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Frequency by Decades of Unicuspid, Bicuspid, and Tricuspid Aortic Valves in Adults Having Isolated Aortic Valve Replacement for Aortic Stenosis, With or Without Associated Aortic Regurgitation

William C. Roberts, MD; Jong M. Ko, BA

Background—Aortic valve stenosis (with or without aortic regurgitation and without associated mitral stenosis) in adults in the Western world has been considered in recent years to most commonly be the result of degenerative or atherosclerotic disease.

Methods and Results—We examined operatively excised, stenotic aortic valves from 932 patients aged 26 to 91 years (mean±SD, 70±12), and none had associated mitral valve replacement or evidence of mitral stenosis: A total of 504 (54%) had congenitally malformed valves (unicuspid in 46 [unicommissural in 42; acommisural in 4] and bicuspid in 458); 417 (45%) had tricuspid valves (either absent or minimal commissural fusion); and 11 (1%) had valves of undetermined type. It is likely that the latter 11 valves also had been congenitally malformed. Of the 584 men, 343 (59%) had either a unicuspid or a bicuspid valve; of the 348 women, 161 (46%) had either a unicuspid or a bicuspid aortic valve.

Conclusions—The data from this large study of adults having isolated aortic valve replacement for aortic stenosis (with or without associated aortic regurgitation) and without associated mitral stenosis or mitral valve replacement strongly suggest that an underlying congenitally malformed valve, at least in men, is more common than a tricuspid aortic valve. (*Circulation*. 2005;111:920-925.)

Key Words: aorta ■ heart defects, congenital ■ valves ■ regurgitation

The most common cardiac operation today, of course, is coronary artery bypass grafting. The second most common is aortic valve replacement for aortic valve stenosis. During the past 11 years, we have examined 932 operatively excised, stenotic aortic valves from adults. This study describes the frequency of the various aortic valve structures (unicuspid, bicuspid, and tricuspid) in each of 8 decades of life in a group of patients who had isolated aortic valve replacement. This study differs from previously reported similar analyses in that children and patients with concomitant mitral valve replacement or associated mitral stenosis were excluded. The hypothesis was that if cases of rheumatic heart disease could be excluded, then the frequency of an underlying congenital heart disease of those undergoing aortic valve replacement would be higher than previously realized.

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Methods

From January 1993 through June 2004, every cardiac valve operatively excised at Baylor University Medical Center and submitted to

the surgical pathology department of the same medical center has been examined by one of us (W.C.R.). Among the valves examined during this >11-year period were 932 aortic valves that had some degree of stenosis (a peak left ventricular to aortic systolic pressure gradient ≥ 10 mm Hg or clear anatomic evidence of aortic valve stenosis) with or without some degree of aortic regurgitation. Excluded from this study were patients having combined aortic and mitral valve replacement, patients with mitral stenosis whether or not the mitral valve was excised or the patient had a mitral valvuloplasty, patients ≤ 20 years of age at the time of aortic valve replacement, patients who had had a previous aortic valvulotomy, and patients who also had hypertrophic cardiomyopathy. Thus, patients included herein were those in whom only the aortic valve was excised and the aortic valve had some degree of stenosis.

Each stenotic aortic valve was received in the surgical pathology department in a container of formaldehyde. The valve structure in all cases was determined by one of us (W.C.R.). In recent years, the operatively excised stenotic valve was weighed. The age and sex of each patient was recorded from the surgical slip accompanying the operatively excised aortic valve. The preoperative cardiac catheterization and echocardiographic reports were obtained from either the respective laboratory or the patient's medical chart or, in more recent years, from the Apollo cardiovascular database of Baylor University Medical Center.

Hemodynamic data from cardiac catheterization was available for 689 (74%) patients, 43 of whom had transvalvular peak pressure

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TABLE 1. Aortic Valve Structure in 584 Men and 348 Women Aged 26 to 91 Years With Operatively Excised Stenotic Aortic Valves Unassociated With Mitral Valve Disease and Excised From 1993 to 2004

Aortic Valve Structure	Cases, n (%)	Ages (y) of Patients by Decades at Time of Aortic Valve Replacement							
		21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
Men									
Unicuspid	34 (6)	3	4	11	8	4	4	0	0
Bicuspid	309 (53)	1	4	20	54	111	94	24	1
Tricuspid	234 (40)	0	0	0	14	50	119	51	0
Uncertain	7 (1)	0	0	0	0	3	2	2	0
Subtotals, n (%)	584 (100)	4 (<1)	8 (1)	31 (5)	76 (13)	168 (29)	219 (38)	77 (13)	1 (<1)
Women									
Unicuspid	12 (3)	1	2	3	1	4	1	0	0
Bicuspid	149 (43)	1	5	10	20	44	55	14	0
Tricuspid	183 (53)	0	0	2	11	43	79	47	1
Uncertain	4 (1)	0	0	1	0	0	3	0	0
Subtotals, n (%)	348 (100)	2 (<1)	7 (2)	16 (5)	32 (9)	91 (26)	138 (46)	61 (18)	1 (<1)

Values in parentheses are percentages.

gradients between 10 and 20 mm Hg. Nearly all of the remaining 243 patients also had undergone cardiac catheterization, but those studies were performed before the patient was referred to Baylor University Medical Center, and the data were not available to us. Another 111 patients had echocardiographic data available but no cardiac catheterization data available. Thus, for 800 (86%) of the 932 patients, either cardiac catheterization data or echocardiographic data before aortic valve replacement were available. The transvalvular peak systolic pressure gradients ranged from 10 to 141 mm Hg (mean±SD, 53±25); in the patients not having simultaneous coronary bypass surgery, the peak gradients ranged from 10 to 141 mm Hg (mean±SD, 57±26), and in those patients having coronary bypass surgery at the time of aortic valve replacement, from 10 to 133 mm Hg (mean±SD, 49±24; *P*<0.001). Aortic valve areas (637 patients) ranged from 0.18 to 1.90 cm² (mean±SD, 0.74±0.25) and were significantly different in those having versus those not having simultaneous coronary bypass surgery (mean±SD, 0.72±0.25 versus 0.76±0.25; *P*=0.037). All 932 patients had structurally abnormal aortic valves including calcific deposits, including those patients with peak transvalvular pressure gradients as low as 10 mm Hg.

Statistical analysis was performed with SigmaStat version 2.0 software (SPSS Inc). To compare the percentages in 2 different groups, the *z* test was used. To compare the mean transvalvular peak systolic pressure gradients and the mean aortic valve areas in patients with and without simultaneous coronary bypass surgery, the non-parametric Mann-Whitney rank-sum test was used instead of a parametric test because the data to be analyzed did not pass the normality and equal-variance assumption tests. To compare the mean ages among patient groups with unicuspid, bicuspid, and tricuspid valves, the nonparametric Kruskal-Wallis 1-way ANOVA on ranks test was used. A probability value <0.05 was considered statistically significant. The institutional review board of Baylor University Medical Center approved the study protocol.

Results

The numbers and percentages of patients in each of the 8 decades subdivided by aortic valve structure and sex are shown in Table 1. Among the 932 patients, 46 (5%) had unicuspid unicommisural valves, 458 (49%) had bicuspid valves, 417 (45%) had 3-cuspid aortic valves, and 11 (1%) had valves excised in several pieces, such that the underlying valve structure was not clearly discernible. (We believe that these 11 valves with uncertain structure were also congeni-

tally malformed because they all contained a very large amount of calcific deposits.) More men than women had congenitally malformed valves (59% versus 46%, *P*=0.008; Table 1), and fewer men than women had tricuspid aortic valves (40% versus 53%, *P*=0.011; Table 1).

The unicuspid aortic valves were all heavily calcified, and their cusps were rigid. Of these 46 valves, 42 had a single, unfused commissure, and the valve orifice was linear (similar to an exclamation point), eccentrically triangular, or oval (Figure 1); the other 4 had triangular, more central orifices, and 3 “undeveloped commissures” (Figure 2).

The bicuspid aortic valves were of 2 types (Figure 3). All had been excised in 2 pieces. In 432, the free margins of both cusps were relatively linear in appearance, or the margins of one of the 2 cusps had a V-shaped configuration, with the apex of the V pointing toward a raphe (false commissure). In

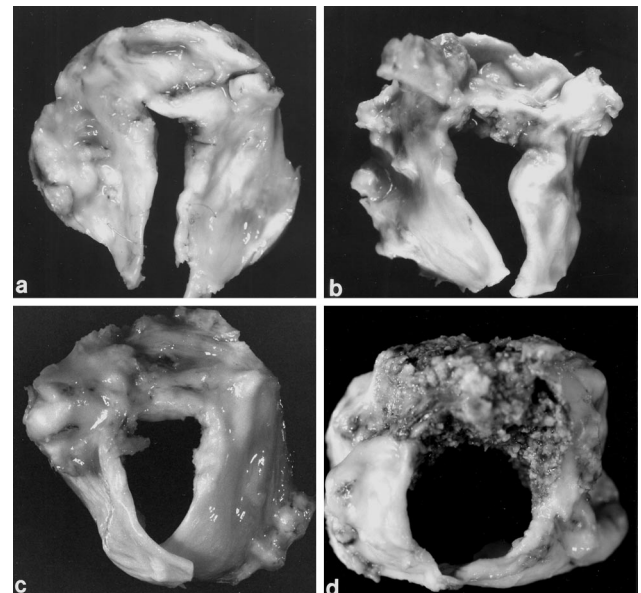


Figure 1. Unicuspid unicommisural aortic valves. See Table 3.

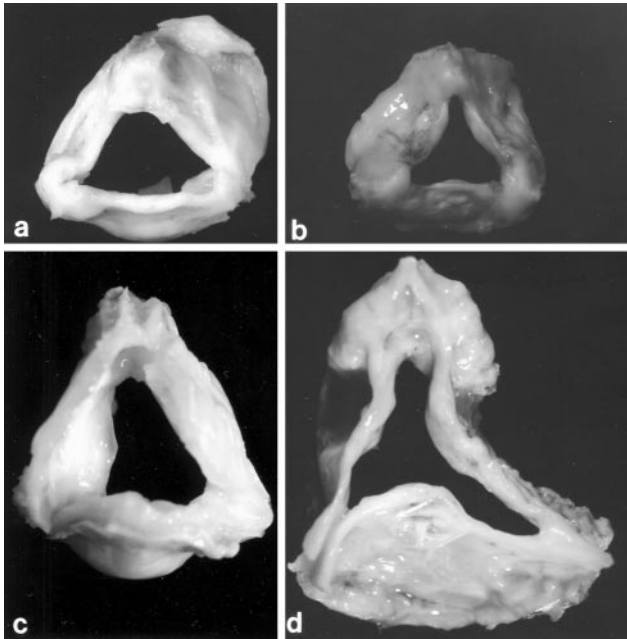


Figure 2. Unicuspid aortic valves. See Table 3.

the latter situation, the free margins of the raphe cusp were concave, and the free margins of the nonraphe cusp were convex, such that the valvular orifices were nevertheless usually competent. The ventricular aspect of the valve beneath the raphe in all instances was flat or nearly so. Furthermore, on the aortic aspect at the site of the raphe, the V-shaped cuspal margins were not visible in the raphe. The cephalad extension of the raphe was always less than that of

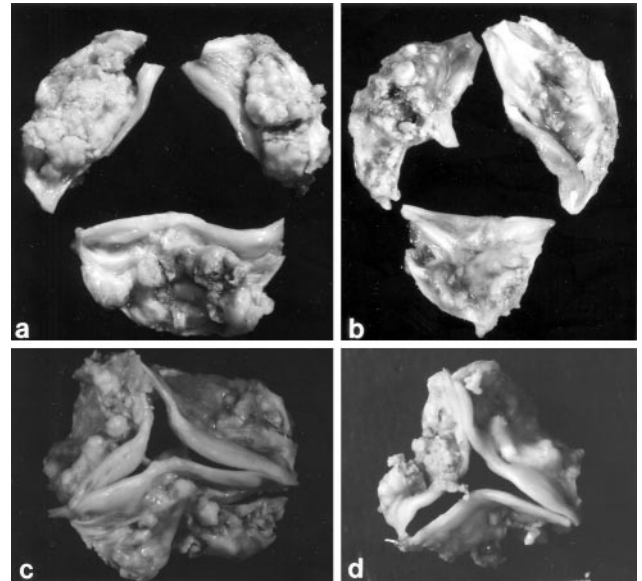


Figure 4. Three-cuspid aortic valves. See Table 3.

the 2 true commissures. In the remaining 26 valves classified as bicuspid, the cusps were fused at one commissure, and the length of the fusion was ≥ 4 mm and usually ≈ 10 mm. In these circumstances, the free margins were visible cephalad to the cuspal fusion, which was located caudal to the margins. The fused cusps beneath the visible free margins (which extended to the aortic wall) were either flat or not. Additionally, the cephalad extension of the fused commissure appeared to be on the same horizontal plane as the other 2 commissures.

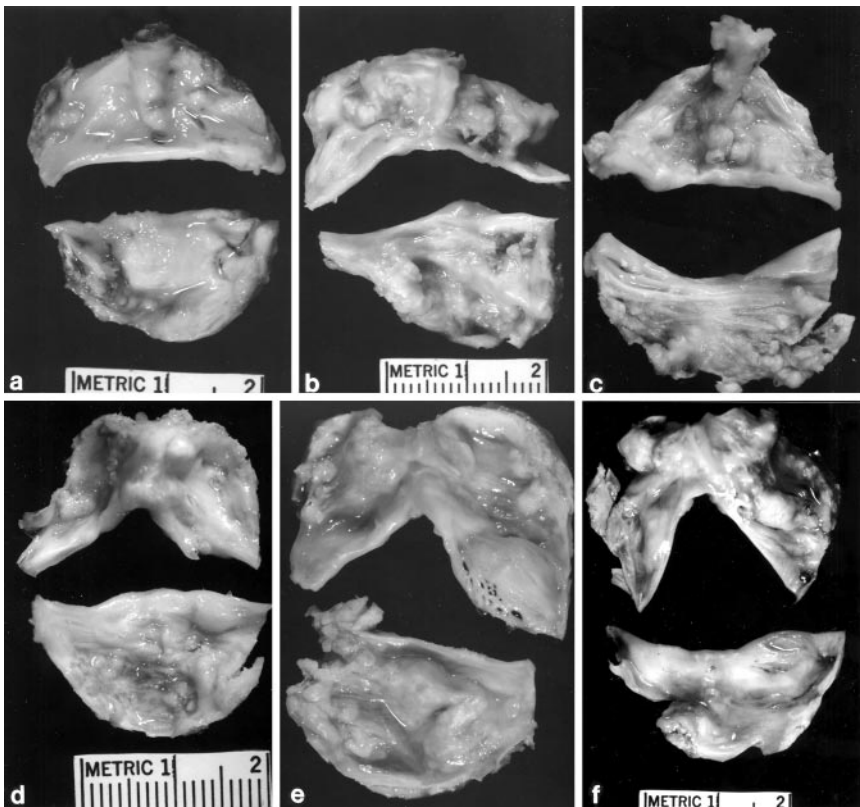


Figure 3. Congenitally bicuspid aortic valve. See Table 3.

TABLE 2. Aortic Valve Structure in Patients With Isolated Aortic Stenosis Subdivided Into Those With and Without Concomitant Coronary Artery Bypass Grafting

Aortic Valve Structure	Cases	Ages (y) of Patients by Decades at Time of Aortic Valve Replacement							
		21–30	31–40	41–50	51–60	61–70	71–80	81–90	91–100
Without coronary artery bypass grafting									
Men									
Unicuspid	28	3	4	10	6	3	2	0	0
Bicuspid	151	1	4	15	31	50	41	8	1
Tricuspid	76	0	0	0	3	19	37	17	0
Uncertain	4	0	0	0	0	2	1	1	0
Women									
Unicuspid	11	1	1	3	1	4	1	0	0
Bicuspid	96	1	5	6	13	30	33	8	0
Tricuspid	73	0	0	2	6	16	30	19	0
Uncertain	3	0	0	1	0	0	2	0	0
Totals, n (%)	442 (100)	6 (1)	14 (3)	37 (8)	60 (14)	124 (28)	147 (33)	53 (12)	1 (<1)
With coronary artery bypass grafting									
Men									
Unicuspid	6	0	0	1	2	1	2	0	0
Bicuspid	158	0	0	5	23	61	53	16	0
Tricuspid	158	0	0	0	11	31	82	34	0
Uncertain	3	0	0	0	0	1	1	1	0
Women									
Unicuspid	1	0	1	0	0	0	0	0	0
Bicuspid	53	0	0	4	7	14	22	6	0
Tricuspid	110	0	0	0	5	27	49	28	1
Uncertain	1	0	0	0	0	0	1	0	0
Totals, n (%)	490 (100)	0 (0)	1 (<1)	10 (2)	48 (10)	135 (28)	210 (43)	85 (17)	1 (<1)

Values in parentheses are percentages.

The tricuspid aortic valves were of 2 types (Figure 4). None of the 3 commissures were fused, such that each cusp was excised separately (340 cases), or there was slight (≤ 3 mm) fusion of one or more commissures (77 cases); in nearly all cases, the fusion extended for only 1 or 2 mm.

The fewer the number of aortic valve cusps, the younger was the patient. Patients with 3-cuspid aortic valves had higher mean ages than did patients with fewer cusps. The ages of the 46 patients with unicuspid valves ranged from 26 to 75 years (mean \pm SD, 51 \pm 14); that of the 458 patients with bicuspid valves, from 27 to 91 years (mean \pm SD, 67 \pm 11); and that of the 417 patients with 3-cuspid valves, from 45 to 91 years (mean \pm SD, 74 \pm 8; $P < 0.001$). Of the 932 patients, 176 (19%) were in the 4 younger decades (21 to 60 years), and 756 (81%) were in the 4 older decades (61 to 100 years). Nearly two thirds (66%) of the 932 patients were aged 61 to 80 years at the time of aortic valve replacement. Of the 46 patients with unicuspid valves, 33 (72%) were in the 4 younger decades, and the other 13 were in the next 2 older decades (61 to 80 years). Of the 458 patients with bicuspid valves, 115 (25%) were in the 4 younger decades (21 to 60 years), and 343 (75%) were in the 4 older decades (61 to 100 years). Of the 417 patients with tricuspid aortic valves, 27 (6%) were in the 4 younger decades (21 to 60 years; 25 of the

27 in the sixth decade); the other 390 (94%) were in the 4 older decades (61 to 100 years). Of the 176 patients in the 4 younger decades, the aortic valves in 33 (19%) were unicuspid; in 115 (65%), bicuspid; and in 27 (15%), tricuspid. In contrast, of the 756 patients in the 4 older decades (61 to 100 years), the aortic valves were unicuspid in 13 (2%); bicuspid in 343 (45%); and tricuspid in 390 (52%).

The age range of the 932 patients was 26 to 91 years (mean \pm SD, 70 \pm 12). The 584 men ranged in age from 26 to 91 years (mean \pm SD, 69 \pm 11), and the 348 women, from 27 to 91 years (mean \pm SD, 71 \pm 11). Of the 584 men, 119 (20%) were in the 4 younger decades (21 to 60 years), and 465 (80%) were in the 4 older decades (61 to 100 years); of the 348 women, 57 (16%) were in the 4 younger decades, and 291 (84%) were in the 4 older decades.

Of the 932 patients, 490 (53%) also had coronary artery bypass grafting at the time of aortic valve replacement (Table 2). Coronary artery bypass grafting was performed in 7 (15%) of the 46 patients with unicuspid valves, in 211 (46%) of the 458 patients with bicuspid valves, in 268 (64%) of the 417 patients with tricuspid aortic valves, and in 4 (36%) of the 11 with undetermined valve structure. Of the 176 patients in the 4 younger decades (21 to 60 years), 59 (34%) had concomitant coronary bypass surgery; of the 756 patients in the 4

TABLE 3. Data in Patients Whose Stenotic Aortic Valves Are Shown in Figures 1–4

Aortic Valve Structure	Age, y	Sex	LV-Aorta PSG (S/D), mm Hg	LV-Aorta Mean Gradient (S/D), mm Hg	Aortic Valve Area, cm ²	Aortic Valve Weight, g
Unicuspid (unicommissural)						
Figure 1a	41	F	1.10	2.50
Figure 1b	48	M	23	23	1.40	5.84
Figure 1c	43	M	...	28
Figure 1d	39	M	41	...	1.00	7.39
Unicuspid (acommissural)						
Figure 2a	30	F	42	35	0.84	2.07
Figure 2b	75	F	53	54	0.57	1.67
Figure 2c	62	F	22	19	0.62	1.02
Figure 2d	73	M	25	32	1.12	2.73
Bicuspid						
Figure 3a	60	F	80	64	0.66	2.09
Figure 3b	72	M	46	46	0.88	3.46
Figure 3c	80	M	37	31	0.58	3.72
Figure 3d	63	M	71	...	0.70	1.61
Figure 3e	68	M	2.55
Figure 3f	69	M	...	25	...	2.97
Tricuspid						
Figure 4a	78	M	77	57	0.41	3.93
Figure 4b	53	M	2.90
Figure 4c	68	M	97	42	0.80	2.62
Figure 4d	85	F	82	...	0.50	1.69

LV indicates left ventricular; PSG, peak systolic gradient; and S/D, peak systole/end diastole.

older decades, 431 (57%) had concomitant coronary bypass surgery.

Discussion

The present study of 932 stenotic aortic valves operatively excised from 1993 to 2004 in patients >20 years of age has demonstrated that slightly more patients had congenitally malformed aortic valves (either unicuspid or bicuspid) than tricuspid aortic valves (54% versus 45%; indeterminate structure=1%). Among the 46 patients with unicuspid aortic valves, 42 (91%) had valves with 2 rudimentary commissures and 1 true commissure (Figure 1): Four had valves with 3 rudimentary commissures and no true commissures (Figure 2). We classify these latter 4 cases as unicuspid aocommissural aortic valves. These 4 cases in the past would have been classified by most investigators, we suspect, as rheumatic in origin. We, however, searched the medical records thoroughly for evidence of mitral valve disease in these 4 cases and found none. It is possible, of course, in rheumatic heart disease for aortic valve disease to be clinically apparent before the appearance of clinical evidence of mitral disease, and that could be the situation in these 4 cases. It is also possible that the cuspal fusion at each of the 3 rudimentary commissures was present at the time of birth, and therefore, this multifusion represents congenital heart disease. Lack of separation of each of 3 cusps before birth appears to us a more reasonable explanation of the valve disease in these 4 cases

than rheumatic heart disease manifesting itself clinically as isolated aortic valve disease.

Although the patients with unicuspid or bicuspid aortic valves clearly had congenital heart disease underlying their aortic stenosis, the cause of the aortic stenosis in the patients with 3-cuspid aortic valves is almost certainly acquired in origin. Although stenosis involving a 3-cuspid aortic valve unassociated with mitral valve disease has in the past most commonly been called “degenerative” in origin—a consequence of aging—we prefer to call these stenotic, 3-cuspid aortic valves (unassociated with mitral disease) “atherosclerotic” in origin. The evidence for attributing the calcific and other deposits on the aortic aspects of the 3 cusps in these patients to atherosclerosis is the following: (1) Patients with homozygous familial hypercholesterolemia (individuals with serum total cholesterol levels >800 mg/dL from the time of birth) develop aortic stenosis by the teenage years (without lipid-lowering therapy)¹; (2) patients >65 years of age with aortic stenosis involving a 3-cuspid aortic valve (unassociated with mitral valve disease) usually have extensive atherosclerosis involving the major epicardial coronary arteries and usually other arterial systems^{2,3}; (3) serum total cholesterol levels tend to be higher in patients with aortic stenosis involving a 3-cuspid aortic valve than in patients of similar age and sex without aortic stenosis⁴; (4) the use of lipid-lowering therapy (statins) has been demonstrated to slow the progression of aortic valve stenosis⁵; and (5) histological study of 3-cuspid, stenotic aortic valves has demonstrated that

these valves have features similar to those in arterial atherosclerotic plaques. It has been demonstrated that the cusps of congenitally bicuspid, stenotic valves are usually of unequal size; ie, that they differ in weight.⁶ Likewise, the cusps of 3-cuspid, stenotic aortic valves also often differ in weight. Roberts and Ko⁷ weighed 260 operatively excised, stenotic 3-cuspid aortic valves from patients having no evidence of mitral valve disease and found that all 3 cusps differed (by >0.1 g) in weight in 69 patients (26%), that one cusp differed in weight from the other 2 in 158 patients (61%), and that in only 33 patients (13%) were all 3 cusps of similar weight.

The first institution where a large number of operatively excised stenotic aortic valves were examined was the Mayo Clinic. Subramanian and colleagues⁸ in 1984 described 374 valves with "pure aortic stenosis" (no associated aortic regurgitation or only mild regurgitation); Passik and colleagues⁹ in 1987 examined another 646 operatively excised valves with "pure aortic stenosis"; and Subramanian et al¹⁰ in 1985 examined another group of operatively excised valves with "combined aortic stenosis and insufficiency." The difficulty in comparing their findings with those in the present study is that the former also included patients with coexistent mitral disease and children. Combining the findings of the 3 studies from the Mayo Clinic together indicated that 44 (4%) of their 1219 patients with operatively excised, stenotic aortic valves had unicuspid valves, 459 (38%) had bicuspid valves, 431 (35%) had "postinflammatory" valves, 257 (21%) had "degenerative" valves, and 28 (2%) had valves of indeterminate structure. Their inclusion of children appeared to increase the likelihood of congenitally malformed valves. These authors also intermixed etiology with structure, a process that prevented us from being entirely clear about valve structure in their cases. Their patients as a group were younger than those included in the present study because the earlier studies included both children and patients with unambiguous rheumatic heart disease. The present study, in contrast, made every reasonable attempt to exclude patients whose valve disease was of rheumatic etiology.

Turri and colleagues¹¹ in 1990 described operatively excised aortic valves from 602 patients having valve replacement, but these authors combined data from patients with pure regurgitation and those with some degree of aortic stenosis. That study also included patients who had concomitant mitral valve disease, and indeed, the most common cause of aortic stenosis (\approx 348 patients) in their patients was rheumatic heart disease (undefined; in 172 [49%]). Only 17 (5%) of their patients had congenitally bicuspid aortic valves, and only 44 (13%) had the "senile" type of stenotic valve, presumably 3-cuspid ones. Although it was not possible to separate the ages of their patients with stenotic valves from those with purely regurgitant valves, the mean ages of their stenotic cases were clearly much younger than patients included in the present study (mean age, \approx 50 versus 70 years).

Agozzino and associates¹² in 1992 described operatively excised aortic valves from 912 patients having valve replace-

ment in the 1980s: A total of 787 valves had some degree of stenosis, but there was no attempt to describe valve structure. These authors also included patients with associated mitral valve disease, and indeed, rheumatic heart disease was the most common etiology of the aortic valve stenosis (573 of 787 [73%]). "Degenerative calcification" was the explanation for the stenosis in the other 214 patients (27%). These authors also included children in their study. The mean ages of their patients with aortic stenosis was 47 years.

Several features of the present study make it different from previous studies on operatively excised, stenotic aortic valves. First, the study was limited to adults >20 years of age and excluded those patients who had had a previous aortic valvulotomy. Second, it excluded patients with associated mitral stenosis, which in adults is virtually always of rheumatic origin, and it also excluded patients having mitral valve replacement for any reason. Third, it included only patients whose stenotic aortic valve was excised in the last decade of the 20th century or the first decade of the 21st century. Fourth, the structure of the operatively excised stenotic aortic valve was determined by a single physician (W.C.R.), who has studied the aortic valve for >40 years. Fifth, it made no attempt to separate stenotic valves into those that were purely stenotic versus those that were both stenotic and regurgitant, a division that is fraught with error unless an aortogram or echocardiogram has been used for this determination.

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