Doppler echocardiographic assessment of long-term progression of mitral stenosis in 103 patients: Valve area and right heart disease

7 authors, including:

Alex Sagie
Meir Medical Center
209 PUBLICATIONS   **4,742** CITATIONS

SEE PROFILE

Luis Rodríguez-Padial
Complejo Hospitalario de Toledo
256 PUBLICATIONS   **1,308** CITATIONS

SEE PROFILE

Doppler Echocardiographic Assessment of Long-Term Progression of Mitral Stenosis in 103 Patients: Valve Area and Right Heart Disease

ALEX SAGIE, MD, NELMACY FREITAS, MD, LUIS R. PADIAL, MD, MARCIA LEAVITT,
ELEANOR MORRIS, RDCS, ARTHUR E. WEYMAN, MD, FACC, ROBERT A. LEVINE, MD, FACC

Boston, Massachusetts

Objectives. The purpose of this study was to determine, in a large referral population, the rate of echocardiographic change in mitral valve area (MVA) without interim intervention, to determine which factors influence progression of narrowing and to examine associated changes in the right side of the heart.

Background. Little information is currently available on the echocardiographic progression of mitral stenosis, particularly on progressive changes in the right side of the heart and the ability of a previously proposed algorithm to predict progression.

Methods. We studied 103 patients (mean age 61 years; 74% female) with serial two-dimensional and Doppler echocardiography. The average interval between entry and most recent follow-up study was 3.3 ± 2 years (range 1 to 11).

Results. During the follow-up period, MVA decreased at a mean rate of 0.09 cm²/year. In 28 patients there was no decrease, in 40 there was only relatively little change (<0.1 cm²/year) and in 35 the rate of progression of mitral valve narrowing was more rapid (≥0.1 cm²/year). The rate of progression was significantly greater among patients with a larger initial MVA and milder mitral

stenosis (0.12 vs. 0.06 vs. 0.03 cm²/year for mild, moderate and severe stenosis, p < 0.01). Although the rate of mitral valve narrowing was a weak function of initial MVA and echocardiographic score by multivariate analysis, no set of individual values or cutoff points of these variables or pressure gradients could predict this rate in individual patients. There was a significant increase in right ventricular diastolic area (17 to 18.7 cm²) and tricuspid regurgitation grade (2+ to 3+; p < 0.0001 between entry and follow-up studies). Progression in right heart disease occurred even in patients with minimal or no change in MVA. Patients with associated aortic regurgitation had a higher rate of decrease in MVA than did those with trace or no aortic regurgitation (0.19 vs. 0.086 cm²/year, p < 0.05).

Conclusions. The rate of mitral valve narrowing in individual patients is variable and cannot be predicted by initial MVA, mitral valve score or transmitral gradient, alone or in combination. Right heart disease can progress independent of mitral valve narrowing.

(J Am Coll Cardiol 1996;28:472–9)

Several clinical studies from the presurgical era have shown that the rate of progression of rheumatic mitral stenosis varies widely among patients (1–3). Although clinical progression has been thoroughly investigated, there is little information currently available regarding the echocardiographic progression of mitral stenosis and mitral valve area as such. Only one previous echocardiographic study (4) investigated the rate of mitral valve narrowing and the factors that influence it in 50 patients (16 with progressive narrowing). That study proposed that progression could be predicted by mitral valve echocar-

diographic score and transmitral gradient, with implications for the frequency of follow-up and prognosis. However, that predictive algorithm has not been subsequently confirmed in another patient group, and mitral valve area (MVA) in that study was determined by the indirect pressure half-time method, which is affected by factors other than MVA (5,6).

Although the hemodynamic consequences of mitral stenosis affect mainly the pulmonary vascular bed and right side of the heart, there are no available data obtained with two-dimensional and Doppler color flow echocardiography regarding the rate of progression of right heart and pulmonary vascular disease. Such data are important because clinical deterioration may reflect changes in the right-sided response to mitral stenosis unrelated to changes in mitral valve area.

The purpose of the present study, therefore, was 1) to determine the rate of change in mitral valve area in the absence of intervention by using direct two-dimensional echocardiographic planimetry and the pressure half-time method in a large referral population with mitral stenosis (never studied before by planimetry); 2) to determine which factors influence progression of mitral valve narrowing; and 3) to determine which changes occur in right atrial, annular and ventricular size and function, including tricuspid regurgitation and pulmonary

hypertension, as a function of the progression of mitral stenosis.

Methods

Study patients. Between 1983 and 1993, a total of 118 patients with mitral stenosis had an entry and follow-up two-dimensional echocardiogram with a ≥1-year follow-up interval and without interim intervention (surgical or percutaneous valvulotomy). Of these patients, 103 had a rheumatically deformed mitral valve and measurable MVA by either planimetry, pressure half-time method, or both, and were retrospectively reviewed. There were 76 women (74%) and 27 men (26%); the mean age was 61 ± 16 years (range 22 to 84). The average interval between entry and most recent follow-up echocardiographic study was 3.3 ± 2 years (range 1 to 11). Two patients had had commissurotomy before their initial study and none had had previous percutaneous valvulotomy.

Echocardiographic analysis. A complete two-dimensional and Doppler echocardiographic examination was performed by using a Hewlett-Packard ultrasound imager with a 2.5-MHz phased array transducer. Mitral valve area was assessed by both direct planimetry (7) and the pressure half-time method (8) whenever possible. With the short-axis view, care was taken to scan the mitral valve from tips to base to obtain the smallest valve orifice in early diastole. Transmitral inflow velocities were recorded by Doppler echocardiography from the apical four-chamber view. Valve areas were measured by using an average of five beats during sinus rhythm and seven during atrial fibrillation. Studies were reviewed and measured by one trained observer who did not know whether a study was initial or follow-up. Doppler spectra were traced and analyzed to determine peak and mean transmitral gradients. Mitral valve area assessment at entry and follow-up study was available by planimetry in 92 patients and by the pressure half-time method in the remaining 11 (evenly distributed over the range of values for mitral valve area decrease/year). Mitral valve area by the pressure half-time method was available in a total of 51 patients (the 11 with pressure half-time only and 40 more) so that both planimetry and half-time areas at entry and follow-up were available for comparison in 40 patients. A previously described semiquantitative echocardiographic assessment of mitral valve score (9) was obtained in each patient at entry by assigning a value of 0 to 4 (with increasing abnormality) to each of four morphologic characteristics of the valve: leaflet mobility, thickening, calcification and subvalvular thickening. The presence of mitral regurgitation on the initial study was assessed with pulsed Doppler study or color flow mapping, or both. The severity of regurgitation was evaluated in multiple views and graded from 0 to 4+ (severe) according to jet penetration into the left atrium (10,11). The presence and severity of aortic regurgitation (grade 0 to 4) was judged from the ratio of cross-sectional area of the proximal regurgitant jet and left ventricular outflow tract, as previously described (12). The progression of both mitral and aortic regurgitation was analyzed in patients in whom Doppler flow mapping was

available both at entry and follow-up studies (43 with mitral, 44 with aortic regurgitation).

Right heart measurements. Echocardiographic images were obtained during quiet end-expiration in a standard apical four-chamber view optimized to obtain the longest right ventricular long-axis and its largest short-axis diameters at the base and midventricular level, with the greatest visualized excursion of the tricuspid leaflets (13,14). The right ventricular end-systolic and end-diastolic cavity areas were traced in the same view, and the percent change in area was calculated. The maximal diastolic tricuspid annulus diameter was measured from insertion of the septal to insertion of the anterior tricuspid leaflet. Right ventricular systolic pressures were estimated by continuous wave Doppler study by using the modified Bernoulli equation ($4 \times$ [peak tricuspid regurgitation velocity]^2), adding 10 mm Hg for the estimated right atrial pressure (15–18).

Tricuspid regurgitation was evaluated in multiple views and graded from 0 to 4+ by integrating both Doppler extent of the regurgitant jet and evidence of systolic flow reversal in the inferior vena cava or hepatic veins (18). Regurgitation was graded as trace [1] if jet area occupied <10% of right atrial area; mild [2] if it occupied <20%; moderate [3] if it occupied 20% to <33%; and severe [4] if it occupied ≥33%, on the basis of reported correlations with surgical and angiographic data (19–21). If the ratio of jet area to right atrial area was close to a cutoff point, jet eccentricity increased the grade to the next higher value because eccentric wall jets appear smaller than comparable free jets (22,23). Systolic flow reversal in the inferior vena cava or hepatic veins by pulsed Doppler echocardiography was considered to indicate at least moderate regurgitation regardless of the other findings (20).

Data analysis. Data were expressed as mean value ± SD. Entry and follow-up data were compared by two-way repeated measures analysis of variance by using the statistical program BMDP 4V (BMDP Statistical Software, 1993), with multiple comparisons protection by means of an overall T^2 test. This analysis was also used to compare changes in right heart measurements in the group with progression of stenosis (decrease in MVA ≥0.1 cm^2/year) and the group without progression (decrease in MVA <0.1 cm^2/year, see later). Missing data were filled in as necessary by the BMDPAM statistical routine. Multiple stepwise linear regression analysis was performed to identify predictors for the rate of decrease in MVA/year.

The variables initially entered into the model were age, gender, initial MVA, mitral valve morphologic score, peak and mean transmitral gradients, degree of mitral regurgitation, left atrial size and prior commissurotomy. The univariate correlation coefficients for these variables were determined and were also entered into a multivariate model for predicting the rate of change of MVA with use of the RS1 statistical package (Bolt, Beranek and Newman, 1993). Forward stepping was used, with the F to enter and F to remove any variable selected so that the corresponding significance level (outer tail area) was <0.05; no variables were forced into the model. The same set of variables was also used to identify predictors for the rate

Table 1. Characteristics of 103 Study Patients at Entry and at Follow-Up

	Entry	Follow-Up (mean 3.3 yr)	p Value
Age (yr)	61 ± 16	64 ± 16	
Female	76 (74%)	76 (74%)	
Atrial fibrillation	48 (47%)	51 (50%)	NS
Heart rate (beats/min)	75 ± 15	73 ± 14	NS
Mitral valve area (cm^2)	1.7 ± 0.6	1.4 ± 0.6	0.00005
Peak mitral gradient (mm Hg)	14.0 ± 6	14.5 ± 7	NS
Mean mitral gradient (mm Hg)	6.4 ± 3.3	6.7 ± 3.1	NS
Left atrial dimension (cm)	5.0 ± 10	5.1 ± 11	NS
Mitral regurgitation (0 to 4+)	1.8 ± 0.8	2.3 ± 0.8	0.00005

Data presented are mean value ± SD or number (%) of patients.

of change in right heart size in terms of univariate correlation coefficients and multiple stepwise linear regression analysis, as before; analysis was repeated by excluding four patients with images suggesting the possibility of organic tricuspid valve disease (one with mild doming tricuspid stenosis and three with leaflet thickening). Right ventricular systolic pressure from tricuspid regurgitant velocities could not readily be included in the model for right heart size because of a large number of missing values (no regurgitation or insufficient signal).

Results

Characteristics of study patients at entry and at follow-up (Table 1). Over the follow-up period (mean 3.3 years, range 1 to 11) there were a significant decrease in MVA (1.69 to 1.45 cm^2, p < 0.00005) and an increase in mitral regurgitation grade by Doppler color flow mapping (1.8 to 2.4 [out of 4+], p < 0.00005); however, there were no significant changes in peak or mean transmitral gradient, frequency of atrial fibrillation, heart rate or left atrial size (p > 0.20).

Determinants of mitral valve narrowing. The mean rate of mitral valve narrowing was 0.09 ± 0.13 cm^2/year. Examination of the individual data (Fig. 1) shows that the rate of decrease in MVA was variable. In 28 patients there was no decrease in area over a mean follow-up period of 3.3 years; in 40 there was only a slight change (<0.1 cm^2/year) and in 35 the rate of
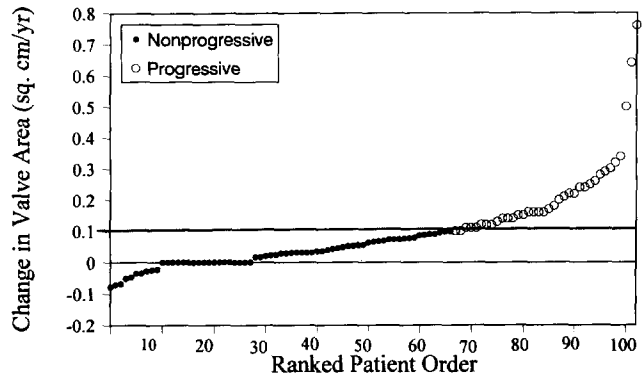

Figure 1. Rate of decrease in mitral valve area (patient rank order) for all 103 patients studied. Patients were stratified into two groups: progressive disease (**open circles:** valve narrowing ≥0.1 cm^2/year, n = 35) and nonprogressive disease (**closed circles:** valve narrowing <0.1 cm^2/year, n = 68). sq. = square.

progression of narrowing was more rapid (≥0.1 cm^2/year [4]). The rate of progression was significantly greater among patients with a larger initial MVA. It was 0.12 cm^2/year in the 61 patients with mild mitral stenosis (valve area >1.4 cm^2), 0.06 cm^2/year in the 29 patients with moderate stenosis (valve area 1.0 to 1.4 cm^2) and 0.03 cm^2/year in the 13 patients with severe stenosis (valve area ≤1.0 cm^2, p < 0.05 for mild vs. moderate or severe mitral stenosis). Figure 2 shows the progression of mitral stenosis in patients with different degrees of stenosis. Overall, 19% of the study patients had an increase of at least one grade in the severity of mitral stenosis over the follow-up period. There was no significant difference in the rate of progression between patients >50 or <50 years old, men or women, patients with sinus rhythm or atrial fibrillation, echo-cardiographic score >8 or <8, or entry mitral regurgitation grade ≥2+ or <2+ (Fig. 3).

In a univariate analysis only initial MVA was weakly correlated (r = 0.4) with the rate of decrease in MVA (p < 0.001). The univariate correlation coefficients of the variables entered into the model were as follows: age = 0.07, mitral valve score = 0.23, gender = −0.013, peak transmitral gradient = 0.026, mean transmitral gradient = −0.011, degree of mitral regurgitation = −0.09, left atrial size = −0.18; prior
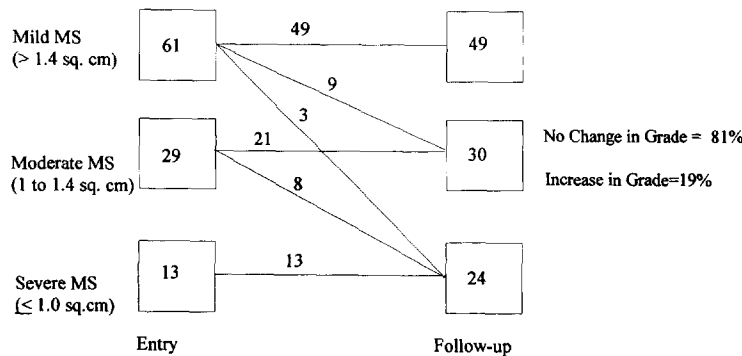

Figure 2. Changes in mitral stenosis (MS) grade in 103 patients over a mean period of 3.3 years. A change in grade required a ≥0.3-cm^2 decrease in mitral valve area over the follow-up period. sq. = square.
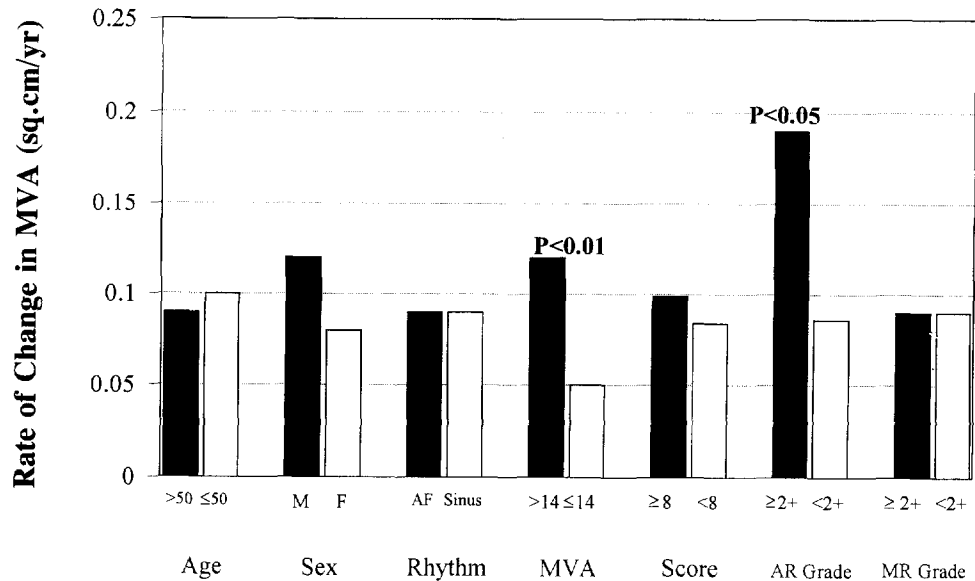
Figure 3. Rate of change in mitral valve area (MVA, cm²/year) in relation to age, gender, cardiac rhythm, mitral valve area, echocardiographic score and mitral (MR) and aortic (AR) regurgitation grade. AF = atrial fibrillation; F = female; M = male; sq. = square.

commissurotomy = −0.12. The rate of change of MVA normalized to initial MVA did not significantly correlate with initial MVA. In multivariate regression analysis, initial mitral valve area and echocardiographic score emerged as weak predictors for the rate of decrease in MVA/year, but their overall combined predictive power was low: Only 22% of the change in MVA/year could be explained by these two variables (r^2 = 0.22). Furthermore, no single value for initial MVA, echocardiographic score or gradient or combination of such values could separate the groups with and without progression or allow confident prediction of changes in MVA in any individual patient.

Planimetry versus pressure half-time determination of MVA. In 40 patients both planimetry and pressure half-time methods for assessing MVA were available at entry and follow-up studies. There was strong correlation between planimetry and Doppler-determined MVA (r = 0.94), and the rate of decrease in MVA was almost identical (planimetry 0.8 cm²/year, pressure half-time 0.82 cm²/year) in these patients. Mitral valve area was available for both entry and follow-up studies in 51 patients by the pressure half-time method and in 92 patients by planimetry. Separate univariate and multiple stepwise linear regression analysis performed by using the data based on the Doppler method alone (n = 51) or planimetry alone (n = 92) provided essentially the same results as those for the entire group (n = 103). Although initial MVA and echocardiographic score made weak contributions to the rate of change in MVA/year, progression in the individual patient could not be predicted by any entry demographic or echocardiographic variable regardless of the method (planimetry or pressure half-time) used to assess MVA.

Mitral regurgitation. At entry, 55 patients (53%) had no or trace mitral regurgitation, 25 (24%) had mild and 23 (23%) had moderate mitral regurgitation. The mean mitral regurgitation grade (0 to 4+) significantly increased between entry

and follow-up study (1.8 ± 0.7 vs. 2.4 ± 0.85, p < 0.001). In the 43 patients with available color flow assessment of mitral regurgitation, regurgitation did not change in 17 (40%), increased by one grade in 23 (53%), by two grades in 2 (5%) and by three grades in only 1 patient (2%). In multivariate analysis only initial MVA and mitral regurgitation grade were significant predictors of progressive mitral regurgitation.

Progression of right heart disease (Tables 2 and 3). Over the follow-up period there was a significant increase in right ventricular systolic and diastolic areas, right atrial area, tricuspid annulus diameter, tricuspid regurgitation grade and Doppler-derived right ventricular systolic pressure (p < 0.001 for all comparisons, Table 2). Significant changes in right heart measurements were found in the groups with and without progression (Table 3). The rate of change of tricuspid regurgitant jet area divided by right atrial area was significantly higher in the group with progression versus nonprogression (29%/year vs. 6%/year, p < 0.00005). Significant changes over the follow-up period also occurred in the 28 patients with unchanged MVA over time, with right ventricular diastolic area increasing from 16.6 ± 4.4 to 18.8 ± 5 cm² (p = 0.02),

Table 2. Right Heart Measurements of Study Patients at Entry and at Follow-Up

	Entry	Follow-Up (mean 3.3 years)	p Value
RV end-systolic area (cm²)	9.4 ± 3.6	10.6 ± 4	0.00005
RV end-diastolic area (cm²)	17 ± 5	18.7 ± 6	0.0001
RV area change (%)	45 ± 9	44 ± 9	0.2
RA area (cm²)	16.4 ± 7	19.3 ± 8	0.00005
Annular diameter (cm)	3.4 ± 0.6	3.6 ± 0.6	0.001
TR grade (1-3)	2.0 ± 1.3	3.0 ± 1.7	0.00005
RV systolic pressure (mm Hg)	42.9 ± 12	48.7 ± 16	0.001

Data presented are mean value ± SD. RA = right atrial; RV = right ventricular; TR = tricuspid regurgitation.

Table 3. Changes in Right Heart Measurements From Entry to Follow-Up in the Groups With Progression and Nonprogression of Disease

	Progression (n = 35)			Nonprogression (n = 68)		
	No.	Entry	Follow-Up	No.	Entry	Follow-Up
RV end-systolic area (cm²)	33	9.6 ± 3.8	10.9 ± 4.6†	63	9.3 ± 3.4	10.4 ± 5.3†
RV end-diastolic area (cm²)	32	17.6 ± 5.9	19.6 ± 7.4*	62	16.6 ± 4.6	18.2 ± 5.3†
RV area change (%)	32	45.0 ± 9	43.1 ± 9	62	44.8 ± 9	44.1 ± 9
RA area (cm²)	33	16.7 ± 7	18.1 ± 8*	63	16.2 ± 6	19.9 ± 8.5†
Annular diameter (cm)	33	3.4 ± 0.6	3.6 ± 0.7	63	3.4 ± 0.6	3.56 ± 0.6†
RV systolic pressure (mm Hg)	12	43.9 ± 11	51 ± 17†	31	42.1 ± 12	46 ± 14
TR jet area (cm²)	10	5.2 ± 4.2	8.9 ± 8†	21	4.1 ± 3.2	6.0 ± 5.5†
JA/RAA ratio	10	31 ± 16%	49 ± 23%†	21	25 ± 15%	30 ± 15%†

*p < 0.05, †p < 0.01 between entry and follow-up study. Data presented are mean value ± SD or number of patients. JA = jet area; RAA = right atrial area; other abbreviations as in Table 2.

right atrial area from 16.5 ± 4.5 to 19.1 ± 6.7 cm² (p = 0.04) and tricuspid regurgitant jet area from 3.8 ± 2.4 to 5.2 ± 3.6 cm² (p = 0.02).

The changes in right heart measurements at entry and follow-up were also evaluated in relation to mitral stenosis severity. Although at entry, right ventricular chamber size, systolic pressure and severity of tricuspid regurgitation were higher for patients with severe versus mild mitral stenosis, they increased from entry to follow-up study in patients with all degrees of mitral stenosis. For example, even in patients with mild stenosis, right ventricular end-diastolic area increased from 16.6 ± 5 to 17.7 ± 6 cm², right atrial area from 15 ± 6 to 18 ± 8 cm² and tricuspid regurgitant jet area from 4.1 ± 2.1 to 7.4 ± 5.3 cm² (p < 0.05).

Both univariate and multiple stepwise linear regression analyses identified the change in mean transmitral gradient as the only significant predictor for the rate of increase in right ventricular end-diastolic area (r = 0.4, p < 0.006) and decrease in right ventricular area change (r = 0.5, p < 0.001). Age, gender, initial MVA, change in MVA and mitral valve score did not emerge as independent predictors for progression of right heart disease. Repeating the analysis excluding the four patients with echocardiographic evidence of possible organic tricuspid valve disease did not change the predictors identified by these analyses.

Aortic regurgitation. At entry, 68 patients (66%) had no or trace aortic regurgitation, 25 (24%) had mild, 9 (9%) had moderate and 1 (1%) had severe aortic regurgitation. In the 44 patients with available Doppler color flow assessment of aortic regurgitation both at entry and follow-up studies, regurgitation severity did not change in 35 patients (80%) and increased by one grade in 9 (20%). The rate of decrease of mitral valve area determined by planimetry over the follow-up period was significantly higher in patients with mild, moderate or severe aortic regurgitation than in patients with trace or no regurgitation (0.19 ± 0.24 vs. 0.086 ± 0.11 cm²/year, p < 0.05) (Fig. 3).

Discussion

The present study provides important information regarding three aspects of the progression of mitral stenosis in the

absence of intervention: mitral valve narrowing, progression of right heart disease and the influence of associated valvular lesions. It does so in the largest reported patient group studied by echocardiography with relatively long-term follow-up.

Determinants of mitral valve narrowing. Mitral valve area in these patients decreased at a mean rate of 0.09 cm²/year, but the rate of progression of disease varied among patients. Some patients had progression from mild to critical mitral stenosis over several years, but others remained in stable condition over a long period of time. More than two thirds had minimal or no change in MVA over several years, whereas one third (34%) had a more progressive course. The rate of mitral valve narrowing could not be predicted by several variables included in the multivariate analysis. Although the rate of mitral valve narrowing was a weak function of initial MVA and mitral valve score (and only initial MVA by the less sensitive univariate analysis), no set of individual or cutoff values could predict the rate of progression in the individual patient.

These results agree with some of the findings but contrast with others reported by Gordon et al. (4) in a similar echocardiographic study of 50 patients with mitral stenosis over a mean period of 3.5 years. In that study, MVA was determined by the indirect pressure half-time method, which is affected by factors other than valve area (5,6). The mean rate of mitral valve narrowing and the percent of those with progressive versus nonprogressive disease (defined the same way as in our study) were remarkably similar to our findings. However, their finding that patients whose valve disease progresses more rapidly are those with a higher mitral valve score and transmitral gradient was not supported in our study. We found that no set of individual or cutoff values could predict the rate of decline in MVA in the individual patient and we observed no significant differences in mitral valve score or transmitral gradient between the groups with and without progression of disease. These differences cannot readily be explained on the basis of different methods used to measure MVA (planimetry in the majority of our patients vs. pressure half-time), because separate analyses performed in 51 of our patients with MVA determined by the pressure half-time method, and 92 patients with MVA determined by planimetry provided essentially the same results as those of the overall analysis of all 103 patients.

It may be that the smaller number of patients in the study of Gordon et al. (4), particularly in the group with progression (16 in their study vs. 35 in ours), may account for differences in ability to predict progression.

The variable rate of mitral valve narrowing is also in accord with the classic clinical natural history studies of Olesen (1) and Rowe et al. (2), who showed that, as judged by symptoms and clinical course, disease progression varies widely among patients. For example, Rowe et al. found that during a 10-year period, 40% of patients died and the condition of 40% remained unchanged. In 20 years, 80% died and 13% had no change in condition. Our findings are also comparable to those of Dubin et al. (24), who similarly found two subgroups of patients with and without progression of disease based on hemodynamic studies (catheterization-derived MVA) and reported a rate of mitral valve narrowing in their group with progression similar to that in our patients with progression. Leutenegger et al. (25), who followed up 13 patients with mild mitral stenosis using M-mode echocardiographic indexes to assess MVA, also identified a subgroup (23%) with a more progressive course.

Despite an overall significant decrease in mitral valve area in our patients, there were no significant changes in peak or mean transmitral gradient, findings that are in accord with those of Gordon et al. (4). The level of left atrial pressure, and therefore the gradient, is also influenced by factors other than the severity of mitral stenosis, such as cardiac output, heart rate, atrial size and compliance, as well as blood volume (influence of diuretic drugs). This may explain why there was no increase in transmitral gradient associated with the decrease in MVA.

The observation that patients with mild stenosis had more rapid progression than those with severe stenosis raises some interesting pathophysiologic questions regarding progressive mitral valve narrowing, for which two mechanisms have been proposed (26): 1) a continuing rheumatic process with either repetitive rheumatic insults or a "smoldering" chronic rheumatic activity; or 2) a nonspecific process, particularly late in the disease, resulting from trauma to the valve caused by altered flow patterns, analogous to the mechanism suggested for calcific aortic stenosis (27). It may be that the patients in our study with a severely narrowed mitral valve did not have rapid progression simply because most of the damage to the valve had already been done and not much tissue was available for further damage; on the other hand, in patients with mild or moderate mitral stenosis, even a mild degree of narrowing might be sufficient to alter flow patterns so as to traumatize the valve leaflets and lead to further thickening, fibrosis and calcification. Because our patients had a mean age of 61 years, we believe that most of the progression is more likely to be attributable to the nonspecific process resulting from trauma to the valve rather than to a continuing rheumatic process.

Progression of right heart disease. Although the hemodynamic consequences of mitral stenosis affect mainly the right side of the heart as mediated by pulmonary vascular disease, there are few reported data regarding the changes in right heart size and function and the progression of associated tricuspid regurgitation in mitral stenosis. This lack may relate to technical difficulties in evaluating right ventricular size and function and tricuspid regurgitation by contrast angiography as well as the limitation of the technique for repeated follow-up (28). Therefore, echocardiography, especially when integrating information from two-dimensional, pulsed and color Doppler techniques, provides a readily available tool to assess the progression of right heart disease noninvasively. In this study there was significant progression in pulmonary hypertension and tricuspid regurgitation, gradual increase in right heart size, and slight decrease in right ventricular function over time. However, progression in right heart disease occurred even in patients with minimal or no change in MVA. Additionally, severe pulmonary hypertension (≥ 60 mm Hg) developed in some patients with severe mitral stenosis (MVA ≤ 1.0 cm^2), whereas milder pulmonary vascular disease occurred in others. This phenomenon is well recognized: For unknown reasons, reactive pulmonary hypertension (and as a consequence right heart failure) is more likely to develop in some patients with tight mitral stenosis than in others (29). Mean transmitral gradient, which reflects changes in the severity of valve narrowing as well as cardiac output and left atrial compliance, was the only predictor for changes in right ventricular size and function by multivariate linear regression analysis. The mean gradient also causes increases in pulmonary artery pressure; however, pulmonary artery pressure, an important determinant of right ventricular decompensation, could not readily be entered into the model for right heart changes because of a large number of missing values (no or insufficient signal of tricuspid regurgitation).

Influence of associated aortic regurgitation. Although aortic regurgitation is commonly associated with rheumatic mitral stenosis (30), there is no available information regarding its influence on the progression of mitral stenosis. By Doppler color flow mapping, 25% of our study patients initially had associated mild or moderate aortic regurgitation that increased to 30% (mild 18%, moderate 12%) at follow-up. An observation not previously shown was that patients with associated aortic regurgitation had a higher rate of decrease in MVA (0.19 vs. 0.086 cm^2/year, p < 0.05) than did those with trace or no aortic regurgitation. Two explanations are possible: 1) Associated aortic regurgitation is a marker for more severe rheumatic disease; and 2) the continuous hemodynamic stress on the anterior mitral leaflet from the aortic regurgitant jet may accelerate the damage to the mitral leaflet and may cause a more rapid rate of valve narrowing.

Study limitations. The method used for MVA assessment in the majority of patients was echocardiographic planimetry. Although this method is not always obtainable with ideal quality imaging, it has been confirmed to provide accurate data by comparison with invasive and necropsy measurements (7,29,31) and to be feasible in up to 96% of patients with rheumatic mitral stenosis (13). We therefore excluded those patients (n = 11) in whom the image quality of the mitral valve limited such measurement. The advantage of using direct

planimetry is that it is not affected by factors such as heart rate, error in cardiac output measurement and mitral and aortic regurgitation.

This study used the same design as that recently reported by Gordon et al. (4) and was therefore able to test their proposed algorithm for predicting progression, adding MVA by planimetry in a larger number of patients. Gordon et al. commented that all such retrospective follow-up studies may possibly select patients with less severe disease because those with severe disease are more likely to undergo intervention; the results will then be the lower limits to the rate of mitral stenosis progression. We have therefore carefully stated that the purpose of our study was to examine patients without interim intervention, to whom the results apply most precisely. However, this theoretic concern is less likely to be actually important in the current study: 1) *In our institution, an echocardiographic study is almost always acquired before intervention; therefore, intervention does not cause loss of follow-up.* For example, we reviewed the records of 65 consecutive patients undergoing surgical or catheter interventions from our institutional data base of cardiac procedures; of these 65 patients, 60 had an echocardiogram within the month before the intervention, and 63 within the preceding 3 months. Thus, having two echocardiographic studies did not importantly select against those undergoing intervention. 2) The study group comprised a reasonable spectrum of mitral stenosis severity: As >40% had an MVA <1.5 cm^2, moderate to severe disease was not excluded. However, patients with more progressive disease might be expected to have more frequent follow-up and thus be overrepresented. Despite this possibility, two thirds of our study patients belonged to the group without progression of disease, a proportion similar to that reported by Gordon et al. (4); this combination of patients with and without progression should also allow a reasonable assessment of risk factors by multivariate analysis. Nevertheless, a prospective natural history would be necessary to limit the potential for such biases in either direction.

Clinical implications. The present study represents the largest group of patients with mitral stenosis studied by two-dimensional and Doppler echocardiography over a long period of time and adds important information regarding the progression of mitral stenosis, including the progression of right heart disease and the influence of associated valvular lesions. The finding that the rate of progression of mitral stenosis is variable among patients suggests that follow-up by echocardiography is a reasonable measure to determine such progression for all patients with mitral stenosis regardless of severity because the rate of progression does not seem to be predictable by any of the variables tested. (Such objective follow-up information is widely used, for example, to explore symptomatic changes because of the lack of good correlation between symptoms and objective hemodynamic measures.) Follow-up appears particularly important in patients with associated aortic regurgitation, in whom mitral stenosis progressed more rapidly. Because changes in right heart disease, an important factor in determining intervention, can be de-

tected by echocardiography and can occur independent of changes in MVA, monitoring of these changes in addition to the change in MVA could potentially be helpful for decision-making regarding the ideal time for intervention.

References

1. Olesen KH. The natural history of 271 patients with mitral stenosis under medical treatment. Br Heart J 1962;24:349–57.
2. Rowe JC, Bland EF, Sprague HB, White PD. The course of mitral stenosis without surgery: ten and twenty-year perspective. Ann Intern Med 1960;53:741–9.
3. Stollerman GH. Global strategies for the control of rheumatic fever [editorial]. JAMA 1983;249:931.
4. Gordon SP, Douglas PS, Come PC, Manning WJ. Two-dimensional echocardiographic determination of the natural history of mitral valve narrowing in patients with rheumatic mitral stenosis: implication for follow-up. J Am Coll Cardiol 1992;19:968–73.
5. Thomas JD, Wilkins GT, Choong CY, et al. Inaccuracy of mitral pressure half-time immediately after percutaneous mitral valvotomy: dependence on transmitral gradient and left atrial and ventricular compliance. Circulation 1988;78:980–93.
6. Flachskampf FA, Weyman AE, Gillam L, Liu C-M, Abascal VM, Thomas JD. Aortic regurgitation shortens Doppler pressure half-time in mitral stenosis: clinical evidence, in vitro simulation and theoretical analysis. J Am Coll Cardiol 1990;16:396–404.
7. Henry WL, Griffith JM, Michaelis LL, McIntosh CL, Morrow AG, Epstein SE. Measurement of mitral valve orifice area in patients with mitral valve disease by real-time, two-dimensional echocardiography. Circulation 1975;51:827–36.
8. Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. Circulation 1979;60:1096–104.
9. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous mitral valvotomy: an analysis of echocardiographic variables related to outcome and mechanism of dilatation. Br Heart J 1988;60:299–308.
10. Abbasi AS, Allen MW, DeCristofaro D, Ungar I. Detection and estimation of the degree of mitral regurgitation by range-gated pulsed-Doppler echocardiography. Circulation 1980;61:143–7.
11. Spain MG, Smith MD, Grayburn PA, Harlamert EA, DeMaria AN. Quantitative assessment of mitral regurgitation by Doppler color flow imaging: angiographic and hemodynamic correlations. J Am Coll Cardiol 1989;13:585–90.
12. Perry GI, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. J Am Coll Cardiol 1987;9:952–9.
13. Weyman AE. Cross-sectional Echocardiography. Philadelphia: Lea & Febiger, 1982:150–9.
14. Tajik DT, Seward JB, Hagler DJ, Mair DP, Lie JT. Two-dimensional real-time ultrasound imaging of the heart and great vessels: technique, image orientation, structure identification and validation. Mayo Clin Proc 1978;53:271–303.
15. Currie PJ, Seward JB, Chan K, et al. Continuous wave Doppler determination of right ventricular systolic pressure: a simultaneous Doppler-catheterization study in 127 patients. J Am Coll Cardiol 1985;6:750–6.
16. Himmelman RB, Stulbarg M, Kircher B, et al. Noninvasive evaluation of pulmonary artery pressure during exercise by saline-enhanced Doppler echocardiography on chronic pulmonary disease. Circulation 1989;79:863–71.
17. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure using continuous wave Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657–62.
18. Mintz GS, Kotler MN, Parry WR, Iskandrian AS, Kane SA. Real time inferior vena caval ultrasonography: normal and abnormal findings and its use in assessing right-heart function. Circulation 1981;64:1018–85.

19. Chopra HK, Nanda NC, Fan P, et al. Can two-dimensional echocardiography and Doppler color flow mapping identify the need for tricuspid valve repair? J Am Coll Cardiol 1989;14:1266–74.

20. Cooper JW, Nanda NC, Philpot E, Fan P. Evaluation of valvular regurgitation by color Doppler. J Am Soc Echocardiogr 1989;2:56–66.

21. Mugge A, Daniel WG, Herrmann G, Simon R, Lichtlen PR. Quantification of tricuspid regurgitation by Doppler color flow mapping after cardiac transplant. Am J Cardiol 1990;66:884–7.

22. Cape EG, Yoganathan AP, Weyman AE, Levine RA. Adjacent solid boundaries alter the size of regurgitant jets on Doppler color flow maps. J Am Coll Cardiol 1991;17:1094–102.

23. Chen C, Thomas JD, Anconina J, et al. Impact of impinging wall jet on color Doppler quantification of mitral regurgitation. Circulation 1991;84:712–20.

24. Dubin AA, March HW, Cohn K, Selzer A. Longitudinal hemodynamic and clinical study of mitral stenosis. Circulation 1971;44:381–9.

25. Leutenegger F, Raeder EA, Fromer M, Follath F, Burckhardt D. Progression of mild mitral stenosis and incidence of restenosis after open commissurotomy: a study using echocardiography. Am Heart J 1979;98:562–6.

26. Selzer A, Cohn KE. Natural history of mitral stenosis: a review. Circulation 1972;45:878–90.

27. Edwards JE. The congenital bicuspid aortic valve. Circulation 1961;23:878–90.

28. Ahn AJ, Segal BL. Isolated tricuspid insufficiency: clinical features, diagnosis and management. Prog Cardiovasc Dis 1967;9:166–93.

29. Dalen ED, Alpert JS. Valvular Heart Disease. Boston: Little, Brown, 1987:49–103.

30. Delahaye F, Delaye J, Ecochard R, et al. Influence of associated valvular lesions on long-term prognosis of mitral stenosis. A 20-year follow-up of 202 patients. Eur Heart J 1991;12:77–80.

31. Nichol PM, Gilbert BW, Kisslo JA. Two-dimensional echocardiographic assessment of mitral stenosis. Circulation 1977;55:120–8.