดิ์ ลักษณบุญส่ง, ปุณณฤกษ์ ทองเจริญ, ยงยุทธ สหัสกุล

วัตถุประสงค์ *: เพื่อศึกษาพยาธิสภาพ สาเหตุของความผิดปกติและอัตราการเกิดโรคของลิ้นหัวใจเอออร์ติก จากลิ้นหัวใจที่ได้จากการผ่าตัด*

วัตถุและวิธีการ *: ได้ทำการศึกษาลิ้นหัวใจเอออร์ติก ที่ได้รับการผ่าตัดในโรงพยาบาลศิริราชในช่วงมิถุนายน 1997 ถึง มีนาคม 1999 (22 เดือน) โดยการตรวจพยาธิสภาพด้วยตาเปล่าและด้วยกล้องจุลทรรศน์, และแบ่งประเภทการทำงานผิดปกติของลิ้นหัวใจโดยอาศัยการตรวจ echocardiography ก่อนผ่าตัด และลักษณะพยาธิสภาพด้วยตาเปล่าออกเป็น aortic stenosis(AS), aortic regurgitation(AR) และ aortic stenosis with regurgitation(AS-AR)*

ข้อมูลทางคลินิกของผู้ป่วยได้จากการซักประวัติ,สืบค้นและรวบรวมจากเวชระเบียน การจำแนกสาเหตุของโรคอาศัยข้อมูลการตรวจทางพยาธิสภาพทั้งด้วยตาเปล่าและด้วยกล้องจุลทรรศน์ร่วมกับประวัติและการสืบค้นที่สำคัญในทางคลินิก

ผล *: จาก ลิ้นหัวใจเอออร์ติก 110 ราย (รวม 34 รายที่ได้รับการผ่าตัดที่ลิ้นหัวใจไมตรัลด้วย) ของผู้ป่วยอายุตั้งแต่ 15-96 ปี อายุเฉลี่ย 47.54 ปี เป็นชาย:หญิง = 1.39:1 พบเป็น AS 25 ราย(22.73%), AS-AR 34 ราย(30.91%), และ AR 51ราย(46.36%); 76.36% เป็นชนิด tricuspid, 14.54% เป็นชนิด bicuspid; พบว่าASทุกรายมีหินปูนเกาะเด่นชัด สาเหตุที่สำคัญได้แก่ postinflammatory disease ซึ่งส่วนใหญ่เกิดจาก rheumatic fever (14 ราย, 56%; อายุตั้งแต่ 38-67 ปี อายุเฉลี่ย 53.29 ปี ชาย:หญิง = 0.56:1) และdegenerative calcific change(11 ราย, 44%, ซึ่ง 5 ราย เป็นชนิด tricuspid มีอายุเฉลี่ย 69 ปี และ 6 รายเป็นชนิด bicuspid มีอายุเฉลี่ย 60.83 ปี) AS-AR ที่เกิดจาก postinflammatory disease พบ 29 ราย(85.29%, อายุเฉลี่ย 47.10 ปี ชาย:หญิง = 1.23:1) ที่เหลืออีก 5 ราย อายุเฉลี่ย 71.20 ปี เกิดจาก degenerative calcific change. ส่วน AR เกิดจาก postinflammatory disease 21 ราย (21.51%, อายุเฉลี่ย 29.76 ปี), infective endocarditis 14 ราย (อายุเฉลี่ย 42.21ปี, 10 ราย พบแบคทีเรียชนิดกลมกรัมบวก), ความผิดปกติแต่กำเนิดชนิด bicuspid ร่วมกับความเสื่อม 1 ราย, dilated aortic root (ลิ้นหัวใจปกติ) 8 ราย, สาเหตุอื่นๆ 5 ราย และไม่ทราบสาเหตุแน่นอน 2 ราย. พบ Aschoff body(chronic stage) ใน AR 3 ราย. ผู้ป่วย postinflammatory AS-AR 4 ใน 18 ราย และ postinflammatory AR 4 ใน 14 รายมีประวัติเดิมของ rheumatic fever มาก่อน. พบเชื้อแบคทีเรียกลมกรัมบวกใน postinflammatory AS อยู่เดิม 1 ราย โดยไม่ปรากฏอาการ. จากการศึกษาประวัติร่วมด้วย พบว่า degenerative calcific change มีอุบัติการของโรคเบาหวาน (3 ใน15 ราย, 20%), ความดันโลหิตสูง (8 ใน11 ราย, 57.14%) และไขมันในเลือดสูง (9 ใน 13 ราย,69.23%) ร่วมด้วย สูงกว่าในโรคลิ้นหัวใจเอออร์ติกชนิดอื่น ๆ ซึ่งพบโรคเบาหวานร่วมด้วย 3.37% (3 ใน 89 ราย), ความดันโลหิตสูง 9.09% (8ใน 88 ราย) และไขมันในเลือดสูง 30.99% (22 ใน 71 ราย)*

สรุป *: พบว่าสาเหตุที่พบบ่อยของโรคลิ้นหัวใจเอออร์ติก ที่จำเป็นต้องได้รับการผ่าตัด ได้แก่ postinflammatory disease (58.18%), degenerative calcific change(15.45%), infective endocarditis (12.72%) และ dilated aortic root (7.27%). ผู้ป่วย degenerative calcific change จะมีอุบัติการณ์ของโรคเบาหวาน ความดันโลหิตสูง และโรคไขมันในเลือดสูงมากกว่าโรคอื่น ๆ การประเมินหาสาเหตุของโรคลิ้นหัวใจเอออร์ติกจำเป็นต้องอาศัยข้อมูลประวัติ การตรวจทางคลินิก ผลการตรวจทาง echocardiography และลักษณะที่ตรวจพบจากการผ่าตัด โดยเฉพาะอย่างยิ่งในรายที่มีหินปูนเกาะมากจนไม่สามารถผ่าตัดได้ชิ้นส่วนของลิ้นหัวใจที่สมบูรณ์*