Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement

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ABSTRACT Passive diastolic properties were determined in 10 control patients and 21 patients with aortic valve disease before and 17.5 months after successful valve replacement. Ten patients had severe aortic stenoses (AS), five had combined aortic valve lesions (AS + aortic insufficiency [AI]), and six patients had severe AI. Left ventricular endomyocardial biopsies were obtained before and after surgery in patients with AS, AS + AI, and AI. Simultaneous echocardiographic and high-fidelity pressure measurements were made in all patients, and left ventricular chamber stiffness was calculated from a viscoelastic pressure-circumference relationship and left ventricular myocardial stiffness from a viscoelastic stress-strain relationship. The constant of chamber stiffness, $\beta'$, was slightly although not significantly increased in patients with AS (0.27 before and 0.24 after surgery), but was normal in those with AS + AI (0.22 before and 0.17 after surgery) and slightly decreased in those with AI (0.18 before and 0.16 after surgery) when compared with in control subjects (0.21). The constant of myocardial stiffness $\beta$ was normal in patients with AS (13.2), AS + AI (11.5), and AI (11.7) before surgery compared with in the control group (12.5). $\beta$ increased, however, significantly in those with AS (25.2; p < .02), but not in those with AS + AI (16.3; NS) and AI (12.8; NS) after surgery. Myocardial morphologic characteristics showed a significant decrease in muscle fiber diameter in patients with AS, AS + AI, and AI, as well as a significant increase in interstitial fibrosis from 15% to 26% (p < .05) in those with AS and a slight increase from 15% to 22% (NS) in those with AS + AI and from 19% to 24% (NS) in those with AI. Left ventricular fibrous content (left ventricular muscle mass index multiplied by interstitial fibrosis) remained, however, unchanged in all three groups after aortic valve replacement. In conclusion, left ventricular chamber stiffness is increased in AS but decreased in AI, whereas LV myocardial stiffness is normal in patients with aortic valve disease before surgery. After surgery, left ventricular myocardial stiffness increased significantly in AS patients but remained unchanged in those with AI. Postoperative changes in myocardial structure were characterized by a decrease in muscle fiber diameter and a relative increase in interstitial fibrosis, whereas fibrous content remained unchanged. Thus, regression of myocardial hypertrophy in aortic valve disease is accompanied by an increase of myocardial stiffness in concentric hypertrophy that is not seen in eccentric hypertrophy.


MYOCARDIAL HYPERTROPHY is a basic adaptive mechanism of the heart to compensate for an increased mechanical load. An increase in myocardial muscle mass permits the ventricle to maintain normal pump function and to keep myocardial wall stress at normal or slightly increased levels. However, longstanding overload is associated with a decrease in myocardial contractility and systolic pump function as well as with alterations in myocardial structure.¹⁻⁴ In this study we have investigated in patients with aortic valve disease whether, after mechanical unloading consequent to valve replacement, changes in the structure of the hypertrophied myocardium occur and whether these changes influence the passive diastolic properties of the postoperative left ventricular myocardium.

Patients and methods
Twenty-one patients (five women and 16 men) with a mean age of 47 years (range, 25 to 62) were included in the study. All patients underwent left and right heart catheterization before and after a mean of 17.5 months (range, 9 to 25) after successful valve replacement. Ten patients had severe aortic stenoses (group 1) with a mean systolic pressure gradient of 69 mm Hg...
and no or only slight aortic regurgitation (regurgitant fraction as determined by threedilution<0.20, mean 0.11), five patients had combined aortic valve lesions (group 2; systolic pressure gradient ≥20 mm Hg, regurgitant fraction ≥0.20) with a mean systolic pressure gradient of 53 mm Hg and a regurgitant fraction of 0.46, and six patients had severe aortic insufficiency (group 2) with a mean regurgitant fraction of 0.59 and no or only a mild systolic pressure gradient <20 mm Hg (mean systolic pressure gradient 2 mm Hg). A coronary arteriographic examination was carried out in each patient, and in only one patient was a 50% stenosis of the anterior descending coronary artery observed. Ten patients with no or minimal heart disease served as control subjects (five women and five men). All patients were in sinus rhythm and the duration of the QRS complex did not exceed 0.11 sec.

After successful valve replacement there was a mild systolic pressure gradient in eight patients of group 1 (mean systolic pressure gradient 8 mm Hg), three patients of group 2 (mean systolic pressure gradient 11 mm Hg), and three patients of group 3 (mean systolic pressure gradient 5 mm Hg). One patient of group 2 had trivial aortic regurgitation (regurgitant fraction 0.05) after valve replacement.

**Catheterization and cineangiography.** Informed consent was obtained from all patients. Premedication consisted of 10 mg chloraloxazepoxide (Librium) given orally 1 hr before the procedure. Left ventricular pressure was measured with a transseptally introduced No. 7F Millar micromanometer. The micromanometer was calibrated by superimposing the high-fidelity pressure tracing on the conventional pressure tracing. Aortic pressure was measured through a fluid-filled No. 8F pigtail catheter. A peripheral lead of the standard electrocardiogram and the phonocardiogram were recorded together with the high-fidelity pressure measurements (figure 1). Aortic valve closure was determined from the second heart sound of the phonocardiogram. M mode echocardiographic examinations were carried out with an Ekoline 20A echocardiograph (Smith-Kline Instruments) interfaced to an Electronics for Medicine DR 16 recorder or with an echocardiograph Electronics for Medicine V-3280 interfaced to a VR 12 oscillograph. The recordings were made with a 2.25 MHz transducer with the patient in the anteroposterior or slight right anterior decubitus position according to our standard technique. The echocardiographic and pressure tracings were digitized by hand on an electronic digitizer (Numonics) interfaced to a PDP 11/10 computer equipped with a printplotter (Versatec). The resolution of the digitizer was 0.25 mm at a paper speed of 100 mm/sec. The following variables were calculated and printed out by the computer 130 times per cardiac cycle: left ventricular internal diameter (D), posterior wall thickness (h), left ventricular pressure (P), dP/dt, left ventricular meridional wall stress (σ), left ventricular midwall circumference (l = π [D + h]), and the first derivative of the midwall circumference (dl/dt). dP/dt and dl/dt were calculated from P and l, respectively, by digital differentiation with a five-point formula. Interobserver variability has been shown to be small (1.2% for D at end-diastole, 6.1% for h at end-diastole, and 6.6% for peak systolic wall stress). Two of 52 echocardiograms were not of good quality and were not included in the present analysis.

Left ventricular cineangiography was performed in the right and left anterior oblique projections according to our standard technique. The range of normality for volumetric data was established from 20 patients with atrial septal defect or functional mitral regurgitation. An ejection fraction from 57% to 83% (mean 68%) was considered to be normal. Left ventricular muscle mass was calculated according to the technique of Rackley et al.

At the end of the catheterization procedure left ventricular

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**FIGURE 1.** Original tracings in a patient with aortic stenosis before (top) and after (bottom) successful valve replacement. At the top of each tracing is the M mode echocardiogram with the interventricular septum (IVS) and the posterior wall (PW). In the postoperative echocardiogram note the echo of the Millar micromanometer just above the PW and the septal hypokinesia after aortic valve replacement. At the bottom of each panel are the high-fidelity left ventricular pressure (LVP) and the conventional aortic pressure (AoP) tracings as well as the first derivative of LVP (dP/dt') shown. ECG = electrocardiogram; PCG = phonocardiogram.

Endomyocardial biopsies were performed with the King's College Biopette, which was introduced into the left ventricle through a No. 11.5F Brockenbrough catheter. From each patient two to three biopsies were obtained from the anterolateral wall of the left ventricle. Immediately after the biopsy the material was fixed in glutaraldehyde for light (semithin sections) and electron (embedded in epon) microscopic examination (figure 2). Quantitative evaluation of left ventricular biopsies was carried out by morphometry. The muscle fiber diameter was determined from several cross sections at the level of the nucleus with a mechanical-optical pen (MOP, Kontron GmbH, Zurich). At least 100 measurements were obtained with this pen in each patient and the average fiber diameter ± SD was determined. Interobserver variability for muscle fiber diameter has been found to be small (1.3%, n = 22). The extent of interstitial fibrosis was evaluated with the point-counting system. A special ocular with a grid providing 100 intersection points was used to determine the amount of fibrous tissue; more precisely, the amount of nonmuscular tissue was evaluated by counting the number of points overlying interstitial tissue. To term this nonmuscular interstitial tissue "interstitial fibrosis" is somewhat
valve disease, however, morphologic changes in the myocardium are more or less uniformly distributed over the whole left ventricle, although there might be some focal processes that could affect our quantitative analysis. In our patients with aortic valve disease preoperative and postoperative endomyocardial biopsy samples were obtained by the same transseptal technique and it is therefore likely that morphologic measurements from the same endocardial areas were compared (figure 2). Control morphologic data were obtained at autopsy from eight subjects who had been healthy before they died in car accidents.

Indexes of left ventricular diastolic function. Left ventricular diastolic function was evaluated from a viscoelastic stress-strain relationship. This viscoelastic model was used for the determination of diastolic function because it had been demonstrated that deviations from the monoeponential stress-strain relationship occur mainly during rapid early diastolic filling and atrial systole. In our study left ventricular chamber and myocardial stiffness were determined with the use of viscoelastic pressure-circumference and viscoelastic stress-strain relationships, respectively.

Left ventricular chamber stiffness. Diastolic chamber stiffness of the left ventricle was determined from the following equation:

\[ P = \alpha' (e^{\beta t} - 1) + \eta' t \]

where \( P \) = left ventricular pressure (mm Hg); \( \alpha' \) = constant (mm Hg); \( \beta' \) = constant of left ventricular chamber stiffness; \( t = \) left ventricular midwall circumference (cm); \( \eta' \) = constant of chamber viscosity (mm Hg·sec); \( l = \) lengthening rate of the left ventricular midwall circumference (sec\(^{-1}\)). Values for left ventricular pressure, midwall circumference, and lengthening rate from the lowest diastolic pressure to end-diastole were fed into the computer, and the pressure intercept, the constant of chamber stiffness, and the constant of chamber viscosity were calculated with a nonlinear curve-fit program. The three calculated parameters were obtained by iteration until the least squares estimate between the observed and the calculated values was minimal. The calculated variances of the three parameters were tested by a covariance matrix to assure the optimal solution for the three tested parameters.

Left ventricular myocardial stiffness. Diastolic myocardial stiffness of the left ventricle was determined from a viscoelastic stress-strain relationship. In a first step, we determined a reference midwall circumference at a wall stress of 1 g/cm\(^2\) (\( l_i \)) for normalization of left ventricular strain to a common preload. This is especially important in patients with small and large ventricles such as those with aortic stenosis and aortic insufficiency. The reference midwall circumference \( l_i \) was determined from a viscoelastic stress-strain relationship (figure 3) as follows:

\[ \sigma = \alpha' (e^{\beta' t} - 1) + \eta' t \]

where \( \sigma \) = left ventricular meridional wall stress (g/cm\(^2\)); \( \alpha' \) = elastic constant (g/cm\(^2\)); \( \beta' \) = slope of the stress-strain relationship; \( l = \) midwall circumference (cm); \( \eta' \) = constant of viscosity (g·sec/cm\(^2\)); \( l_1 = \) left ventricular lengthening rate of the midwall circumference (sec\(^{-1}\)).

For the determination of the three parameters \( \alpha' \), \( \beta' \), and \( \eta' \) nonlinear regression analysis was used. From the calculated parameters the reference midwall circumference at a wall stress of 1 g/cm\(^2\) was determined (\( l_i \)). This reference circumference was used for the calculation of diastolic strain (\( \epsilon \)), which was normalized to a common wall stress of 1 g/cm\(^2\) as follows:

\[ \epsilon = \ln \frac{l}{l_i} \]
where \( \sigma \) = left ventricular meridional wall stress (g/cm\(^2\)); \( \alpha \) = elastic constant (g/cm\(^2\)); \( \beta \) = constant of left ventricular myocardial stiffness; \( \varepsilon \) = normalized diastolic strain; \( \eta \) = constant of myocardial viscosity (g/sec/cm\(^2\)); \( \varepsilon \) = left ventricular strain rate (sec\(^{-1}\)).

The three parameters \( \alpha \), \( \beta \), and \( \eta \) were determined by the nonlinear regression analysis outlined earlier in this report.\(^\text{13}\)

### Statistics

Statistical comparisons were carried out by a one-way analysis of variance (ANOVA) with data from the control subjects, and from patients of group 1 (aortic stenosis), group 2 (combined aortic valve lesion), and group 3 (aortic insufficiency) before and after surgery. If the analysis showed a significant difference, the Duncan procedure was applied. The preoperative/postoperative comparison for the three groups was performed with a paired Student t test. In the case of an uneven number of sets of preoperative and postoperative data a paired comparison was performed only on the available paired data. In all tables and figures data are mean ± SEM.

### Results

Original tracings illustrating the variables measured are shown in figure 1.

#### Clinical symptoms (table 1)

Functional classification according to the New York Heart Association (NYHA) was significantly increased in patients with aortic stenoses (2.4) and combined aortic valve lesions (1.9) compared with in control subjects (1.2). However, NYHA classification was not different in control subjects and in patients with aortic insufficiency. After surgery functional classification was no longer significantly different from that in control subjects in any of the three groups of patients with aortic valve disease. Dyspnea on exertion was observed in 10 of 10 patients with aortic stenoses, one patient with a combined valve lesion, and one with aortic insufficiency. After successful valve replacement two patients with preoper-

### Table 1

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Dyspnea</th>
<th>Angina pectoris</th>
<th>Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1.20±0.13</td>
<td>—</td>
<td>2/10</td>
</tr>
<tr>
<td>AS pre</td>
<td>2.40±0.22</td>
<td>10/10</td>
<td>1/10</td>
</tr>
<tr>
<td>AS post</td>
<td>1.25±0.13</td>
<td>2/10</td>
<td>—</td>
</tr>
<tr>
<td>AS + AI pre</td>
<td>1.90±0.19</td>
<td>1/5</td>
<td>3/5</td>
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<tr>
<td>AS + AI post</td>
<td>1.00±0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>AI pre</td>
<td>1.42±0.27</td>
<td>1/6</td>
<td>1/6</td>
</tr>
<tr>
<td>AI post</td>
<td>1.00±0</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

C = control patients; AS = aortic stenosis; AS + AI = combined aortic valve lesions; AI = aortic insufficiency; pre = before surgery; post = after surgery.

\( p < .05; \) \( \# p < .01; \) \( \dagger p < .001 \).

(A definition of natural strain can be found in an article by Mirsky.\(^\text{14}\)

In a second step, we determined the diastolic myocardial stiffness indexes from a viscoelastic stress-strain relationship (figure 3):

\[
\sigma = \alpha (e^{2\beta} - 1) + \eta \varepsilon
\]
ative aortic stenoses still complained of dyspnea on exertion. Angina pectoris was found in two control subjects, one patient with aortic stenosis, three with combined aortic valve lesions, and one with aortic insufficiency. After surgery no patient complained of anginal pain. Syncopes were seen in five patients with aortic stenoses and two patients with combined valve lesions.

**Hemodynamics (table 2).** Heart rate was not significantly different in any of the groups before or after valve replacement as compared with in control subjects. Left ventricular end-diastolic and peak systolic pressures and the lowest diastolic pressure were significantly elevated in patients with aortic stenoses and combined valve lesions before surgery but were not significantly different from control in patients with aortic insufficiency. After surgery, with the exception of peak systolic pressure in patients with aortic stenoses, end-diastolic, peak systolic, and the lowest diastolic pressures were normal in all three groups. Left ventricular ejection fraction showed no significant differences between the groups. Left ventricular end-diastolic volume index was significantly increased in patients with combined aortic valve lesions and aortic insufficiency. After valve replacement, end-diastolic volume index remained significantly increased in patients with aortic insufficiency, although there was a significant decrease in volume from before to after surgery. Left ventricular muscle mass index was significantly increased in all patients with aortic valve disease. After surgery muscle mass decreased significantly in all three groups and was no longer significantly different from control.

**Diastolic function data (table 3)**

*Left ventricular chamber stiffness.* With respect to the elastic constant $\alpha'$ of the pressure-circumference relationship there were no significant differences between the groups. The left ventricular constant of chamber stiffness $\beta'$ was slightly although not significantly increased both before and after surgery in patients with aortic stenoses. However, $\beta'$ was normal in patients with combined valve lesions before surgery, but was decreased in patients with aortic insufficiency as compared with in control subjects. After surgery the constant of chamber stiffness decreased only slightly in patients with aortic stenoses and aortic insufficiency but significantly in those with combined lesions. The left ventricular constant of chamber viscosity $\eta'$ was small before and after surgery and no significant differences between patients with aortic valve disease and control subjects were observed for this parameter.

*Left ventricular myocardial stiffness.* The reference midwail circumference $l_i$ was significantly increased in all three groups with aortic valve disease as compared with in control subjects. After surgery $l_i$ was no longer significantly different from control in patients with aortic stenoses and combined valve lesions. However, $l_i$ was still significantly increased in patients with aortic insufficiency after valve replacement. The elastic constant $\alpha$ of the stress-strain relationship was not significantly different in patients with aortic valve disease and control subjects, although $\alpha$ was smaller in patients with aortic stenoses after surgery than in the other groups. The constant of myocardial stiffness $\beta$ was not different from control in patients with aortic valve disease. However, after successful valve re-

**TABLE 2**

<table>
<thead>
<tr>
<th>Standard hemodynamics</th>
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<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>----</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>AS pre</td>
</tr>
<tr>
<td>AS post</td>
</tr>
<tr>
<td>AS + AI pre</td>
</tr>
<tr>
<td>AS + AI post</td>
</tr>
<tr>
<td>AI pre</td>
</tr>
<tr>
<td>AI post</td>
</tr>
</tbody>
</table>

HR = heart rate (min⁻¹); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVSP = left ventricular peak systolic pressure (mm Hg); P1 = lowest diastolic pressure (mm Hg); EF = left ventricular ejection fraction (%); EDVI = left ventricular end-diastolic volume index (ml/m²); LMMI = left ventricular muscle mass index (g/m²); other abbreviations are as in Table 1.

*p < .05; **p < .01; ***p < .001.
TABLE 3
Data on diastolic function

<table>
<thead>
<tr>
<th></th>
<th>Chamber stiffness data</th>
<th>Myocardial stiffness data</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>α'</td>
</tr>
<tr>
<td>C</td>
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<td>0.3±0.1</td>
</tr>
<tr>
<td>AS pre</td>
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<td>0.3±0.2</td>
</tr>
<tr>
<td>AS post</td>
<td>9</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>AS + Al pre</td>
<td>4</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td>AS + Al post</td>
<td>5</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>Al pre</td>
<td>6</td>
<td>0.1±0.1</td>
</tr>
<tr>
<td>Al post</td>
<td>6</td>
<td>0.2±0.1</td>
</tr>
</tbody>
</table>

α' = elastic constant of the pressure-circumference relationship (mm Hg); β' = constant of chamber stiffness; η' = constant of chamber viscosity (mm Hg sec); i = reference midwall circumference at a common wall stress of 1 g/cm² (cm); α = elastic constant of the stress-strain relationship (g/cm²); β = constant of myocardial stiffness; η = constant of myocardial viscosity (g/cm²); other abbreviations are as in Table 1.

*p < .05; **p < .01.

placement β increased significantly in patients with aortic stenoses and increased slightly in patients with combined valve lesions. In patients with aortic insufficiency there was no change in β from before to after surgery. The constant of myocardial viscosity η was larger in all three groups with aortic valve disease than in control subjects. After aortic valve replacement η decreased slightly although not significantly in all three groups.

Left ventricular morphology (Table 4). Quantitative analysis of endomyocardial biopsy samples showed that there was significant hypertrophy of left ventricular muscle fibers that was of a similar extent in patients with pressure and volume overload. After successful valve replacement there was a significant decrease in muscle fiber diameter in patients with aortic valve disease. However, muscle fiber diameter was significantly larger in patients after surgery than in control subjects. The amount of interstitial fibrosis was small in control patients but was significantly increased in patients with aortic valve disease before surgery. After surgery there was a further increase in interstitial fibrosis in all groups but the increase was only statistically significant in patients with aortic stenoses. In contrast, fibrous content remained unchanged in all three groups before and after surgery.

Discussion

Left ventricular hypertrophy as assessed by cineangiography has been shown to be reversible in patients with aortic valve disease after successful valve replacement.15,16 The effect of aortic valve replacement on myocardial structure is, however, not yet established, and it is not known whether there is a regression of hypertrophy at the cellular level parallel to the decrease in angiographically measured muscle mass, or whether interstitial fibrosis remains unchanged after aortic valve replacement. Since myocardial structure is the major determinant of diastolic myocardial function,4,14 we determined diastolic chamber and myocardial stiffness from viscoelastic pressure-circumference and stress-strain relationships in 21 patients with aortic

TABLE 4
Left ventricular morphologic characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>MFD</th>
<th>IF</th>
<th>FC</th>
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<td>C</td>
<td>8</td>
<td>14±1</td>
<td>2±1</td>
<td></td>
</tr>
<tr>
<td>AS pre</td>
<td>10</td>
<td>31±1</td>
<td>15±1</td>
<td>28±4</td>
</tr>
<tr>
<td>AS post</td>
<td>10</td>
<td>26±1</td>
<td>26±1</td>
<td>31±4</td>
</tr>
<tr>
<td>AS + Al pre</td>
<td>5</td>
<td>31±1</td>
<td>15±4</td>
<td>25±6</td>
</tr>
<tr>
<td>AS + Al post</td>
<td>5</td>
<td>27±1</td>
<td>22±4</td>
<td>27±6</td>
</tr>
<tr>
<td>Al pre</td>
<td>6</td>
<td>31±1</td>
<td>19±2</td>
<td>30±4</td>
</tr>
<tr>
<td>Al post</td>
<td>6</td>
<td>27±2</td>
<td>24±1</td>
<td>29±4</td>
</tr>
</tbody>
</table>

MFD = muscle fiber diameter (μm); IF = interstitial fibrosis (%); FC = fibrous content (g/cm²); other abbreviations are as in Table 1.

*p < .05; **p < .01.
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valve disease before and after successful valve replacement and compared these data to structural findings obtained from left ventricular endomyocardial biopsies taken during cardiac catheterization. To evaluate the clinical significance of data on diastolic function, we studied the relationship between changes in chamber stiffness and left ventricular filling pressures and possible congestive symptoms.

Clinical symptoms (table 1) such as dyspnea on exertion, angina pectoris, and the occurrence of syncope were evaluated in all patients before and after surgery. Patients with severe aortic stenoses and combined aortic valve lesions had more symptoms than patients with aortic insufficiency. Functional class according to the NYHA was therefore significantly higher in these two groups than in patients with aortic insufficiency or in control subjects. Diastolic filling pressures (lowest diastolic and end-diastolic pressures; table 2) were significantly elevated in those with aortic stenoses and combined valve lesions. The increased filling pressure is, however, responsible for the occurrence of congestive symptoms, whereas systolic valvular gradient is responsible for the occurrence of syncope in these patients. After successful valve replacement of 19 of 21 patients with aortic valve disease were free of symptoms and only two patients with preoperative aortic stenoses still complained of dyspnea on exertion. Increased filling pressures in patients with aortic stenoses are probably due to increased muscle mass; on the other hand increased muscle mass is probably responsible for the increased chamber stiffness in concentric hypertrophy. In contrast, patients with aortic insufficiency usually have decreased left ventricular chamber stiffness because filling pressure is only moderately elevated while the left ventricle is significantly enlarged. Decreased chamber stiffness in patients with chronic volume overload is associated with only a low incidence of congestive symptoms. The same phenomenon can be observed in patients with dilated cardiomyopathy, who often have no symptoms in the presence of severely depressed myocardial function. Thus, changes in chamber stiffness help to explain the occurrence or absence of congestive symptoms in patients with concentric or eccentric hypertrophy. Regression of myocardial hypertrophy after successful valve replacement is associated with a decrease in muscle mass and in chamber stiffness. This decrease is probably responsible for the clinical improvement with respect to congestive symptoms seen in patients with severe aortic stenoses and combined aortic valve lesions after successful valve replacement.

Left ventricular angiographic data (table 2) suggest that left ventricular ejection performance in all three groups with aortic valve disease was normal before and after valve replacement. Left ventricular end-diastolic volume was normal in patients with aortic stenoses before surgery but significantly increased in patients with combined valve lesions and aortic insufficiency when compared with in control subjects. Left ventricular muscle mass was significantly increased before surgery in all three groups to a similar extent, and muscle mass decreased significantly in all three groups after valve replacement. There was some residual hypertrophy after aortic valve replacement, although muscle mass was no longer significantly different from control. This residual hypertrophy of the left ventricle after aortic valve replacement has been observed previously and has been attributed to a compensatory process that maintains left ventricular ejection performance at a normal level in the presence of structural changes in the myocardium (see below).

Left ventricular diastolic function was determined in our study with the use of a viscoelastic pressure-circumference relationship for the assessment of chamber properties and with the use of a viscoelastic stress-strain relationship for the assessment of myocardial properties. This difference between chamber and myocardial properties is important because chamber properties are dependent on the size and geometry of the left ventricle (not normalized data), but are directly related to clinical symptoms and diastolic compliance failure, whereas myocardial properties reflect mechanical and structural factors of the myocardium per se (normalized data for size and geometry) and are not necessarily related to clinical symptoms and diastolic compliance failure. A viscoelastic model for the determination of chamber and myocardial properties was used since it has been demonstrated that the diastolic stress-strain relationships are characterized more adequately by a viscoelastic than a simple elastic relationship with a monoexponential curve fit. Our data show only minor viscous effects for the whole ventricle when chamber properties are studied, but increased viscous effects in patients with aortic valve disease before surgery when myocardial properties are examined (table 3). Thus, overall viscous effects seem to be small, but myocardial viscous effects seem to be important in patients with myocardial hypertrophy. In dogs instrumented over a long term it was shown that viscous forces are not only filling-rate dependent but also length dependent. Increased wall thickness and muscle mass in patients with aortic valve disease suggest increased viscous resistance during diastolic filling when more muscle has to be distended than in
normal subjects. The slight decrease in the constant of myocardial viscosity after surgery supports this concept of increased viscous forces in patients with myocardial hypertrophy.

Diastolic chamber and myocardial stiffness are characterized by the elastic constant ($\alpha'$ and $\alpha$) and the slopes of the pressure-circumference ($\beta'$) and the stress-strain relationships ($\beta$). The two constants $\alpha$ and $\beta$ describe the diastolic properties of the left ventricle. However, it was suggested that the slope of pressure-circumference represents the constant of chamber stiffness and the slope of the stress-strain relationship the constant of myocardial stiffness because the stiffness of an elastic material is proportional to the slope of its passive length-tension relationship. Therefore, the constants of left ventricular chamber and myocardial stiffness were used in our study as measures of left ventricular chamber and myocardial stiffness.

Left ventricular stress-strain relationships suggested normal myocardial stiffness in our patients with aortic valve disease before surgery. Apparently, myocardial hypertrophy is not always associated with increased myocardial stiffness. Increased filling pressure in aortic valve disease is, therefore, not due to increased myocardial stiffness but simply to the increased muscle mass, which requires a higher filling pressure for diastolic filling of the hypertrophied left ventricle. After surgery, however, myocardial stiffness (figure 4) increased significantly in patients with aortic stenoses, despite a significant decrease of left ventricular angiographic muscle mass. The increase in $\beta$ was associated with a decrease in $\alpha$, the biologic significance of which is so far unknown. Myocardial stiffness increased slightly in patients with combined aortic valve lesions and remained unchanged in patients with aortic insufficiency (figure 4). Thus, although muscle mass and diastolic filling pressure decreased significantly in pa-
patients with aortic stenoses after successful valve replacement, myocardial stiffness became abnormal. This contradiction can only be explained by the structural alterations that seem to occur despite relief of the pressure burden. In patients with aortic insufficiency myocardial stiffness remained unchanged from before to after surgery. These differences in myocardial properties in patients with chronic pressure and volume overloads can be explained only by the different types of myocardial hypertrophy in patients with aortic stenoses and those with aortic insufficiency. In patients with aortic stenoses there is no change in left ventricular volume from before to after surgery and hypertrophy is concentric and in those with aortic insufficiency there is a significant decrease in left ventricular volume after aortic valve replacement and hypertrophy is eccentric. Apparently, regression of myocardial hypertrophy in concentric and eccentric hypertrophy has different consequences with respect to diastolic function. Peterson et al.17 found increased myocardial stiffness in some patients with aortic stenoses, and in one patient they were able to show, after valve replacement, normalization of myocardial stiffness that had been abnormally high. Improved diastolic stiffness after aortic valve replacement was reported by Schwarz et al.,11 who demonstrated, after valve replacement, a reduction in wall stiffness in 10 patients with aortic stenoses. This reduction in wall stiffness may have been due mainly to the decrease in left ventricular end-diastolic pressure since they used a mathematical model that is based on end-diastolic pressure-volume data. These findings are, however, in accordance with our observations that chamber stiffness decreases slightly in patients with aortic stenoses after surgery. Normal myocardial stiffness was reported in six dogs with moderate left ventricular hypertrophy after chronic, gradually developing pressure overload.22 Thus, the effect of left ventricular hypertrophy in patients with aortic valve disease on diastolic myocardial stiffness and the effect of its regression after successful valve replacement have been a matter of debate for years. Our data suggest that myocardial stiffness is normal in patients with aortic valve disease before surgery but becomes abnormal in patients with aortic stenoses and remains unchanged in patients with aortic insufficiency after successful valve replacement. The explanation for this observation has to be made in the light of structural changes in the myocardium before and after valve replacement.

With regard to left ventricular morphology, quantitative analysis of endomyocardial biopsy samples showed increased muscle fiber diameter before as well as after surgery in all three groups with aortic valve disease. There was, however, a significant decrease in fiber diameter in all three groups after valve replacement. Muscle fiber diameters were similar in patients with chronic pressure and volume overloads, suggesting that the stimulus for myocardial hypertrophy seems to be the same for both pressure and volume overloads. Moreover, interstitial fibrosis and fibrous content were similar in all three groups with aortic valve disease before and after surgery. Regression of hypertrophy was, however, different for angiographic muscle mass and muscle fiber diameter in our three groups: muscle mass decreased by 37% in those with aortic stenoses, by 39% in those with combined valve lesions, and by 30% in those with aortic insufficiency, whereas muscle fiber diameter decreased by 16%, 13%, and 13% in the three groups, respectively. However, if the change in muscle fiber "volume" is compared with the change in muscle mass, the postoperative decrease in angiographic mass was close to the decrease in muscle fiber volume. The volume of the muscle fibers was calculated with the equation of a sphere (V = 4/3 π r³). Fiber volume decreased by 41% in patients with aortic stenoses, by 34% in those with combined valve lesions, and by 34% in those with aortic insufficiency. Thus, the decrease in angiographic muscle mass after aortic valve replacement is just due to the decrease in muscle fiber volume. Despite the decrease in muscle mass and fiber volume the muscle fibers remain significantly hypertrophied after aortic valve replacement. The nature of this residual hypertrophy is not clear, but might be the result of irreversible myocyte alterations that occur when critical myocyte size is exceeded during preoperative mechanical overload.3 Another explanation for the muscle fiber hypertrophy after successful valve replacement is that hypertrophy is necessary to maintain normal pump function in the presence of increased interstitial fibrosis. Finally, we cannot exclude the possibility that the postoperative follow-up period of 17.5 months was just too short to permit the heart muscle cells to return to normal size.

A finding of this study that had not been documented before was that interstitial fibrosis increased significantly (p < .05) from 15% to 26% in patients with aortic stenoses, from 15% to 22% (NS) in those with combined aortic valve lesions, and from 19% to 24% (NS) in patients with aortic insufficiency after valve replacement. The increase in fibrosis was, however, only a relative one due to the decrease in myocardial cell volume. The total amount of fibrous tissue (the left ventricular fibrous content) remained unchanged in all three groups before and after valve replacement, sug-
gesting that the decrease in myocardial cell volume was responsible for the relative increase in interstitial fibrosis after successful valve replacement. The increase in fibrosis was, however, associated with hemodynamic consequences, since myocardial stiffness increased significantly in patients with aortic stenoses after aortic valve replacement. In contrast, myocardial stiffness remained unchanged in patients with aortic insufficiency, despite an increase in interstitial fibrosis after surgery. Apparently the type of left ventricular hypertrophy (concentric or eccentric hypertrophy) is important for changes in myocardial elastic properties. In other words, the total amount of fibrous tissue is not the only determinant of diastolic myocardial function — left ventricular geometry also plays an important role, since a certain amount of fibrous tissue has a different meaning in a small or a large ventricle. Thus, we determined the total amount of fibrous tissue (fibrous content or FC) in relation to left ventricular end-diastolic volume (FC/EDVI) in all patients before and after aortic valve replacement (figure 5) and found an increase in FC/EDVI from 0.24 to 0.30 g/ml in patients with aortic stenoses (NS), from 0.17 to 0.26 g/ml in patients with combined valve lesions (NS), and from 0.14 to 0.21 g/ml in patients with aortic insufficiency (NS). When the index FC/EDVI was plotted against the constant of myocardial stiffness \( \beta \) (figure 5), an exponential relationship between the \( \beta \) and FC/EDVI was observed. Apparently myocardial stiffness is normal up to FC/EDVI \( \leq 0.20 \) g/ml and then gradually increases when this index value becomes larger. Since FC/EDVI can be rewritten as IF-LMMI/EDVI:100, myocardial stiffness is inversely related to the volume/mass ratio for a given interstitial fibrosis. Thus, the same amount of fibrous tissue has a different effect on diastolic stiffness in eccentric or concentric hypertrophy.

In summary, structural changes in the left ventricular myocardium are responsible for the observed changes in myocardial stiffness in patients with aortic stenoses when interstitial fibrosis is increased relative to the decrease in left ventricular muscle volume. The postoperative increase in interstitial fibrosis is important in patients with concentric hypertrophy when a large part of the left ventricle consists of fibrous tissue and the fibrous content/end-diastolic volume ratio is larger than 0.20 g/ml.

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Diastolic stiffness and myocardial structure in aortic valve disease before and after valve replacement.
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