

Congenitally Bicuspid Aortic Valves: A Surgical Pathology Study of 542 Cases (1991 Through 1996) and a Literature Review of 2,715 Additional Cases

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• **Objective:** To describe a clinicopathologic study of a large group of congenitally bicuspid aortic valves surgically excised at a single institution.

• **Material and Methods:** The medical charts and bicuspid valves from patients undergoing aortic valve replacement at Mayo Clinic Rochester between 1991 and 1996 were retrospectively reviewed.

• **Results:** The age of the 542 patients ranged from 1 to 86 years (mean, 61), and 372 (69%) were men. Among these, 409 (75%) had pure aortic stenosis (AS), 73 (13%) had pure aortic insufficiency (regurgitation) (AI), 53 (10%) had combined AS and AI, and 7 (1%) had normal function. The mean age was higher for those with AS than AI (65 versus 46 years; $P < 0.001$), whereas the male-to-female ratio was higher for AI than AS (17.3:1 versus 1.7:1; $P < 0.001$). The two cusps were not equal in size in 95%, and a raphe was present in 76% (67% typical, 9% atypical). Raphal position was described in 315 and was between the right and left cusps in 270 (86%). Raphal absence occurred more often in valves with equal-sized

cusps than unequal (33% versus 14%; $P = 0.005$). Moderate to severe calcification affected valves with AS more frequently than AI (99% versus 41%; $P < 0.001$). In contrast, annular dilatation was associated with AI more than AS (48% versus 11%; $P < 0.001$). Acquired commissural fusion involved valves with combined AS and AI more often than the other functional states (31% versus 14%; $P = 0.002$). Sixteen patients (age range, 18 to 78 years; 13 men) had infective endocarditis (6 active, 10 healed), including 10 with AI (9 men), 3 with AS plus AI, 2 with AS, and 1 with normal function but embolization.

• **Conclusion:** Functionally, the most common fate of congenitally bicuspid aortic valves was calcific stenosis with or without regurgitation (85%). Because approximately 4 million US citizens have bicuspid valves and because valve replacement is currently the only treatment of symptomatic AS, this disorder will continue to affect health-care costs.

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Congenitally bicuspid aortic valves occur in 1 to 2% of the general population and thereby affect approximately 4 million US citizens.^{1,2} Their usually normal function at birth belies the fact that most will become progressively stenotic or regurgitant as the ravages of mechanical stress, degenerative calcification, and infection take their toll, and eventually surgical intervention will be necessary. The current study was undertaken to evaluate quantitatively a large number of bicuspid aortic valves that were excised at a single institution, as a continuation of our ongoing investigation of the surgical pathology of valvular heart disease.³⁻¹³

METHODS

Study Group

Patients at Mayo Clinic Rochester were identified in whom a surgical pathology diagnosis of a congenitally

bicuspid aortic valve was made between Jan. 1, 1991, and Dec. 31, 1996. Valves were obtained from the institutional tissue registry and were reviewed by the authors (H.Y.S., W.D.E., and H.D.T.), as described previously from this institution.^{3-5,7,8,12} Of the 550 valves, 8 were reinterpreted as nonbicuspid; thus, the study group consisted of 542 valves. In 510 (97%) of 524 cases (data unavailable in 18), the valve had been excised in one or two pieces, such that recognition of a congenitally bicuspid state was readily apparent. All statistical analyses involved a comparison of two groups by using the χ^2 test.

Clinical Information

For each case, patient age (at operation) and gender, functional state of the valve (as determined by the most recent preoperative echocardiogram or cardiac catheterization and by intraoperative assessment), and the two cusps described by the surgeon as congenitally fused were obtained from the medical record. For patients with infective endocarditis, the activity and causative organism were recorded, if known. In patients who had previously undergone an aortic valve reparative procedure, the surgical date

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Table 1.—Age and Gender Versus Functional State of 542 Surgically Excised Congenitally Bicuspid Aortic Valves (1991-1996)*†

Functional state	Cases		Age (yr)		Gender		
	No.	%	Mean	Range	M	F	M:F ratio
Pure AS	409	75	65	1-86	257	152	1.7:1
Pure AI	73	13	46	5-81	69	4	17.3:1
AS and AI	53	10	51	1-83	42	11	3.8:1
Normal	7	1	47	20-66	4	3	1.3:1
Total	542		61	1-86	372	170	2.2:1

*AI = aortic insufficiency (regurgitation); AS = aortic stenosis.

†From 1,877 surgically excised aortic valves, of which 542 (29%) were bicuspid (see Table 3 for percentages by functional state).

and preoperative valve function were listed. Only moderate or severe degrees of valvular dysfunction were recorded. There were four functional categories: pure stenosis, pure regurgitation, combined stenosis and regurgitation, and normal function.

Pathology Information

Data were collected for 524 (97%) of the 542 valves (18 valves had been sectioned for microscopy or were no longer available). A raphe was designated as present or absent and, if present, was characterized as typical or atypical (that is, fenestrated or cordlike). If marked calcification obscured its presence, the state of the raphe was considered indeterminate.

Cusps were inspected with regard to relative size. Valves with two cusps of similar size were designated as "equal," and those with a conjoined cusp twice the size of its nonconjoined cusp were categorized as "thirds." All other pairs of cusps were considered "unequal" in size.

The extent of valvular calcium was categorized semiquantitatively as either absent to mild or moderate to severe. Both true commissures were inspected for the presence or absence of acquired fusion. Annular dilatation was recorded if the measured diameter of the specimen exceeded 3.5 cm. For valves with infective endocarditis, the number and size of all perforations, the state of the process (active or healed), and the type of organism were recorded.

RESULTS

Relationship of Age and Gender to Functional State

Of the entire group of 542 patients, ages ranged from 1 to 86 years (mean, 61), and 69% were men (Table 1). Clinically, 85% of the valves were stenotic, either alone or in combination with regurgitation. The mean age at operation was significantly higher for patients with pure stenosis

than with pure regurgitation (65 versus 46; $P < 0.001$) (Fig. 1). In contrast, the ratio of male to female patients was 10-fold higher for those with pure regurgitation than pure stenosis (17.3:1 versus 1.7:1; $P < 0.001$). Seven valves with normal function or only mild stenosis or regurgitation were removed surgically (five during repair of an ascending aortic aneurysm, one with noninfective thrombotic endocarditis, and one with enterococcal endocarditis and embolization).

Congenital Raphe and Relationship to Cusp Size

A congenital raphe was identified along the midportion of the conjoined cusp in 76% and was typical in 353 and atypical in 46 (Table 2; Fig. 2). The position of the raphe was listed in 315 (60%) of 524 cases and was between the right and left cusps in 270 (Fig. 3).

The two cusps were unequal in size in 92% of 524 cases (Table 3; Fig. 3 and 4). Of the 484 cases with unequal-sized cusps, the raphe was typical in 327, absent in 66, atypical in 43, and indeterminate in 48. In contrast, among the 27 valves with equal-sized cusps, the raphe was typical in 16, absent in 9, atypical in 1, and indeterminate in 1. Thus, a raphe was absent in 33% of valves with equal-sized cusps but in only 14% with unequal-sized cusps ($P = 0.005$).

Acquired Features and Relationship to Functional State

Acquired commissural fusion was observed in 83 of 524 cases and affected 31% of valves with combined stenosis and regurgitation in contrast to only 14% with the other three functional states ($P = 0.002$) (Table 3; Fig. 5). Moderate to severe calcification was detected in 468 of 524 valves and affected 99% of the valves with pure stenosis but only 41% with pure regurgitation ($P < 0.001$) (Table 3). Annular dilatation, as defined for this study, was present in 98 of 524 cases and occurred in 48% of the valves with

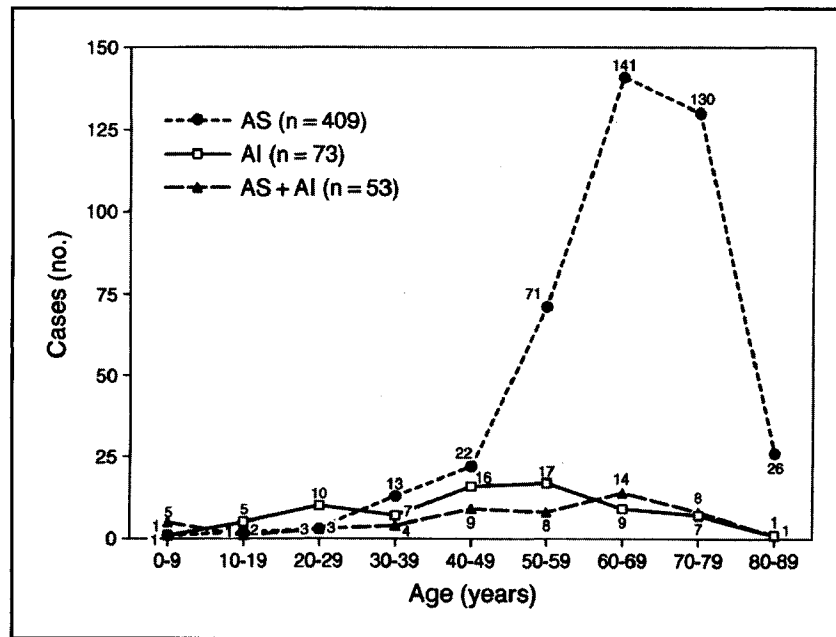


Fig. 1. Age (by decades) versus functional state of 535 congenitally bicuspid aortic valves (data for the 7 normally functioning valves are not shown). AI = aortic insufficiency (regurgitation); AS = aortic stenosis.

pure regurgitation but in only 11% with pure stenosis ($P < 0.001$) (Table 3; Fig. 6).

Infective Endocarditis

Among all 542 patients, 16 (3%) had infective endocarditis; the age range was 18 to 78 years (mean, 52), and 13 (81%) were men. Infection was associated with pure regurgitation in 10, combined stenosis and regurgitation in 3, pure stenosis in 2, and normal function with systemic embolization in 1. Of those with pure regurgitation, 90% were men.

The infecting organism was known in seven patients: *Staphylococcus aureus* in two, viridans streptococci in two, *S. epidermidis* in one, enterococcus in one, and group G streptococcus in one. The infection was active in 6 and healed in 10 (Fig. 7). Nine valves had perforations that were 1 to 10 mm in diameter (eight healed, one active; seven with one hole, two with two).

Associated Abnormalities

Of the 542 patients, 61 (11%) clinically had aortic root dilatation, an ascending aortic aneurysm, or an acute as-

Table 2.—Raphal Features Versus Functional State of 524 Surgically Excised Congenitally Bicuspid Aortic Valves (1991-1996)*†

Functional state	No. of specimens				Presence of raphe				Position of raphe‡				
	1	2	3	≥4	Typical	Atypical	Absent	Indeter	R-L	R-P	L-P	Absent	Unkown
Pure AS	57	332	9	1	279	34	52	34	207	27	5	52	108
Pure AI	13	51	2	0	37	8	13	8	38	4	0	13	11
AS and AI	16	34	1	1	32	3	10	7	22	4	3	10	13
Normal	1	6	0	0	5	1	1	0	3	2	0	1	1
Total	87	423	12	2	353	46	76	49	270	37	8	76	133
Percent	17	81	2	<1	67	9	15	9	52	7	2	15	25

*AI = aortic insufficiency (regurgitation); AS = aortic stenosis; Indeter = indeterminate.

†Data not available for 18 of the 542 cases.

‡See Figure 3 for explanation of abbreviations.

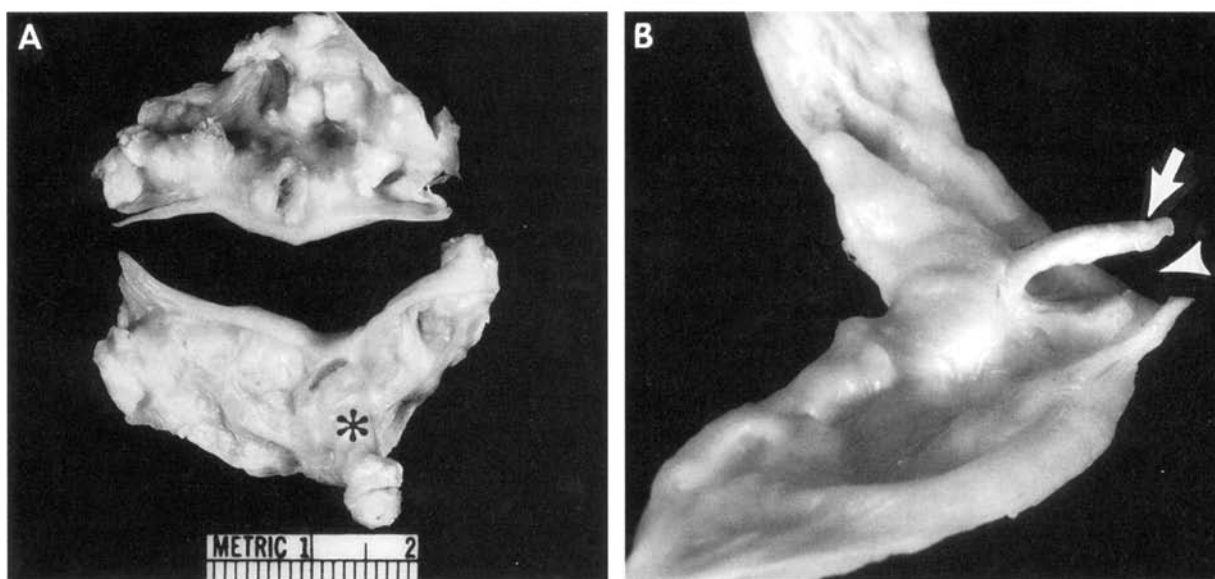


Fig. 2. Typical and atypical raphes. *A*, Calcified typical raphe (*) in valve with pure stenosis. *B*, Atypical raphe showing large fenestration (arrowhead) and residual cordlike raphe (arrow; conjoined cusp viewed obliquely), associated with pure regurgitation.

ending aortic dissection. Among this group, the age range was 2 to 81 years (mean, 56), and 49 (80%) were men.

In 17 patients, cystic medial degeneration was identified microscopically in ascending aortic tissue removed at the time of aortic valve replacement. The age of the patients ranged from 17 to 71 years (mean, 50), and 14 (82%) were men. The process was moderate to severe in eight patients, and it was mild in nine (three and four of whom had ascending aortic dilatation or aneurysm, respectively).

Eight (1.5%) of the 542 patients had congenital coarctation of the aorta. Their ages ranged from 7 to 64 years (mean, 36), and five (63%) were men. A 35-year-old woman had the Turner syndrome, and a 7-year-old boy had the Shone syndrome. All eight bicuspid aortic valves had unequal-sized cusps, of which six were stenotic, one was regurgitant, and one was functioning normally.

A 29-year-old woman had the Marfan syndrome, an ascending aortic aneurysm, and a normally functioning bicuspid aortic valve. A 15-year-old boy had the Bardet-Biedl syndrome.

Finally, as a coincidental occurrence, 17 (3%) of the 542 patients had a past history of rheumatic fever. Their ages ranged from 40 to 77 years (mean, 60), and 10 (59%) were men. Functionally, their bicuspid aortic valves were stenotic in 12, both stenotic and regurgitant in 3, and normal in 2. Chronic rheumatic disease had presumably contributed to valve dysfunction.

Aortic Valve Dysfunction at Birth

Among the 542 patients, 16 (3%) had congenitally bicuspid aortic valves that were stenotic at birth. Their ages ranged from 1 to 20 years (mean, 12), and 14 (88%) were male. Thirteen had undergone reparative aortic valvuloplasty (surgical in 9 and balloon in 4) 1 to 20 years before valve replacement. At the time of replacement, 7 of the 16 valves had pure regurgitation, 6 had combined stenosis and regurgitation, 2 had pure stenosis, and 1 had normal function (a 20-year-old woman undergoing repair of an ascending aortic aneurysm and aortic coarctation).

DISCUSSION

Information dealing with bicuspid aortic valves is available from autopsy studies, surgical pathology series, and clinical investigations, for a total of 2,715 cases.^{1-5,7,8,12,14-50} Two unusual features of the current investigation are the extensive quantitative data for a large number of surgical cases from a single institution and the tabulation of pertinent data from other studies on bicuspid valves.

Surgical Frequency of Bicuspid Valves

The frequency of bicuspid valves in patients undergoing aortic valve replacement has varied substantially among individual reports (Table 4). It has been remarkably constant, however, in combined series, with bicuspid valves accounting for 28% of resected aortic valves worldwide (2,181 of 7,746; Table 4), 29% in the current study (542 of

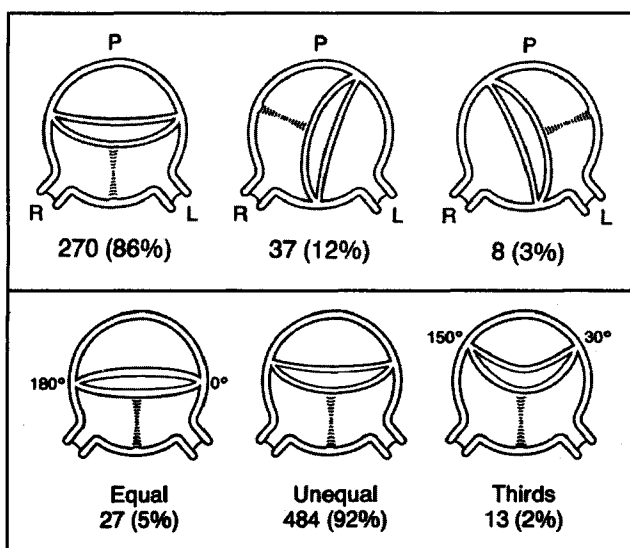


Fig. 3. Variations in bicuspid valves. *Top*, Relative positions of raphe and conjoined cusp in 315 bicuspid aortic valves. *L* = left cusp; *P* = posterior cusp; *R* = right cusp. *Bottom*, Relative cusp sizes in 524 valves (data unavailable in 18 of 542 cases).

1,877; Table 1), and 31% in North America (1,812 of 5,931, including the current study^{3-5,8,12,22,23,25}).

Patient Age and Gender

Although the age range has been considerable, the mean age at operation was similar in two large surgical series: 60 years (range, 1 to 86) for 931 patients in the combined Mayo Clinic studies and 62 years (range, 21 to 86) for 291 Canadian patients described by Walley and associates.²⁵

Bicuspid valves occur in men 2 to 3 times more frequently than in women. Men accounted for 72% (61 of 85) in one autopsy series² and, among surgical series, for 72% (670 of 931) in the combined Mayo Clinic studies, 72% (58

of 81) reported by Turri and colleagues,²⁰ 67% (99 of 148) by Sadee and coworkers,⁴⁹ and 62% (181 of 291) by Walley and associates.²⁵

In the current investigation, the mean age was significantly higher for patients with pure stenosis than pure regurgitation (65 versus 46; $P < 0.001$). Similarly, in other surgical studies of bicuspid aortic valves, the mean age at operation for patients with pure stenosis has ranged from 59 to 67 years, with an overall mean of 63 (Table 4), whereas the mean age at operation for those with pure regurgitation has ranged from 38 to 54 years, with an overall mean of 46.

Morphologic Variants of Bicuspid Valves

Although all bicuspid valves consist of two cusps, tremendous variation exists between individual valves based on differences in relative cusp size, raphe size and structure, and secondary features such as calcification, fibrosis, myxomatous degeneration, annular dilatation, and commissural fusion. In the current investigation, the two cusps were not of equal size in 95% overall and in 95% of stenotic valves. This differs greatly from reports of unequal-sized cusps in only 30% of 104 stenotic bicuspid valves described by Davies²⁶ and 14% of 28 stenotic bicuspid valves by Bacon and Matthews.¹⁴ Nonetheless, the current percentages are similar to echocardiographic observations of unequal-sized cusps in 85% of 28 cases reported by Brandenburg and coworkers.³³

A fibrous ridge (or raphe), representing the site of congenital fusion between the two components of the conjoined cusp, can be identified in about 75% of bicuspid valves (range, 59 to 88%); it may be tall or short and can be solid or fenestrated.^{3-5,26,29} The site of the raphe was described in 713 bicuspid valves in 10 studies; in each, the right and left cusps were most commonly conjoined, accounting for 45 to 91% in individual reports and 76% overall (Table 5). In the current study,

Table 3.—Pathologic Features Versus Functional State of 524 Surgically Excised Congenitally Bicuspid Aortic Valves (1991-1996)*†

Functional state	Cusp size			Fused commissures			Calcification‡		Annular dilatation	
	Equal	Unequal	Thirds	One	Both	None	Present	Absent	Present	Absent
Pure AS	21	369	9	45	12	342	395	4	43	356
Pure AI	5	58	3	8	1	57	27	39	32	34
AS and AI	1	50	1	13	3	36	44	8	21	31
Normal	0	7	0	1	0	6	2	5	2	5
Total	27	484	13	67	16	441	468	56	98	426
Percent	5	92	2	13	3	84	89	11	19	81

*AI = aortic insufficiency (regurgitation); AS = aortic stenosis.

†Data not available for 18 of the 542 cases.

‡Present = moderate to severe; Absent = none to mild.

a raphe was absent in 33% of the valves with equal-sized cusps but in only 14% with unequal-sized cusps ($P = 0.005$).

Atypical bicuspid valves, characterized by a fenestrated raphe, were first described by Carter and associates³⁴ in 1971. The raphe remnant may consist of only cordlike or bandlike structures (type A) or may contain both cords and an underlying shallow raphe ridge (type B).²⁵ In 17 cases reported by Walley and colleagues²⁵ and 46 cases in the current investigation, the age of patients ranged from 45 to 76 years (mean, 63) and from 18 to 81 years (mean, 61), respectively, and 15 (88%) and 35 (76%) were men, respectively. For these 63 cases plus 11 atypical valves from three previous Mayo Clinic studies,³⁻⁵ valve function was stenotic in 43 (58%), regurgitant in 27 (36%), stenotic and regurgitant in 3 (4%), and normal in 1 (1%). Thus, in comparison with all patients who have bicuspid aortic valves, those with the atypical variant were similar in age but included a higher percentage of males and a higher frequency of pure regurgitation. *Acute* aortic regurgitation can result from spontaneous rupture of the raphe, particularly if it forms only a single cord attached along the free edge of the cusp.²⁵ This occurrence has been reported in at least five patients.^{4,25,34-36}

Associated Conditions

Patients with congenitally bicuspid aortic valves tend to have cystic medial degeneration and an inherently weaker ascending aorta in comparison with normal persons.^{1,32,37} Accordingly, they are prone to the development of dilatation of the valve annulus and dilatation, aneurysm, dissection, or rupture of the ascending aorta, regardless of the functional state of the valve.^{38,39} In the current study, these conditions affected the ascending aorta in 61 (11%) of the 542 patients.

Of 1,407 patients with bicuspid valves in eight studies, an acute aortic dissection had also occurred in 35 (2.5%) (Table 6). From another perspective, among 347 patients with aortic dissection in two autopsy studies, bicuspid valves were observed in 32 (9%), about 6 times their incidence in the general population.^{1,32} Their function before dissection had been normal in 19, stenotic in 10, and regurgitant in 3. In these two studies, the risk of aortic dissection was related to the bicuspid state (and a

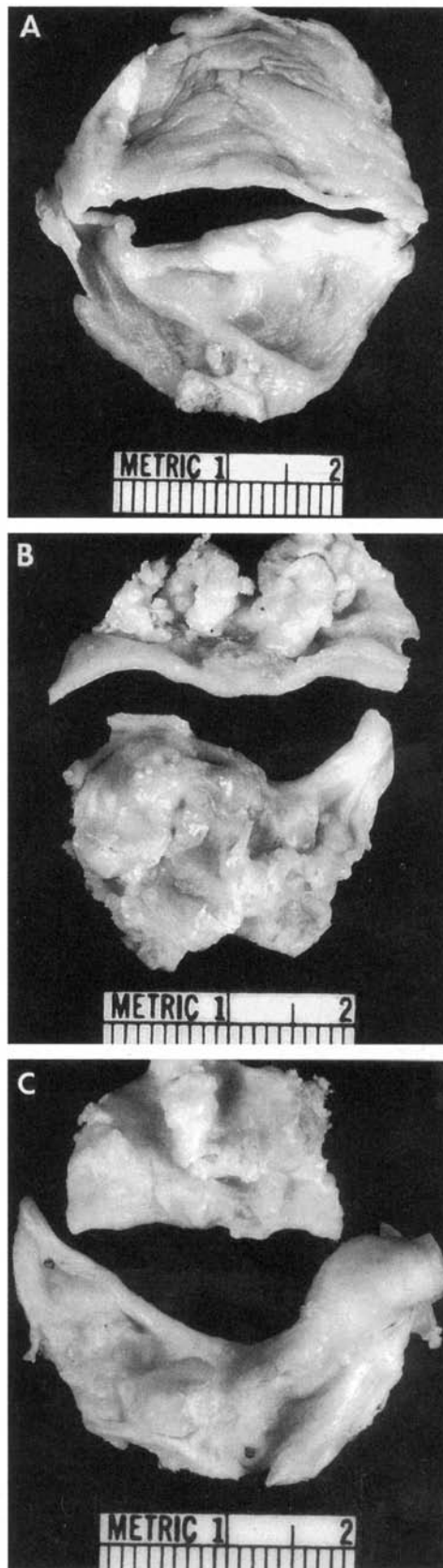


Fig. 4. Variations in relative cusp sizes. A, Equal-sized cusps, in valve with pure regurgitation and no raphe. B, Unequal-sized cusps, in heavily calcified valve with pure stenosis. C, Thirds (conjoined cusp is twice as large as nonconjoined cusp), in markedly calcified valve with combined aortic stenosis and regurgitation.

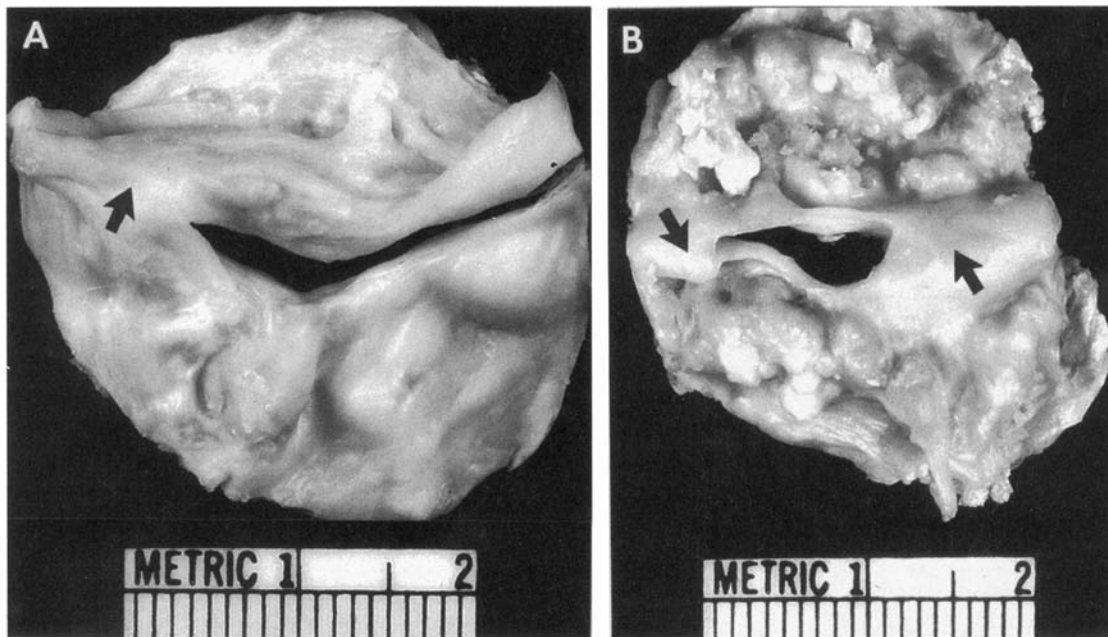


Fig. 5. Commissural fusion. Acquired fusion (*arrows*), involving one (A) and both (B) true commissures, in calcified valves with pure stenosis.

weakened ascending aorta) but unrelated to valve dysfunction.

Bicuspid aortic valves and weakened ascending aortas may also coexist with mitral valve prolapse or its morphologic correlate, a myxomatous (floppy) valve. In a surgical pathology study by Olson and coworkers⁴ of 225 patients with pure aortic regurgitation, 5 had a bicuspid aortic valve and a regurgitant myxomatous mitral valve (1 of whom also had aortic infective endocarditis).

About 50% of patients with coarctation of the aorta also have a bicuspid aortic valve.⁴⁰ In the general population, a congenitally bicuspid aortic valve affects 1 to 2%, whereas aortic coarctation occurs in only 0.04%.⁴¹ Thus, bicuspid valves occur about 40 times as frequently as coarctation. Not surprisingly, only 8 (1.5%) of the 542 patients in the current study also had coarctation. In a study by Folger and Stein,⁴² all 11 patients with coarctation and a bicuspid valve had equal-sized aortic cusps in contrast to all 8 patients with coarctation in the current study who had unequal-sized cusps. Either coarctation or a bicuspid valve may occur in patients with the Turner syndrome.¹

Chronic rheumatic disease may affect congenitally bicuspid aortic valves. In the current investigation, 17 (3%) of the 542 patients had a past history of rheumatic fever, and chronic rheumatic disease apparently contributed to their valvular dysfunction. The coexistence of these two otherwise unrelated aortic valve disorders has been previously reported.^{29,43,44}

Infective Endocarditis

Valves deformed by either congenital or acquired conditions are more susceptible to infection than are normal valves.^{51,52} In three autopsy studies of bicuspid aortic valves, infective endocarditis affected 15% (13 of 85) of those reported by Roberts,² 38% (20 of 52) by Datta and associates,¹⁹ and 39% (60 of 152) by Fenoglio and colleagues.¹⁶ In two surgical studies from Italy, infection involved bicuspid valves in 12% (10 of 81) reported by Turri and coworkers²⁰ and in 22% (13 of 59) by Agozzino and associates.²⁴ Among bicuspid aortic valves excised because of pure regurgitation, infective endocarditis affected 14% (10 of 70) of cases in the current study, 17% (9 of 54) reported by Olson and colleagues,⁴ and 38% (10 of 26) by Davies.²⁶

In contrast, active or healed endocarditis was detected overall in only 3% of 931 surgically excised bicuspid aortic valves from six Mayo Clinic reports, including the current study.^{3,5,8,12} Pure aortic regurgitation was the most common functional state, accounting for 20 of the 30 cases. Morphologic substrates for infection-related regurgitation included cusp perforations, defects, and scarring with retraction. The remaining 10 cases included 7 with stenosis and regurgitation, 2 with pure stenosis, and 1 with normal function but embolization.

In surgical studies, men have shown a striking predilection for aortic valve endocarditis and accounted for 29 (94%) of 31 infected valves (14 of which were bicuspid)

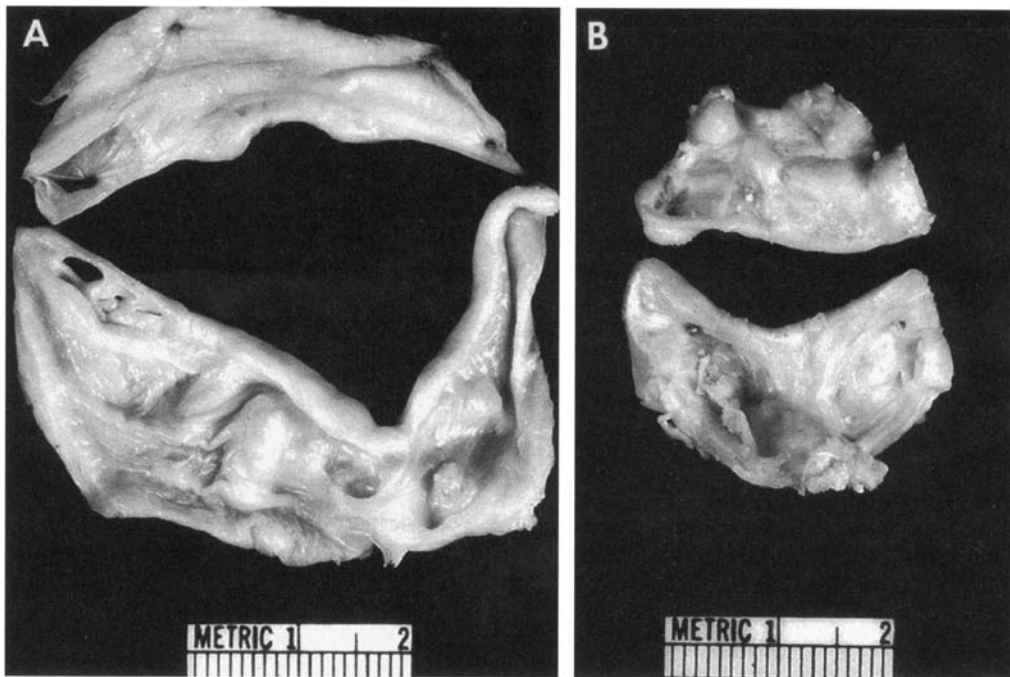


Fig. 6. Annular dilatation. A, Present (diameter >3.5 cm), in mildly calcified valve with pure regurgitation. B, Absent (diameter ≤ 3.5 cm), in calcified valve with pure stenosis.

that were removed at our institution between 1965 and 1990.^{3-5,8,12} Of the 16 patients with infected bicuspid valves in the current study, their ages ranged from 18 to 78 years (mean, 52), and 13 (81%) were men; the infecting organism was staphylococcus in 3, streptococcus in 4, and unknown in 9.

Pure Aortic Stenosis

Among patients undergoing valve replacement for pure aortic stenosis in 11 surgical series (Table 4), congenitally bicuspid valves were identified in 34% (1,760 of 5,132). Of the 1,078 patients whose age (at operation) and gender were reported, ages ranged from 15 to 89 years (mean, 63), and 68% were men. At the Mayo Clinic, the percentage of cases of aortic stenosis due to bicuspid valves has decreased over time, from 49% in 1965 to 36% in 1990, primarily due to an increasing number of elderly patients with degenerative aortic stenosis.^{3,12}

From another perspective, among 1,071 congenitally bicuspid aortic valves in eight surgical series (including the current study and two earlier Mayo studies^{4,5}), pure stenosis was consistently the most commonly reported dysfunctional state, affecting 766 (72%) overall and ranging from 59 to 81%.^{3,8,12,20,24} Personal autopsy experience (by W.D.E.) and the autopsy observations by Roberts² and Fenoglio and associates¹⁶ indicate that a normally functioning bicuspid valve is exceptionally uncommon in pa-

tients older than 60 years. Thus, calcific stenosis is the most common eventual fate of congenitally bicuspid aortic valves.

Unquestionably, calcification has represented the most frequent cause of stenosis in bicuspid aortic valves.^{2,3,7,8,12,18,21,26,45,46} Its extent was moderate to severe in 99% of the purely stenotic bicuspid valves in the current study. Fibrotic thickening of the cusps (also known as aortic valve sclerosis) begins as early as the second decade of life and is accompanied by progressive calcification from the fourth decade onward.^{47,48} Of interest, the progressions of fibrosis, calcification, and severity of stenosis are more rapid in valves with unequal-sized cusps and in those with congenitally fused right and left cusps than in the other morphologic variants.⁴⁷

Typically, calcium deposition first occurs along the raphe. Later, extension onto the valve annulus often results in the formation of a rigid T-shaped calcific strut that markedly hinders flexion and opening of the conjoined cusp. With time, calcific deposits form in the valve pockets along the aortic aspect of both cusps. These eventually coalesce to form calcified arches that become anchored to the annulus and result in further immobilization.

Fibrosis and lipidosis also cause cusp thickening and stiffening and thereby contribute to the stenosing process. Acquired fibrotic fusion of true commissures represents yet another mechanism for impaired valve opening. Among

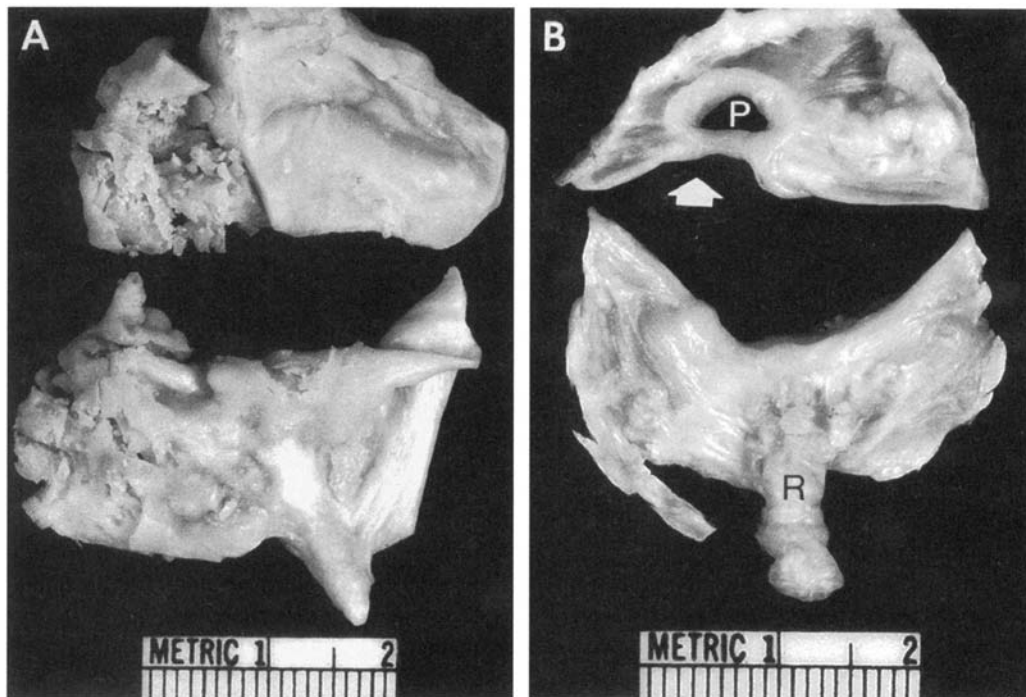


Fig. 7. Infective endocarditis. *A*, Active disease, due to *Staphylococcus aureus*, with ragged vegetations along left side of both cusps, associated with pure regurgitation. *B*, Old healed disease, with defect (arrow) and perforation (*P*) of nonconjoined cusp and with unrelated calcification of raphe (*R*), resulting in combined aortic stenosis and regurgitation.

stenotic bicuspid valves, fusion of one or both commissures was observed in 19% of autopsy cases reported by Fenoglio and colleagues,¹⁶ in 26% of surgical valves by Subramanian and coworkers,³ and in 14% of surgical cases in the current study.

Pure Aortic Regurgitation

In 10 surgical series, bicuspid valves accounted for 18% of cases (292 of 1,608) with pure aortic regurgitation (Table 4). The 160 patients whose age and gender were recorded ranged from 5 to 82 years (mean, 46) and included 93% men. Patients with aortic regurgitation underwent valve replacement at a younger age (46 versus 63 years) and included a higher percentage of men (93% versus 68%; $P < 0.001$) than those with stenosis. At the Mayo Clinic, the percentage of surgical cases with aortic regurgitation due to bicuspid valves has changed little over time, from 17% in 1965 to 14% in 1990.^{4,12}

Of 1,071 patients with bicuspid aortic valves in eight surgical series (including the current study and two earlier Mayo studies^{3,5}), pure regurgitation affected 176 (16%) overall, ranging from 13 to 22%.^{4,8,12,20,24} Similarly, among 237 patients with bicuspid valves in two autopsy studies, 16% had pure aortic regurgitation (11 of 85 and 28 of 152).^{2,16}

As expected, regurgitant bicuspid valves have more annular dilatation and less calcification or commissural fusion than their stenotic counterparts. In the current study, annular dilatation was a feature in 48%, whereas commissural fusion was observed in only 14%. Among purely regurgitant valves, calcification was either absent or mild in all autopsy cases reported by Roberts² and Fenoglio and associates¹⁶ and in 96% of the surgical cases by Olson and colleagues⁴ but in only 59% of the current cases. Otherwise, raphal features and relative cusp size were similar to the overall group of bicuspid valves. A raphe was present in 68% of regurgitant valves in the current study and in 77% of the surgical cases reported by Roberts and coworkers²⁸ and was typical in 82% and 90%, respectively. Cusps were not equal in size in 92% of the current cases and in all the noninfected cases reported by Roberts and associates.²⁸

The most commonly reported mechanisms leading to chronic regurgitation among congenitally bicuspid valves, acting either alone or in various combinations, have been annular dilatation and cusp prolapse or retraction.^{2,4,8,12,16,20,23-26,28,29,34,35,37,39} Annular dilatation is generally associated with dilatation of the ascending aorta. Prolapse usually affects the conjoined cusp and results from the

Table 4.—General Features Versus Functional State of 2,181 Congenitally Bicuspid Aortic Valves in 16 Surgical Pathologic Studies*

Study	Reference	Years studied	Age (yr)		Gender			No. of cases	
			Mean	Range	M	F	M:F ratio	BAV	AV† (% BAV)
<i>Pure aortic stenosis</i>									
Subramanian et al ³		1965, 1970, 1975, 1980	59	21-78	132	39	3.4:1	171	374 (46)
Passik et al ⁷		1981-1985	64	20-88	186	62	3.0:1	248	646 (38)
Edwards ⁸		1985	61	17-81	26	11	2.4:1	37	109 (34)
Dare et al ¹²		1990	65	20-84	32	23	1.4:1	55	154 (36)
Peterson et al ¹⁸		1979-1983	63	53	109 (49)
Turri et al ²⁰		1981-1987	48	140 (34)
Waller et al ²²		1962-1992	535	1,797 (30)‡
Agozzino et al ²⁴		1981-1991	46	250 (18)
Davies ²⁶		1976-1979	62	31-76	64	40	1.6:1	104	187 (56)
Stephan et al ²⁷		1993-1995	67	33-89	31	23	1.3:1	54	115 (47)
Current study		1991-1996	65	1-86	257	152	1.7:1	409	1,251 (33)
Subtotal			63	1-89	728	350	2.1:1	1,760	5,132 (34)
<i>Pure aortic regurgitation</i>									
Olson et al ⁴		1965, 1970, 1975, 1980	48	11-70	46	8	5.8:1	54	225 (24)
Edwards ⁸		1985	38	16-82	11	0	11.0:0	11	40 (28)
Dare et al ¹²		1990	54	32-73	9	0	9.0:0	9	58 (16)
Turri et al ²⁰		1981-1987	16	256 (6)
Waller et al ²³		1962-1992	55	176 (31)
Agozzino et al ²⁴		1981-1991	13	153 (8)
Davies ²⁶		1976-1979	26	100 (26)
Roberts et al ²⁸		1963-1979	43	26-65	13	0	13.0:0	20§	189 (11)
Guiney et al ²⁹		15	72 (21)
Current study		1991-1996	46	5-81	69	4	17.3:1	73	339 (22)
Subtotal			46	5-82	148	12	12.3:1	292	1,608 (18)
<i>Combined aortic stenosis and regurgitation</i>									
Subramanian et al ⁵		1965, 1970, 1975, 1980	55	23-73	34	10	3.4:1	44	213 (21)
Edwards ⁸		1985	55	26-78	4	0	4.0:0	4	24 (17)
Dare et al ¹²		1990	70	54-82	4	0	4.0:0	4	24 (17)
Turri et al ²⁰		1981-1987	17	208 (8)
Agozzino et al ²⁴		1981-1991	0	250 (0)
Current study		1991-1996	52	1-83	42	11	3.7:1	53	247 (21)
Subtotal			54	1-83	84	21	4.0:1	122	966 (13)
<i>Normal function</i>									
Current study		1991-1996	47	20-66	4	3	1.3:1	7	40 (18)
Total			61	1-89	964	386	2.5:1	2,181	7,746 (28)

*AV = aortic valve; BAV = bicuspid aortic valve.

†Total number of surgically excised aortic valves (bicuspid plus all other causes).

‡Includes aortic stenosis with or without regurgitation.

§Includes seven additional patients with infective endocarditis for whom age and gender were not recorded.

combined effects of annular dilatation, myxomatous degeneration and stretching of cusps, and inadequate support by a shallow raphe. Central indentation of the free edge of the conjoined cusp also predisposes to regurgitation.⁴⁹ Age-related fibrosis, due to hemodynamic wear and tear, may be associated with cusp deformity and scar retraction and may thereby interfere with proper coaptation and com-

plete closure of the two cusps. Although calcification most frequently impedes valve opening and leads to stenosis, it can also fix the conjoined cusp in a partially opened position and cause insufficiency.

The most common cause of acute regurgitation in a bicuspid aortic valve is infective endocarditis, which either destroys cusps or forms bulky vegetations that prevent

Table 5.—Site of Raphe in 713 Congenitally Bicuspid Aortic Valves in 10 Studies*

Study	Reference	Source	Site of raphe†				Total no. of cases
			R-L (%)	R-P (%)	L-P (%)	R-P or L-P (%)‡	
Roberts ²		A	16 (53)	14 (47)	30
Datta et al ¹⁹		A	23 (44)	29 (56)	52
Moore et al ³⁰		A	39 (65)	18 (30)	3 (5)	...	60
Lerer & Edwards ³¹		A	36 (72)	13 (26)	1 (2)	...	50
Roberts & Roberts ³²		A	10 (77)	3 (23)	0 (0)	...	13
Subramanian et al ³		S	73 (79)	15 (16)	4 (4)	...	92
Olson et al ⁴		S	10 (91)	1 (9)	0 (0)	...	11
Subramanian et al ⁵		S	22 (85)	3 (12)	1 (4)	...	26
Angelini et al ¹⁷		S	41 (64)	23 (36)	64
Current study		S	270 (86)	37 (12)	8 (3)	...	315
Total		A, S	540 (76)	90 (13)	17 (2)	66 (9)	713

*A = autopsy; S = surgery.

†See Figure 3 for explanation of abbreviations.

‡Not distinguished by authors.

adequate coaptation. With time, endocarditis can heal and lead to chronic regurgitation. In some cases, the infecting organism is never identified, and in others, the episode of endocarditis is clinically occult (perhaps attributed to pneumonia, for example, and treated with antibiotics). Among noninfected valves, three types of rupture can produce severe acute regurgitation in valves with or without previous chronic insufficiency. The most frequent is acute aortic dissection, with retrograde disruption and commissural prolapse. In a rare variant of this process, a small intimal tear localized to one commissure can cause acute valve rupture.⁵⁰ Spontaneous rupture of the fenestrated cordlike raphe of an atypical bicuspid valve can cause acute

prolapse and regurgitation.^{4,25,34-36} Chronic hypertension may induce any of the noninfective ruptures.

Combined Aortic Stenosis and Regurgitation

Of 966 patients with combined stenosis and regurgitation in six surgical studies, bicuspid valves were present in 13% (Table 4). The percentage was higher in four Mayo Clinic studies (21%)^{5,8,12} than in two Italian studies (4%), in which rheumatic disease remains prevalent.^{20,24} Percentages at our institution have not changed appreciably over time.^{5,12} The 105 patients whose age and gender were reported ranged from 1 to 83 years old (mean, 54), and 80% were men.^{5,8,12} Thus, patients with combined stenosis and

Table 6.—Frequency of Aortic Dissection in 1,407 Patients With Congenitally Bicuspid Aortic Valves in Eight Studies*

Study	Reference	Years studied	Source	Functional state					No. of cases	
				Pure AS	Pure AI	AS and AI	Normal	Unknown	Diss	BAV (%)
Larson & Edwards ¹		1961-1981	A	4	3	2	9	0	18	293 (6.1)
Roberts ²		Before 1970	A	0	0	0	0	2	2	85 (2.4)
Fenoglio et al ¹⁶		1940-1970	A	4†	3	0	1	0	8	152 (5.3)
Subtotal			A	8	6	2	10	2	28	530 (5.3)
Mayo series ³⁻⁵		1965, 1970, 1975, 1980	S	0	3	0	0	0	3	268 (1.1)
Dare et al ¹²		1990	S	0	1	0	0	0	1	67 (1.5)
Current study		1991-1996	S	0	3‡	0	0	0	3	542 (0.6)
Subtotal			S	0	7	0	0	0	7	877 (0.8)
Total			A, S	8	13	2	10	2	35	1,407 (2.5)

*A = autopsy; AI = aortic insufficiency (regurgitation); AS = aortic stenosis; BAV = bicuspid aortic valve; Diss = aortic dissection; S = surgery.

†Includes aortic stenosis with or without regurgitation.

‡Three men (ages 51, 63, and 71 years).

regurgitation underwent valve replacement at a younger age (54 versus 63 years) and included more men (80% versus 68%; $P = 0.01$) than those with pure stenosis. Of 1,071 patients with bicuspid valves in eight surgical series (including the current study and two earlier Mayo studies^{3,4}), 122 (11%) had combined stenosis and regurgitation, with a range of 0 to 21%.^{5,8,12,20,24}

In the current investigation, valves with combined stenosis and regurgitation did not differ substantially from valves with other functional states relative to the presence or position of the raphe or the percentage of unequal-sized cusps. Although they were similar to purely stenotic valves in their extent of calcification, they more closely resembled purely regurgitant valves with respect to annular dilatation. Commissural fusion promoted stenosis rather than regurgitation. In the current study, it occurred more frequently in valves with combined stenosis and regurgitation than in the other functional groups (31% versus 14%; $P = 0.002$), and in earlier Mayo Clinic studies, it was present in 26% with pure stenosis and 25% with combined stenosis and regurgitation but in none with pure regurgitation.^{3,5} As expected, the mechanisms producing combined stenosis and regurgitation included various combinations of the processes causing pure stenosis and those causing pure regurgitation.

Normally Functioning Bicuspid Valves

Only rarely are valves resected for conditions other than stenosis or regurgitation. Among 1,877 aortic valves excised at Mayo Clinic Rochester (1991 through 1996), however, 40 (2.1%) had either normal function or only mild stenosis or regurgitation. Seven (18%) of the 40 were bicuspid, accounting for 1.3% of 542 bicuspid valves in the current study. The age of the seven patients ranged from 20 to 66 years (mean, 47), and 71% were men. Valves were excised during repair of ascending aortic aneurysms in five and because of vegetations in two (one of which was infected).

The two cusps were unequal in size in all seven cases, and a raphe was present in six (typical in five and atypical in one). Among the seven valves, commissural fusion was absent in six, calcification was absent or mild in five, and the annulus was nondilated in five. Thus, as expected, the processes that generally lead to appreciable valvular dysfunction were absent or only mild in most cases.

Future Health-Care Costs

Approximately 4 million US citizens have congenitally bicuspid aortic valves, based on an incidence of 1 to 2% in the general population.^{1,2} In autopsy studies, the frequency of normally functioning bicuspid valves in patients older than 60 years is low. Moreover, in eight surgical series

(including the current study), 83% of bicuspid valves (888 of 1,071) were removed because of either pure stenosis or combined stenosis and regurgitation.^{3-5,8,12,20,24} Consequently, over the course of an average 75-year life span,⁵³ the most common fate of a congenitally bicuspid aortic valve is the development of progressive calcific stenosis, with or without coexistent regurgitation. Currently, most patients with symptomatic disease eventually need an interventional procedure, and the limited benefits of aortic balloon valvuloplasty indicate that an operation is likely to remain the treatment of choice.⁵⁴ Thus, bicuspid aortic valves will continue to contribute substantially to health-care costs related to open heart surgery.

REFERENCES

1. **Larson EW, Edwards WD.** Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol* 1984;53:849-855
2. **Roberts WC.** The congenitally bicuspid aortic valve: a study of 85 autopsy cases. *Am J Cardiol* 1970;26:72-83
3. **Subramanian R, Olson LJ, Edwards WD.** Surgical pathology of pure aortic stenosis: a study of 374 cases. *Mayo Clin Proc* 1984;59:683-690
4. **Olson LJ, Subramanian R, Edwards WD.** Surgical pathology of pure aortic insufficiency: a study of 225 cases. *Mayo Clin Proc* 1984;59:835-841
5. **Subramanian R, Olson LJ, Edwards WD.** Surgical pathology of combined aortic stenosis and insufficiency: a study of 213 cases. *Mayo Clin Proc* 1985;60:247-254
6. **Olson LJ, Subramanian R, Ackermann DM, Orszulak TA, Edwards WD.** Surgical pathology of the mitral valve: a study of 712 cases spanning 21 years. *Mayo Clin Proc* 1987;62:22-34
7. **Passik CS, Ackermann DM, Pluth JR, Edwards WD.** Temporal changes in the causes of aortic stenosis: a surgical pathologic study of 646 cases. *Mayo Clin Proc* 1987;62:119-123
8. **Edwards WD.** Surgical pathology of the aortic valve. *Contemp Issues Surg Pathol* 1988;12:43-100
9. **Hauck AJ, Freeman DP, Ackermann DM, Danielson GK, Edwards WD.** Surgical pathology of the tricuspid valve: a study of 363 cases spanning 25 years. *Mayo Clin Proc* 1988;63:851-863
10. **Altrichter PM, Olson LJ, Edwards WD, Puga FJ, Danielson GK.** Surgical pathology of the pulmonary valve: a study of 116 cases spanning 15 years. *Mayo Clin Proc* 1989;64:1352-1360
11. **Dare AJ, Harrity PJ, Tazelaar HD, Edwards WD, Mullany CJ.** Evaluation of surgically excised mitral valves: revised recommendations based on changing operative procedures in the 1990s. *Hum Pathol* 1993;24:1286-1293
12. **Dare AJ, Velnot JP, Edwards WD, Tazelaar HD, Schaff HV.** New observations on the etiology of aortic valve disease: a surgical pathologic study of 236 cases from 1990. *Hum Pathol* 1993;24:1330-1338
13. **Kent PD, Tazelaar HD, Edwards WD, Orszulak TA.** Temporal changes in the surgical pathology of prosthetic aortic valves—a study of 157 cases spanning 26 years (1970-1995). *Cardiovasc Pathol* 1998;7:9-23
14. **Bacon APC, Matthews MB.** Congenital bicuspid aortic valves and the aetiology of isolated aortic valvular stenosis. *Q J Med* 1959;28:545-560
15. **Waller BF, Carter JB, Williams HJ Jr, Wang K, Edwards JE.** Bicuspid aortic valve: comparison of congenital and acquired types. *Circulation* 1973;48:1140-1150
16. **Fenoglio JJ Jr, McAllister HA Jr, DeCastro CM, Davila JE, Cheltin MD.** Congenital bicuspid aortic valve after age 20. *Am J Cardiol* 1977;39:164-169
17. **Angelini A, Ho SY, Anderson RH, Devine WA, Zuberhuhler JR, Becker AE, et al.** The morphology of the normal aortic valve as compared with

- the aortic valve having two leaflets. *J Thorac Cardiovasc Surg* 1989;98:362-367
18. **Peterson MD, Roach RM, Edwards JE.** Types of aortic stenosis in surgically removed valves. *Arch Pathol Lab Med* 1985;109:829-832
 19. **Datta BN, Bhusnumath B, Khattri HN, Sapru RP, Bidwai PS, Wahi PL.** Anatomically isolated aortic valve disease: morphologic study of 100 cases at autopsy. *Jpn Heart J* 1988;29:661-670.
 20. **Turri M, Thlene G, Bortolotti U, Milano A, Mazzucco A, Gallucci V.** Surgical pathology of aortic valve disease: a study based on 602 specimens. *Eur J Cardiothorac Surg* 1990;4:556-560
 21. **Isner JM, Chokshi SK, DeFranco A, Braimlen J, Slovenkai GA.** Contrasting histoarchitecture of calcified leaflets from stenotic bicuspid versus stenotic tricuspid aortic valves. *J Am Coll Cardiol* 1990; 15:1104-1108
 22. **Waller B, Howard J, Fess S.** Pathology of aortic valve stenosis and pure aortic regurgitation: a clinical morphologic assessment. Part I. *Clin Cardiol* 1994;17:85-92
 23. **Waller BF, Howard J, Fess S.** Pathology of aortic valve stenosis and pure aortic regurgitation: a clinical morphologic assessment. Part II. *Clin Cardiol* 1994;17:150-156
 24. **Agozzino L, De Vivo F, Falco A, De Luca L, Schinosa T, Cotrufo M.** Surgical pathology of the aortic valve: gross and histological findings in 1120 excised valves. *Cardiovasc Pathol* 1994;3:155-161
 25. **Walley VM, Antecol DH, Kyrollos AG, Chan KL.** Congenitally bicuspid aortic valves: study of a variant with fenestrated raphe. *Can J Cardiol* 1994;10:535-542
 26. **Davies MJ.** *Pathology of Cardiac Valves.* London: Butterworths; 1980. pp 1-61
 27. **Stephan PJ, Henry AC III, Hebel RF Jr, Whiddon L, Roberts WC.** Comparison of age, gender, number of aortic valve cusps, concomitant coronary artery bypass grafting, and magnitude of left ventricular-systemic arterial peak systolic gradient in adults having aortic valve replacement for isolated aortic valve stenosis. *Am J Cardiol* 1997;79:166-172
 28. **Roberts WC, Morrow AG, McIntosh CL, Jones M, Epstein SE.** Congenitally bicuspid aortic valve causing severe, pure aortic regurgitation without superimposed infective endocarditis: analysis of 13 patients requiring aortic valve replacement. *Am J Cardiol* 1981; 47:206-209
 29. **Guiney TE, Davies MJ, Parker DJ, Leech GJ, Leatham A.** The aetiology and course of isolated severe aortic regurgitation: a clinical, pathological, and echocardiographic study. *Br Heart J* 1987;58:358-368
 30. **Moore GW, Hutchins GM, Brito JC, Kang H.** Congenital malformations of the semilunar valves. *Hum Pathol* 1980;11:367-372
 31. **Lerer PK, Edwards WD.** Coronary arterial anatomy in bicuspid aortic valve: necropsy study of 100 hearts. *Br Heart J* 1981;45:142-147
 32. **Roberts CS, Roberts WC.** Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol* 1991;17:712-716
 33. **Brandenburg RO Jr, Tajik AJ, Edwards WD, Reeder GS, Shub C, Seward JB.** Accuracy of 2-dimensional echocardiographic diagnosis of congenitally bicuspid aortic valve: echocardiographic-anatomic correlation in 115 patients. *Am J Cardiol* 1983;51:1469-1473
 34. **Carter JB, Sethi S, Lee GB, Edwards JE.** Prolapse of semilunar cusps as causes of aortic insufficiency. *Circulation* 1971;43:922-932
 35. **Roberts WC.** Left ventricular outflow tract obstruction and aortic regurgitation. *Monogr Pathol* 1974;15:110-175
 36. **Becker AE, Düren DR.** Spontaneous rupture of bicuspid aortic valve: an unusual cause of aortic insufficiency. *Chest* 1977;72:361-362
 37. **Braverman AC.** Bicuspid aortic valve and associated aortic wall abnormalities [editorial]. *Curr Opin Cardiol* 1996;11:501-503
 38. **Pachulski RT, Weinberg AL, Chan KL.** Aortic aneurysm in patients with functionally normal or minimally stenotic bicuspid aortic valve. *Am J Cardiol* 1991;67:781-782
 39. **Hahn RT, Roman MJ, Mogtader AH, Devereux RB.** Association of aortic dilation with regurgitant, stenotic and functionally normal bicuspid aortic valves. *J Am Coll Cardiol* 1992;19:283-288
 40. **Becker AE, Becker MJ, Edwards JE.** Anomalies associated with coarctation of aorta: particular reference to infancy. *Circulation* 1970;41:1067-1075
 41. **Edwards WD.** Congenital heart disease. In: Damjanov I, Linder J, editors. *Anderson's Pathology.* Vol 1. 10th ed. St. Louis: Mosby; 1996. pp 1339-1396
 42. **Folger GM Jr, Stein PD.** Bicuspid aortic valve morphology when associated with coarctation of the aorta. *Cathet Cardiovasc Diagn* 1984;10:17-25
 43. **McReynolds RA, Ali N, Cuadra M, Roberts WC.** Combined acute rheumatic fever and congenitally bicuspid aortic valve: a hitherto unconfirmed combination. *Chest* 1976;70:98-100
 44. **Wanderman KL, Gueron M.** Coexistence of congenital bicuspid aortic valve and rheumatic heart disease [letter]. *Chest* 1977; 71:562
 45. **Roberts WC.** The structure of the aortic valve in clinically isolated aortic stenosis: an autopsy study of 162 patients over 15 years of age. *Circulation* 1970;42:91-97
 46. **Pomerance A.** Pathogenesis of aortic stenosis and its relation to age. *Br Heart J* 1972;34:569-574
 47. **Campbell M.** Calcific aortic stenosis and congenital bicuspid aortic valves. *Br Heart J* 1968;30:606-616
 48. **Beppu S, Suzuki S, Matsuda H, Ohmori F, Nagata S, Miyatake K.** Rapidity of progression of aortic stenosis in patients with congenital bicuspid aortic valves. *Am J Cardiol* 1993;71:322-327
 49. **Sadee AS, Becker AE, Verheul HA, Bouma B, Hoedemaker G.** Aortic valve regurgitation and the congenitally bicuspid aortic valve: a clinicopathological correlation. *Br Heart J* 1992;67:439-441
 50. **Ciampricotti R, el Gamal M, Mashhour YA.** Acute aortic regurgitation due to spontaneous rupture of a bicuspid aortic valve: detection by echocardiography. *Clin Cardiol* 1987;10:484-486
 51. **Steckelberg JM, Wilson WR.** Risk factors for infective endocarditis. *Infect Dis Clin North Am* 1993 Mar;7:9-19
 52. **Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al.** Prevention of bacterial endocarditis: recommendations by the American Heart Association. *JAMA* 1997;277:1794-1801
 53. **Schneider EL, Guralnik JM.** The aging of America: impact on health care costs. *JAMA* 1990;263:2335-2340
 54. **Rahimtoola SH.** Catheter balloon valvuloplasty for severe calcific aortic stenosis: a limited role [editorial]. *J Am Coll Cardiol* 1994; 23:1076-1078