Rate of Progression of Valvular Aortic Stenosis in Adults

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Until recently the hemodynamic severity of valvular aortic stenosis (AS) was evaluated only by cardiac catheterization. Now, Doppler echocardiography allows a noninvasive and accurate assessment of AS severity and can be used to study its progression with time. The progression of AS was assessed during a follow-up period of 6 to 45 months (mean 18) by serial Doppler examinations in 45 adult patients (21 men and 24 women, mean age 72 ± 10 years) with isolated AS. The following parameters were serially measured: left ventricular outflow tract diameter and velocity by pulsed Doppler, peak velocity of aortic flow by continuous-wave Doppler, to calculate peak gradient by the modified Bernoulli equation, and aortic valvular area by the continuity equation. At the initial observation, 13 of 45 patients (29%) were symptomatic (1 angina, 1 syncope and 11 dyspnea); during follow-up, 25 (55%) developed new symptoms or worsening of the previous ones (5 angina, 3 syncope and 17 dyspnea); 11 underwent aortic valve replacement and 3 died from cardiac events. Baseline peak velocity and gradient ranged between 2.5 and 6.6 m/s, and 25 and 174 mm Hg, respectively; aortic area ranged between 0.35 and 1.6 cm². With time, mean peak velocity and gradient increased significantly from 4 ± 0.7 to 4.7 ± 0.8 m/s ($p < 0.01$), and 64 ± 30 to 88 ± 30 mm Hg ($p < 0.01$), respectively. A concomitant reduction in mean aortic area occurred (0.75 ± 0.3 to 0.6 ± 0.15 cm²; $p < 0.01$). The rate of progression of AS (−0.72 to +0.14 cm²/year, mean −0.1 ± 0.13) was variable among patients and did not relate to age, sex, follow-up duration or symptoms. Patients with a reduction in left ventricular systolic function had a faster progression than did those with normal systolic function. In conclusion, a significant progression of AS may occur and a mild or moderate stenosis can become critical after a few years. Doppler echocardiography appears to be the ideal method for follow-up and can add new insights to the natural history of the disease.

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Until recently cardiac catheterization was the "reference" method to assess the severity of valvular aortic stenosis (AS) and its changes with time[1–8]; being invasive, however, this method could not be repeated indefinitely to evaluate the hemodynamic progression of the disease. Previous studies were performed in small groups of patients with AS in whom cardiac catheterization was repeated (once and rarely twice) usually because of a change in clinical status such as the appearance of symptoms.[3–7] This bias has limited our understanding of the natural history of AS, mainly in asymptomatic subjects. Currently, Doppler echocardiography allows an accurate assessment of the severity of AS by calculation of the transvalvular pressure gradient and aortic area[9–13]; therefore, this noninvasive technique can be repeated easily to examine the progression of disease with time.[14,15] This study analyzes the rate of progression of AS, using Doppler echocardiographic criteria.

METHODS

Study group: We prospectively followed up 45 adult subjects (24 women and 21 men, mean age 72 ± 10 years, range 42 to 90) with AS. All subjects gave informed consent. Criteria for diagnosis of AS included both physical signs, such as a decreased intensity of the second sound and a harsh systolic ejection murmur, and the presence on Doppler echocardiographic examination of thickened aortic cusps with reduced mobility and a maximal aortic jet velocity ≥2.5 m/s. On the basis of clinical history and 2-dimensional echocardiographic findings, the origin of AS was considered rheumatic in 7 patients and degenerative-calcific in 34; in 4 of the latter group, a bicuspid aortic valve was evident. Finally, the remaining 4 patients had a markedly calcific aortic valve and root, so no cause of AS was clearly identifiable.

Doppler echocardiographic examination: Each patient underwent a complete echo-Doppler examination at entry in the study and serially during a follow-up period of 6 to 45 months (mean 18); the ultrasound evaluation was always performed on request of the cardiologist or internist responsible for the care of the patient. These physicians also provided us with information on the clinical status of patients (appearance or worsening of symptoms, cause of death, and valve replacement) during follow-up. At least 3 echocardiograms were obtained in all but 5 patients in whom only 2 sets of data were available. Two commercial instruments (UM-8 and UM-9, Advanced Technology Laboratories) were used, and the following parameters were measured to assess the severity of AS: (1) peak velocity

of aortic jet, recorded with a nonimaging continuous-wave Doppler transducer from the ultrasound windows (apical, subcostal, right parasternal and suprasternal) that provided the highest velocity signal and the best envelope curve. Because the optimal signal was assumed to be near parallel to the direction of maximal transvalvular flow velocity, no angle correction was performed. From peak velocity (m/s), peak aortic pressure gradient (mm Hg) was calculated according to the modified Bernoulli equation.[9] (2) Aortic valve area was derived by the continuity equation, taking into account, besides the peak velocity of aortic jet, the diameter of the left ventricular (LV) outflow tract (measured from the 2-dimensional parasternal long-axis plane) and the flow velocity in the LV outflow tract (recorded with pulsed Doppler from an apical approach).[10–13] Furthermore, LV end-diastolic and end-systolic diameters and fractional shortening on the transverse plane were measured according to the recommendations of the American Society of Echocardiography[16] for the evaluation of LV function.

All echocardiograms were obtained by the same physician (PF); intraobserver variability was assessed in an independent group of 10 adults with AS. Two Doppler echocardiographic examinations were obtained in each patient, with an interval of 7 to 15 days without changes in clinical status. Mean coefficients of variation were 3% for peak velocity, 1.5% for LV outflow tract diameter, and 5% for aortic area.

Statistical analysis: Data are expressed as mean ± SD. Rates of change of Doppler parameters of AS severity were corrected for the duration of follow-up and indexed for the year of follow-up. Assessment of changes over time was obtained using paired *t* test to

TABLE I Clinical and Doppler Echocardiographic Data in 45 Patients with Aortic Stenosis

Pt.	Age (yr) & Sex	Etiology	Follow-Up (mos)	Maximal Velocity (m/s)		Aortic Valve Area (cm^2)		LV Fractional Shortening (%) (last)
				Entry	Last	Entry	Last	
1	42M	Rheumatic	24	3	3.9	1.2	0.9	50
2	54M	Rheumatic	9	4.5	4.4	0.9	0.6	20
3	55M	Bicuspid	17	4.5	5	0.75	0.65	52
4	55M	Bicuspid	25	3.2	4	1.4	1.1	50
5	59F	Rheumatic	11	4.3	4.8	0.7	0.6	50
6	61F	Rheumatic	33	6.6	6.8	0.4	0.4	44
7	61F	Rheumatic	18	4.1	5.5	0.7	0.5	50
8	62M		34	3.5	4.3	0.9	0.75	45
9	64F	Rheumatic	11	4.3	4.7	0.65	0.6	35
10	65M		24	3	4.3	1.1	0.8	46
11	65F		14	4.3	5	0.45	0.4	50
12	67M		10	3.6	4.5	0.7	0.55	38
13	69F	Rheumatic	24	4.4	5.4	0.6	0.5	50
14	69M	Degenerative	34	3.3	4.3	0.85	0.65	46
15	70F	Degenerative	19	3.5	3.3	0.75	0.8	43
16	70M	Degenerative	25	3	3.9	0.9	0.7	32
17	71M	Bicuspid	7	4.3	4.7	0.75	0.65	23
18	71M	Degenerative	19	4.6	5	0.6	0.55	32
19	72F	Degenerative	12	5.1	5.6	0.4	0.35	48
20	72M	Degenerative	33	3.5	4.9	1.6	0.8	33
21	72F	Degenerative	7	4.7	5.2	0.85	0.75	21
22	73F	Degenerative	13	3.4	4.1	0.65	0.55	40
23	73F	Bicuspid	6	5.2	5.1	0.4	0.4	21
24	73F	Degenerative	6	4	4	0.4	0.4	45
25	74F	Degenerative	21	2.7	4	0.95	0.65	50
26	74F	Degenerative	18	3.2	3.6	0.95	0.85	50
27	75F	Degenerative	13	5	5.4	0.5	0.45	54
28	76M	Degenerative	45	3.5	4.5	0.95	0.75	50
29	77M	Degenerative	31	2.5	3.8	1.3	0.65	22
30	77F	Degenerative	16	4.7	5.5	0.6	0.5	42
31	77M	Degenerative	16	5.5	5.8	0.4	0.4	50
32	77M	Degenerative	12	5	5	0.7	0.7	31
33	79F	Degenerative	31	2.7	4.9	1	0.6	45
34	79F	Degenerative	16	5.7	6.3	0.75	0.65	42
35	79F	Degenerative	30	4	5.3	0.6	0.45	38
36	79F	Degenerative	21	3.5	5.3	0.45	0.45	22
37	80M	Degenerative	11	3.2	3.5	0.6	0.7	25
38	81M	Degenerative	22	4	4.9	1	0.7	41
39	81F	Degenerative	12	4.8	5.3	0.55	0.45	52
40	82F	Degenerative	12	3.2	3.4	0.85	0.8	43
41	82F	Degenerative	9	4.5	4.7	0.35	0.3	23
42	85F	Degenerative	7	3.7	3.9	0.8	0.75	41
43	87M	Degenerative	10	4.7	4.6	0.65	0.5	23
44	87F	Degenerative	18	4.6	5	0.4	0.3	36
45	90M	Degenerative	9	3.1	3.5	0.95	0.4	16

LV = left ventricular.

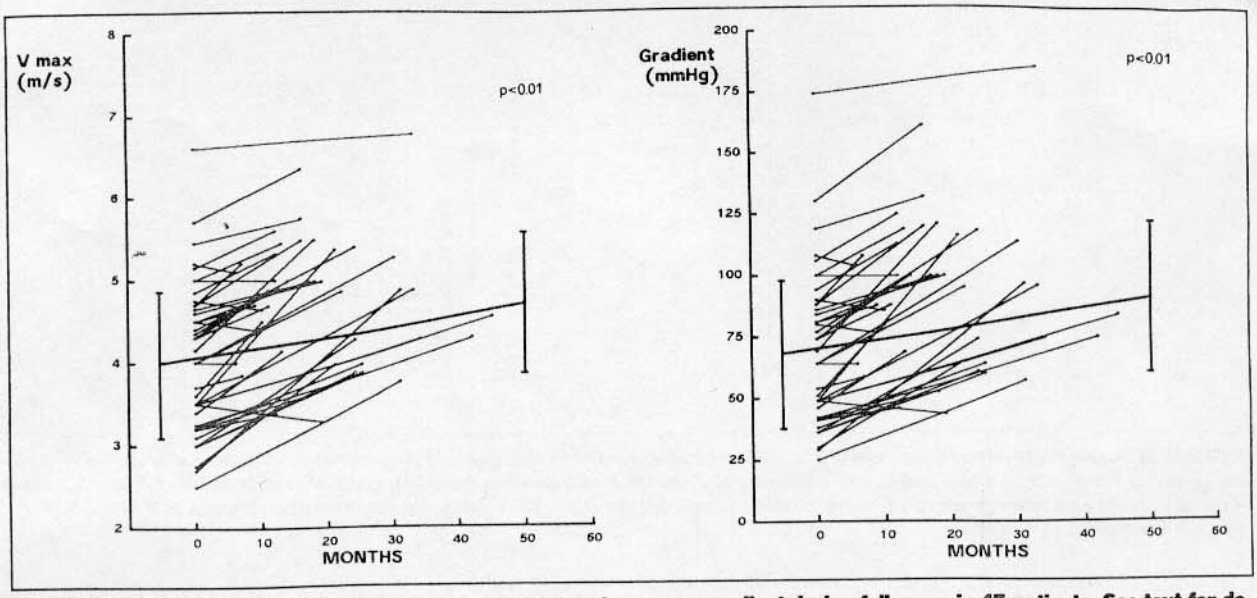

FIGURE 1. Change in maximal aortic jet velocity (V max) and pressure gradient during follow-up in 45 patients. See text for details.

compare the results of the initial and last echocardiographic examinations. Comparison of means between subgroups (with and without symptoms, with and without LV systolic dysfunction, and so forth) was performed with an unpaired *t* test. The effects of clinical features on the progression of AS were evaluated by linear regression analysis.

RESULTS

Clinical data: At entry to the study, 13 of 50 patients (29%) had symptoms probably due to AS (1 angina, 1 syncope and 11 dyspnea). During follow-up, 25 patients (55%) developed new symptoms or worsening of preexisting ones. The most frequent symptoms were angina (n = 5), syncope (n = 3) and dyspnea (n = 17); 13 patients underwent aortic valve replacement and 3 died (1 died suddenly after the recent onset of angina, and 2 died from progressive and refractory congestive heart failure).

Doppler echocardiographic data (Table I): At the initial study, mean peak velocity was 4.0 ± 0.7 m/s (range 2.5 to 6.6) corresponding with a peak pressure gradient of 64 ± 30 mm Hg (range 25 to 174); the aortic area ranged between 0.35 and 1.6 cm^2 (mean 0.75 ± 0.3). A trivial or mild aortic regurgitation was recorded by pulsed Doppler in 29 patients (64%). The last echocardiographic examination showed a peak velocity and pressure gradient significantly increased to 4.7 ± 0.8 m/s (range 3.3 to 6.8; $p < 0.01$) and 88 ± 30 mm Hg (range 44 to 185; $p < 0.01$), respectively (Figure 1). Furthermore, aortic area was significantly reduced during follow-up to 0.6 ± 0.15 cm^2 (range 0.3 to 1.1; $p < 0.01$) (Figure 2). No changes in the prevalence and severity of aortic regurgitation were observed with sequential echocardiograms.

An increase in peak velocity and pressure gradient was seen in most patients (39 of 45; 86.6%), whereas 6 had either no change or a decrease during follow-up; however, the valve area in the latter patients mildly increased in 2 (within the intraobserver mean coefficient of variation), remained unchanged in 2 and decreased in the remaining 2 owing to a concomitant reduction of LV outflow tract velocity.

The rate of progression of AS severity was expressed by the changes in Doppler parameters indexed for the year of follow-up; peak velocity increased with time at a mean rate of 0.4 ± 0.3 m/s/year (range −2 to 1) and peak gradient increased at a mean of 15 ± 10 mm Hg/year (range −8 to 38). However, aortic area decreased at a rate of −0.1 ± 0.13 cm^2/year (range −0.72 to 0.14). The rate of change of AS severity was lower than the mean coefficient of variation (5% for valve area; see Methods) in 8 patients; however, no significant differences in the rate of progression were observed between the study group considered as a whole

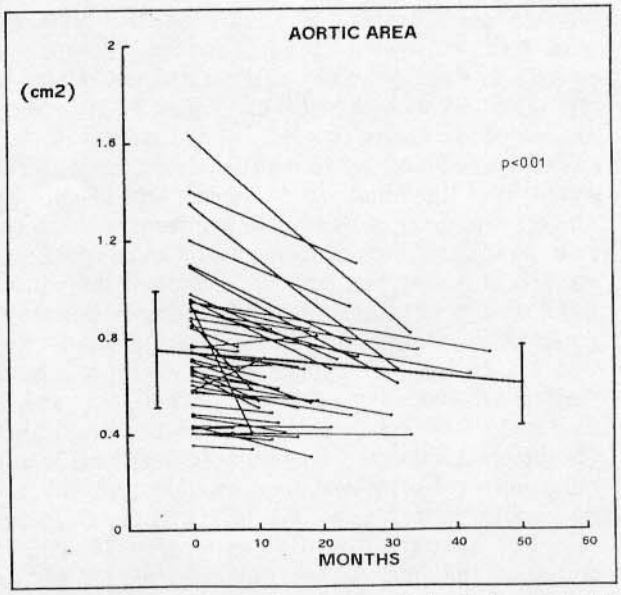

FIGURE 2. Change in aortic valve area during follow-up in 45 patients. See text for details.

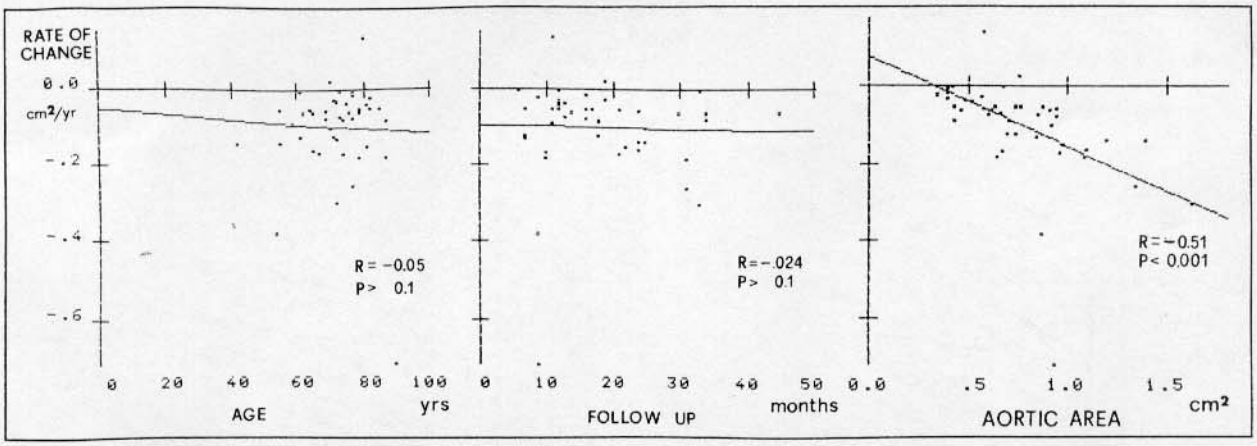

FIGURE 3. Linear regression analysis between rate of progression of aortic stenosis (expressed as rate of change of valve area/year of follow-up *[y axis]*) and age of patients *(left)*, duration of follow-up *(middle)*, and aortic area at entry *(right) (x axis)*. Rate of progression showed only an inverse relation of low degree (r = −0.51) with severity of aortic stenosis at initial Doppler echocardiographic examination.

TABLE II Clinical and Doppler Echocardiographic Features According to Left Ventricular Systolic Function

	Normal (n = 35)	Reduced (n = 10)	p Value
Age (yr)	71 ± 10	76 ± 10	NS
Women/men	20/15	4/6	NS
LV end-diastolic diameter (mm)	45 ± 6.5	61 ± 7	0.001
LV fractional shortening (%)	44 ± 6.5	21 ± 3.5	0.001
Aortic area (cm^2)			
Entry	0.75 ± 0.3	0.7 ± 0.3	NS
Last	0.6 ± 0.1	0.55 ± 0.15	NS
Follow-up (mos)	20 ± 9	12 ± 8	0.05
Rate of change in area (cm^2/yr)	−0.08 ± 0.065	−0.17 ± 0.24	0.05

Values are expressed as group means ± 1 SD. See text for details.
LV = left ventricular; NS = not significant.

and when these 8 patients were excluded. Therefore, in the subsequent analysis of results, the data presented refer to the entire study group. The rate of progression of AS was variable among patients and not related to sex, age or duration of follow-up (Figure 3). An inverse relation of low degree (r = −0.51), but statistically significant, was found between the rate of change of AS severity and the initial value of aortic area (Figure 3). The appearance or worsening of symptoms did not enable the identification of patients with more rapid progression of AS. In fact, although symptomatic patients had a smaller aortic area than did asymptomatic ones at the last echocardiographic examination (0.55 ± 0.15 vs 0.65 ± 0.15 cm^2), the rate of change of aortic area in the former group was −0.11 ± 0.16 cm^2/year and in the latter −0.09 ± 0.06 cm^2/year (p = not significant). On the other hand, the subgroup of 10 patients with a reduction of LV systolic function (identified by LV fractional shortening ≤25%) had a rate of change of aortic area significantly greater (−0.17 ± 0.24 cm^2/year) than that of those with preserved LV systolic function (−0.08 ± 0.065 cm^2/year; p <0.05) (Table II).

DISCUSSION

The results obtained in this prospective study of 45 patients with AS examined by Doppler echocardiography for a mean period of 18 months show that the severity of AS increases with time at a mean rate of 0.1 cm^2/year, but the rate of progression is variable among patients, so that mild or moderate AS can become critical in a few years. Similar results were found by previous studies using cardiac catheterization.[3–7] In accordance with these other studies,[6,7] we found no significant relation between the rate of progression and clinical features such as age, sex and duration of follow-up. Furthermore, as in other studies, the rate of change of AS severity was not different between symptomatic and asymptomatic patients.[4–6] Different results were reported in 2 recent studies that also used Doppler echocardiography. Otto et al[14] found that the appearance of clinical symptoms identified patients with a higher rate of progression (expressed by the rate of increase of pressure gradient or the rate of reduction of valve area, or both). Furthermore, Roger et al[15] found that the worsening of symptoms was related to the increase of pressure gradient.

In our study a significantly higher rate of progression of AS was observed in patients with a reduction of LV systolic function compared to those with normal systolic function. Wagner and Selzer[5] found similar results in their study performed with cardiac catheterization. They hypothesized that a reduction in LV performance (causing a decrease in cardiac output) will reduce the aortic valve opening force; this is another factor responsible for the severity of AS, in addition to the reduction of leaflet mobility. When aortic orifice area is reduced, an impairment of LV systolic function (either due to "afterload mismatch" or secondary to other mechanisms, such as coronary artery disease), by decreasing cardiac output, further reduces valve

area.[5,17] This mechanism of increase of AS severity was found mainly in older patients with degenerative-calcific AS in whom the primary pathologic process affecting the aortic valve is the calcification of the base of the leaflets (without commissural fusion), which become very sensitive to the opening force of LV contraction. We could not statistically evaluate this behavior in our study group because of the small number of patients with rheumatic or congenital AS compared with the degenerative-calcific group. However, the most rapid progression of AS severity (rate of change of aortic area -0.72 cm^2/year) observed in our study was in a 90-year-old man with calcific AS in whom a severe reduction of LV systolic function appeared during follow-up (LV fractional shortening decreased from 36 to 16%).

The role of reduction of cardiac output in determining the severity of AS emphasizes the importance of measuring the valve area, not just the pressure gradient, as an index of AS severity,[18] mainly in follow-up studies. Because valve area depends on pressure gradient as well as transvalvular volume flow (i.e., cardiac output), an increase in the severity of AS may occur, despite no change or even a decrease in pressure gradient, due to a reduction in cardiac output. In 2 of our patients, valve area decreased, despite a reduction in pressure gradient, due to a concomitant reduction of LV outflow tract velocity (see Results); the progression of AS would have been missed if only pressure difference was considered.

Study limitations: The majority of our patients (58%) had an aortic area ≤ 0.75 cm^2 at entry; therefore, the conclusions drawn from this study mainly apply to patients with severe AS. Although we found a significant inverse relation between the initial aortic area and its rate of change during follow-up, according to previous studies,[4,8,17] we recognize that the limited number of patients in our study with aortic area >0.75 cm^2 and the mean duration of follow-up does not allow us to conclude that there is a more rapid progression in patients with mild to moderate AS.

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