JACC Vol. 25, No. 3
February 1995:305–10

Progression of Aortic Stenosis in 394 Patients: Relation to Changes in Myocardial and Mitral Valve Dysfunction

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Objectives. **This study reports the results of echocardiographic follow-up in a large cohort of patients with aortic stenosis and correlates the progression of aortic stenosis with changes in the degree of mitral regurgitation and left ventricular hypertrophy and systolic dysfunction.**

Background. **Progressive aortic stenosis often causes left ventricular dysfunction and mitral regurgitation. Doppler echocardiography has greatly assisted in the noninvasive evaluation and follow-up of aortic stenosis. Nevertheless, the longitudinal follow-up of patients with Doppler echocardiography for the progression of aortic stenosis and the significance of progressive ventricular hypertrophy and mitral regurgitation have not been reported.**

Methods. **Serial Doppler echocardiography was performed in 394 consecutive patients with valvular aortic stenosis at baseline and after a mean follow-up period of 37 ± 16 months. Mean and peak aortic gradients, aortic valve area, left ventricular systolic and diastolic diameters and percent area change (shortening fraction) were expressed as continuous variables, and systolic dysfunction, mitral regurgitation, ventricular hypertrophy and filling properties were tabulated as categoric variables using a semiquantitative grading system.**

Results. **Peak and mean gradients increased by an average of 8.3 and 6.3 mm Hg/year, respectively; end-systolic and end-diastolic diameters increased by 1.9 and 1.6 mm/year, respectively; and aortic valve area decreased by 0.14 cm^2/year during the follow-up interval ($p < 0.001$ for all), indicating progression of aortic stenosis and ventricular dilation. Patients in the lowest quartile of aortic valve area and highest quartiles of mean and peak gradients had the least change compared with those in the highest quartile of aortic valve area and lowest quartile of mean and peak gradients ($p < 0.01$ for all). Patients with more mitral regurgitation at follow-up than at baseline had higher mean percent increase in mean and peak gradients as well as more progression of ventricular dilation and worsening systolic function compared with those with stable or improving mitral regurgitation ($p < 0.05$ for all). Similarly, subjects with worsening left ventricular hypertrophy had larger mean percent increase in mean and peak gradients than those with stable left ventricular hypertrophy ($p < 0.01$) but maintained stable ventricular volumes and systolic function. There was no correlation between the amount of change in mean or peak gradients and degree of deterioration in systolic function.**

Conclusions. **Aortic stenosis progresses predictably over time; however, systolic dysfunction is an inconsistent marker of the hemodynamic consequences of severe aortic stenosis. As an adaptive response to pressure overload, progressive hypertrophy appears to prevent ventricular dilation and development or worsening of mitral regurgitation. Conversely, progressive mitral regurgitation may be seen as a maladaptive consequence of increasing aortic stenosis.**

(J Am Coll Cardiol 1995;25:305–10)

Aortic stenosis is a progressive valvular abnormality resulting either from rheumatic involvement of the commissures or from calcification of a normal or bicuspid aortic valve. Although the symptomatology associated with aortic stenosis may be minimal for years, the appearance of severe symptoms such as angina, syncope or congestive heart failure warrants immediate corrective intervention on the aortic valve. In the past two decades, Doppler echocardiography has provided objective data for the serial follow-up of these patients, allowing the clinician to select the optimal time for operative intervention before irreversible damage to the left ventricle or significant cardiac events have occurred.

As aortic stenosis worsens, a number of hemodynamic and structural changes occur. These include progressive increase in transvalvular gradients and left ventricular hypertrophy, culminating eventually in decreased systolic and diastolic performance accompanied by ventricular dilation. As with other valvular lesions, progressive ventricular dysfunction and dilation may signal the need for operation even in the absence of symptoms. Therefore, a better understanding of how aortic stenosis may lead to progressive myocardial and mitral valve dysfunction would be useful. Various investigators (1–5) have reported the correlation of serial echocardiographic assessment of aortic stenosis with development of symptoms and the

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Manuscript received April 19, 1994; revised manuscript received July 29, 1994, accepted September 16, 1994.

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0735-1097/95/$9.50
0735-1097(94)00406-G

JACC Vol. 25, No. 3
February 1995:305–10

ways in which echocardiographically determined variables may affect the decision for intervention. The importance of mitral regurgitation and left ventricular hypertrophy as markers of significant hemodynamic embarrassment has not been systematically studied. This study's objective was to correlate the progression of aortic stenosis with changes in the degree of left ventricular hypertrophy, mitral regurgitation and left ventricular systolic dysfunction using the echocardiographic data from a large cohort of patients with aortic stenosis followed up at a single institution.

Table 1. Changes in Continuous Variables

	Annual Change	p Value
AVA (cm^2)	−0.4 (−14%)	< 0.001
PG (mm Hg)	8.3 (+30%)	< 0.001
MG (mm Hg)	6.3 (+26%)	< 0.001
EDD (mm)	1.6 (+2%)	< 0.001
ESD (mm)	1.9 (+4%)	< 0.001

AVA = aortic valve area; EDD (ESD) = end-diastolic (end-systolic) diameter; MG (PG) = mean (peak) aortic gradient.

Methods

Patients. From more than 60,000 echocardiographic studies performed between April 1986 and June 1992, 401 patients with aortic stenosis who had at least two studies ≥1 year apart were identified retrospectively. Seven were excluded because of incomplete studies, leaving 394 study patients.

Echocardiographic studies. All echocardiographic studies were performed in a standard manner and included parasternal long- and short-axis, as well as four-chamber, two-chamber and apical long-axis views. Most also had subcostal imaging. Mean and peak transaortic gradients were calculated with the modified Bernoulli equation (6), utilizing continuous-wave Doppler recordings from the highest velocity available from apical, suprasternal, upper right sternal border or subcostal view. The aortic valve area was computed with the continuity equation (6,7), using standard methods. Left ventricular cavity dimensions (end-systolic and end-diastolic diameters) were derived from the M-mode analysis at the level of the mitral valve chordae. Some of the aforementioned variables were not acquired in all studies, especially in the earlier period.

Left ventricular hypertrophy. A qualitative assessment of the severity of left ventricular hypertrophy was made on the basis of visual appraisal of thickness of the walls in different views of the left ventricle. In 287 patients, assessment of left ventricular hypertrophy was assisted by M-mode derived average of the posterior wall and septal thickness in end diastole in the frames permitting adequate visualization of the endocardial borders. The criteria used for translation of the thickness into a grading system for hypertrophy were as follows: *nonexistent* (0 = thickness <13 mm); *mild* (1 = thickness 13 to 16 mm); *moderate* (2 = thickness 16 to 20 mm); or *severe* (3 = thickness >20 mm). When M-mode images of good quality were not available, wall thickness was estimated from two-dimensional echocardiographic images, utilizing the wall thickness in the parasternal short-axis or subcostal view.

Mitral regurgitation was assessed qualitatively from the apical four-chamber view and graded from 0 to 3 (0 = none; 3 = severe) according to the width and length of the regurgitant jet and its spatial extent in the left atrial cavity on the basis of the grading system developed by Helmke et al. (8) and adapted for intraoperative echocardiography to a four-point scale (9). We combined the moderate and moderately severe regurgitation into grade 2. Left ventricular systolic dysfunction was classified using visual assessment of wall motion as none, mild, moderate and severe (0 to 3). In 287 patients in whom adequate measurements of end-diastolic (EDD) and end-systolic diameters (ESD) were available, systolic function (SF) was evaluated as a change in left ventricular area using the following formula (10): $SF = [(EDD)^2 - (ESD)^2]/(EDD)^2 \times 100$. These two methods of estimation of systolic function were independent of each other, and the latter was calculated after interpretation of the study by the reading physician. The ratio of the early (E) to late (A) filling velocities of the left ventricle were assessed from the apical windows placing the pulsed Doppler sample volume at the level of the mitral valve leaflet tips and was categorized as normal (E > A) or abnormal (E < A). All qualitative assessments were performed in blinded manner by independent experienced echocardiographers. When more than two echocardiographic studies were available for an individual patient, only the first and last test before any surgical or percutaneous intervention were evaluated.

Statistics. Analysis of variance was performed to investigate the association between changes in left ventricular hypertrophy, mitral regurgitation, left ventricular systolic dysfunction and changes in aortic valve area, mean and peak gradients and end-systolic and end-diastolic diameters, using the Bonferroni correction for multiple-group comparison. In addition, a linear regression model was used to identify the dependence of changes in aortic valve area and mean and peak gradients on the initial value of the variable and the interval of follow-up. Mitral regurgitation, left ventricular hypertrophy and systolic function were considered to be worsening if the assigned value increased by at least one grade on the scale of 0 to 3 previously described. An unpaired *t* test was used to compare means of categoric variables in different subgroups.

Results

Study patients. Three hundred ninety-four patients with aortic stenosis and adequate follow-up were enrolled in this study (238 [60%] men, 156 [40%] women; mean [±SD] age 65 ± 12 years). They were followed for a mean of 1,016 ± 482 days (37.2 ± 16.2 months), with 67% of the cohort followed up >2 years. Twenty percent of the study patients underwent corrective intervention of the diseased aortic valve after the last echocardiographic study evaluated for this report.

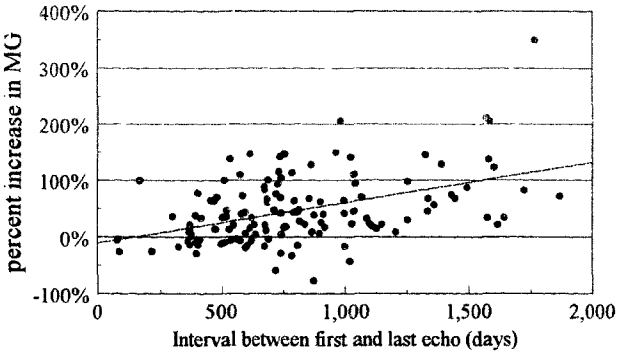


Figure 1. Change in mean aortic gradient (MG) versus interval of follow-up. Even after removal of the outlying value of 350% for mean gradient, the correlation between the mean increase in mean gradient and the interval of follow-up remains highly significant: $y = 0.0006x - 0.03$; $r = 0.40$; $p < 0.0001$. echo = echocardiographic study.

Continuous variables. Aortic valve area, peak and mean gradients and end-systolic and end-diastolic diameters changed significantly during the follow-up period, indicating worsening aortic stenosis and left ventricular dilation ($p < 0.001$ for all) (Table 1). There was a statistically significant correlation between the length of observation and percent change in aortic valve area and peak and mean gradient ($p < 0.007$ for all (Fig. 1)). Analysis of the degree of aortic stenosis severity by quartiles at the time of the initial visit revealed that patients with the most critical stenosis (lowest quartile, aortic valve area of 0.3 to 0.76 cm^2) had a smaller percent decrease in their valve area over the study period than those with the mildest stenosis at presentation (highest quartile, aortic valve area >1.2 cm^2; 5 ± 39% vs. 25 ± 29%, respectively, $p = 0.04$). Age did not correlate with the progression of stenosis ($r = 0.19$). Similarly, the percent change in mean and peak gradients was greater in the quartiles with lowest initial values than in the highest ones (48 ± 64% vs. 19 ± 40%, $p = 0.03$ for mean gradient and 88 ± 98% vs. 21 ± 40%, $p < 0.001$ for peak gradient, respectively). Patients with and without aortic valve calcification at the final study had significantly different changes in peak gradient (62% vs. 40%, respectively, $p = 0.013$).

The following linear regression models describe the dependence of changes in aortic valve area and mean and peak gradients (ΔAVA, ΔMG and ΔPG, respectively) on their initial values and interval of follow-up (t = years):

Table 3. Changes in Left Ventricular Hypertrophy

	Final LVH			
Initial LVH	None	Mild	Moderate	Severe
None	43	44	2	2
Mild	38	159	41	10
Moderate	2	22	11	6
Severe	2	2	3	7

$p = 0.008$; sign test = −18. LVH = left ventricular hypertrophy.

$$\Delta AVA\,(\%) = -25.2 \times AVA - 6.0 \times t + 25.8, \quad r = 0.35, \quad p < 0.001;$$

$$\Delta MG\,(\%) = -1.0 \times MG + 24.8 \times t + 15.1, \quad r = 0.51, \quad p < 0.001;$$

$$\Delta PG\,(\%) = -0.7 \times PG + 14.1 \times t + 36.0, \quad r = 0.38, \quad p < 0.001.$$

Each of the initial values of the variables made a highly significant contribution to this model ($p = 0.003$, 0.004 and 0.0003 for aortic valve area and mean and peak gradients, respectively), and the negative signs indicate that the most severe stenoses were associated with the smallest percent change, independent of the duration of observation.

Categoric variables. *Mitral regurgitation* was present in 160 patients (41%) at the beginning of the study. Over time, there was a trend toward worsening mitral regurgitation, such that 141 of all patients (36%) had worsening mitral regurgitation, 208 (53%) had no change, and 45 (11%) had less mitral regurgitation at the end of the study ($p < 0.001$) (Table 2). The duration of observation did not correlate with the amount of deterioration in mitral regurgitation.

Left ventricular hypertrophy was present in 303 patients (77%) at the time of the first study. One hundred five patients (27%) of the entire cohort demonstrated worsening of left ventricular hypertrophy during the study; 220 (57%) had no change; and 69 (16%) had less left ventricular hypertrophy at the end of the study ($p = 0.008$ for the trend for increasing hypertrophy) (Table 3). There was a significant association between the duration of follow-up and the degree of worsening of left ventricular hypertrophy ($p < 0.001$).

The qualitatively assessed left ventricular systolic function was normal in 318 patients (81%) initially. It deteriorated in 94 (24%), remained unchanged in 279 (71%) and improved in 21 (5%) by the end of the follow-up ($p < 0.001$ for the trend toward worsening function) (Table 4). In 287 patients in whom the percent change in left ventricular area was available (shortening fraction), the two methods demonstrated a signif-

Table 2. Changes in Mitral Regurgitation

	Final MR			
Initial MR	None	Mild	Moderate	Severe
None	132	69	29	4
Mild	21	49	32	3
Moderate	6	14	26	4
Severe	1	1	2	1

$p < 0.001$; sign test = −48. MR = mitral regurgitation.

Table 4. Changes in Left Ventricular Systolic Function

	Final LVSD			
Initial LVSD	None	Mild	Moderate	Severe
None	246	44	24	4
Mild	14	15	16	2
Moderate	0	4	16	4
Severe	0	0	3	2

$p < 0.001$; sign test = −36.5. LVSD = left ventricular systolic dysfunction.

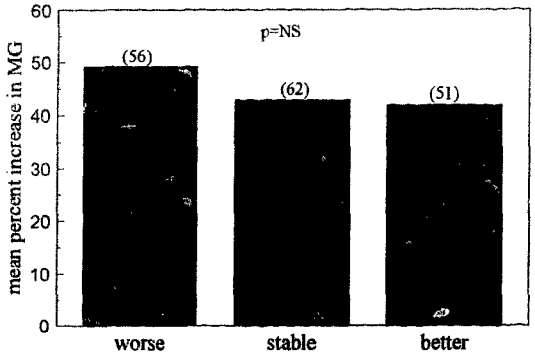


Figure 2. Relation between changes in mean aortic gradient (MG) and changes in systolic function. There was no significant difference between changes in mitral gradient among patients with various degrees of systolic dysfunction. **Numbers in parentheses** = numbers of patients.

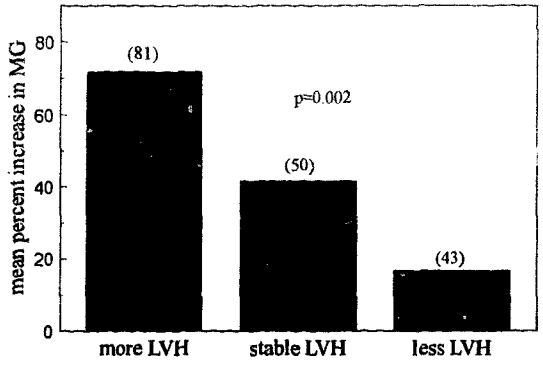
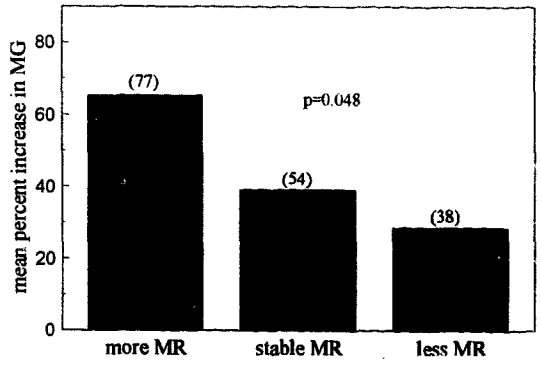


Figure 4. Relation between changes in mean aortic gradient (MG) and changes in left ventricular hypertrophy (LVH). Patients with increasing left ventricular hypertrophy had a greater increase in mean gradient than patients with stable or decreasing hypertrophy. **Numbers in parentheses** = number of patients.

icant relation by the Spearman correlation test ($r = -0.64$, $p < 0.01$). There was no statistical correlation between mean percent change in mean or peak gradients or aortic valve area and changes in systolic function (Fig. 2). The changes in systolic function correlated inversely with percent changes in end-systolic diameter ($p < 0.001$).

Relation between categoric and continuous variables. Patients with increasing mitral regurgitation by at least one grade had a significantly higher mean percent increase in mean gradient compared with the group with no change or decreasing regurgitation (65% vs. 39% vs. 28%, respectively, $p = 0.048$) (Fig. 3). Moreover, the same relation existed for changes in peak gradient, but the association with changes in aortic valve area was not significant. In addition, patients who developed worsening mitral regurgitation during the study demonstrated an increase in end-systolic diameter (from 33.5 ± 9 to 37.2 ± 12 mm, $p = 0.01$), whereas patients without increasing mitral regurgitation had no significant change in end-systolic diameter (from 31.7 ± 8 to 33.1 ± 10 mm, $p = 0.13$). Increasing mitral regurgitation was also associated with a significant decrease in systolic function, expressed as percent change in left ventricular area (from 58 ± 12% to 53 ± 18%, $p = 0.029$), whereas patients without worsening mitral regurgitation exhibited stable systolic function (from 59 ± 11% to 60 ± 15%, p = NS). Finally, there was no significant change in the average left ventricular hypertrophy score in patients with increasing mitral regurgitation (from 0.94 ± 0.67 to 0.99 ± 0.77, p = NS) compared with those with stable mitral regurgitation who had a statistically significant increase in the score (from 0.95 ± 0.70 to 1.09 ± 0.79, $p = 0.03$), using an unpaired *t* test.

Figure 3. Relation between changes in mean aortic gradient (MG) and changes in mitral regurgitation (MR). Patients with increasing mitral regurgitation had a greater increase in mean gradient than patients with stable or decreasing regurgitation. **Numbers in parentheses** = number of patients.



Patients with increasing severity of ventricular hypertrophy by at least one grade had a significantly higher mean percent increase in mean gradient compared with patients with no change or even regressing hypertrophy (72% vs. 41% vs. 17%, respectively, $p = 0.002$) (Fig. 4). Again, this correlation held true for mean percent change in peak gradient, although the association with changes in aortic valve area did not reach statistical significance. Progression of left ventricular hypertrophy was not associated with any significant changes in end-diastolic diameter, end-systolic diameter or systolic function (p = NS for all three). In contrast, patients without increasing wall thickness demonstrated a significant increase in end-diastolic diameter (from 50.3 ± 8 to 52.9 ± 10 mm, $p = 0.002$) and in end-systolic diameter (from 32.5 ± 9 to 35.6 ± 12 mm, $p = 0.001$) as well as significant decrease in systolic function, expressed as percent change in left ventricular area (from 59 ± 12% to 56 ± 17%, $p = 0.04$) and an increase in the average mitral regurgitation grade (from 0.58 ± 0.76 to 0.93 ± 0.87, $p < 0.0001$).

In contrast to these positive correlations, in general, patients with progressive systolic dysfunction (one or more grade increase) did not have significantly different mean percent changes in mean or peak aortic gradients or aortic valve area compared with patients with stable ventricular function ($p = 0.88$, 0.83 and 0.08, respectively) (Fig. 4).

Three hundred sixty-four patients (92%) had a normal left ventricular filling pattern at the beginning of the study. Fifty-

Table 5. Progression of Aortic Stenosis: Comparison Studies

Method	Study	No. of Pts	Follow-Up (mo)	Change in AVA (cm^2/yr)	Change in PG (mm Hg/yr)
Doppler*	Faggiano et al. (1)	45	18	0.10	16
Doppler-cath	Shub et al. (2)	108	22	NA	NA
Phone	Pellikka et al. (3)	143	20	NA	NA
Doppler*	Roger et al. (4)	112	25	NA	NA
Doppler*	Current study	394	37	0.14	12
Doppler	Thoreau et al. (11)	25	57	0.15	NA
Cath	Bogart et al. (12)	11	59	0.1	NA
Cath	Cheitlin et al. (13)	29	43	NA	16
Cath	Wagner and Selzer (14)	50	42	0.13	NA
Cath	Nestico et al. (15)	29	71	NA	0–4
Cath	Davies et al. (16)	65	84	NA	6.5 (MG)
Cath	Jonasson et al. (17)	26	108	0.1	NA

*Most relevant comparison studies. Numbers in parentheses are reference numbers. Cath (cath) = catheterization; NA = not applicable; other abbreviations as in Table 1.

nine patients (15%) developed abnormal filling at the end of the study ($p < 0.001$ for the trend), and the length of observation correlated significantly with the chance of developing an abnormal filling profile ($p = 0.013$).

Discussion

Previous studies. Aortic stenosis is a common valvular abnormality that progresses over time as a result of commissural fusion or calcium deposition. In its late stages, patients with aortic stenosis develop left ventricular systolic and dysfunction and hypertrophy, abnormal ventricular filling, mitral regurgitation and symptoms of heart failure, syncope or angina. Several reports based on results of cardiac catheterization described the evolution of aortic stenosis over long periods of time, correlating the initial hemodynamics to future cardiac events (Table 5). We believe that the echocardiographic progression of aortic stenosis has not been studied in any patients groups as large as that in our study. One small series by Faggiano et al. (1) studied 45 patients followed up for 18 months. Thoreau et al. (11) studied 25 patients for 57 months and documented a faster rate of decrease in aortic valve area in patients with milder degrees of aortic stenosis at the beginning of the observation period. The report by Roger et al. (4) is similar to our study in its retrospective nature. They followed up 112 patients for an average duration of 25 months but used peak aortic velocity and did not calculate the aortic valve area. As these investigators admit, this technique is imprecise because the aortic flow velocity varies significantly with changes in left ventricular function and afterload. Essentially, their findings support ours in that changes in systolic function do not correlate closely with the progression of aortic stenosis. We believe that our study is the first to provide long-term echocardiographic follow-up (average of 3 years) in a large group of patients evaluated serially for the evolution of aortic stenosis. It demonstrates a rate of progression of aortic valve narrowing of 0.14 cm^2/year, similar to that reported by others (Table 5).

Present study. We observed that patients having worsening mitral regurgitation or ventricular hypertrophy demonstrated a greater increase in transaortic gradients than those without these features. Those who had an increase in the degree of mitral regurgitation by one grade or more over the study period had a significant increase in end-diastolic and end-systolic diameters, accompanied by a decrease in systolic function. These patients had no significant change in left ventricular hypertrophy grade. Conversely, patients with a stable degree of mitral regurgitation demonstrated no significant change in end-systolic diameter or systolic function, but their left ventricular hypertrophy grade increased significantly ($p = 0.03$). Similarly, subjects with worsening left ventricular hypertrophy had no change in end-diastolic and end-systolic diameters and systolic function in conjunction with a modest increase in the mitral regurgitation grade. In contrast, patients with stable wall thickness demonstrated a significant increase in end-diastolic and end-systolic diameters as well as a marked decrease in systolic function. These changes were accompanied by an increase in the mitral regurgitation grade.

Implications. The data presented enable us to speculate on the relation between aortic stenosis and the development and progression of mitral regurgitation and wall thickening. It appears that increasing wall thickness is an adaptive mechanism that allows generation of higher intracavitary pressure necessary for blood ejection. It also limits the propensity for left ventricular dilation, which is the likely culprit in the development of mitral regurgitation by means of annular distension. The pressure overload imposed on the left ventricle by the progressive narrowing of the aortic valve can lead to an adaptive increase in the muscle mass in an attempt to preserve the forward output. The progressive left ventricular hypertrophy that develops in some patients allows preservation of cavity size despite increasing pressures. In others, conservation of

forward output is lost because ventricular dilation leads to mitral regurgitation. Whether it is the rapidity with which aortic stenosis progresses or other genetic or environmental factors that determine the morphologic and physiologic response to progressive aortic stenosis is not clear from the present study. As shown by Gunther and Grossman (18), the degree of hypertrophy developed as a consequence of aortic stenosis may reach a point at which it is no longer beneficial. This occurs because of a marked increase in the systolic wall stress, which leads to a reduction in ejection fraction. The defect observed in fiber shortening is not related to intrinsic muscle dysfunction but to a mismatch between the degree of wall thickening and the increased afterload. Sasayama et al. (19) demonstrated this concept in dogs, suggesting reversibility of the process and improvement in fiber shortening when the obstruction is relieved. Patients whose ventricles are able to remodel by developing more hypertrophy and limiting the degree of left ventricular dilation and mitral regurgitation may tolerate their aortic stenosis more favorably. This is supported by the fact that patients with increasing mitral regurgitation or stable ventricular hypertrophy, or both, were more likely to have had a decrease in systolic function, which is an accepted poor predictor of event-free survival. The finding that systolic dysfunction did not correlate with aortic stenosis progression, whereas increases in mitral regurgitation did, may be explained by the systolic dysfunction being masked by the increasing mitral regurgitation, by means of the unloading effect into a low pressure chamber in the presence of significant resistance to forward ejection.

Study limitations. Limitations of this study include its retrospective nature and the qualitative estimation of mitral regurgitation, ventricular hypertrophy and systolic function. Unfortunately, we did not have sufficient data to calculate left ventricular mass, regurgitant fraction or regurgitant orifice area. Moreover, the use of wall thickness as a substitute for left ventricular mass index may have underestimated the development of hypertrophy in patients in whom significant ventricular dilation occurred with minimal or no increase in wall thickness. Nevertheless all qualitative categoric variables were interpreted by experienced echocardiographers unaware of the study at the time of reading. Insufficient follow-up in patients who underwent surgical correction precluded the assessment of regression of hypertrophy and mitral regurgitation, which would have lent further support to the mechanisms proposed above. This subset of patients represents an important subject for future study.

Conclusions. Aortic stenosis, as measured by transaortic gradients and aortic valve area, progresses predictably over time at an average rate of ~0.14 cm^2/year. Increasing wall thickness is an adaptive mechanism to pressure overload that is associated with less ventricular dilation and mitral regurgitation. Conversely, failure to increase the degree of hypertrophy is accompanied by ventricular enlargement, development of mitral regurgitation and systolic dysfunction. Systolic dysfunction is an imperfect predictor of the severity and progression of aortic stenosis. Further research is needed to elucidate the different mechanisms of left ventricular remodeling that occurs in the presence of significant pressure overload.

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