Diastolic Left Ventricular Pressure-Volume and Stress-Strain Relations in Patients with Valvular Aortic Stenosis and Left Ventricular Hypertrophy

Kirk L. Peterson, M.D., Jack Tsui, M.D., Allen Johnson, M.D., Jerry DiDonna, M.D., and Martin LeWinter, M.D.

SUMMARY Left ventricular (LV) chamber and myocardial stiffness were determined in 17 patients, four subjects with normal LV function and 13 subjects with valvular aortic stenosis and concentric myocardial hypertrophy, using simultaneous catheter micromanometry and LV cineangiography. Pressure (P), volume (V), and wall thickness (h) were measured. Variability in both chamber and myocardial stiffness parameters was found with five of the aortic stenosis patients (Group 1, left ventricular end-diastolic pressure = 15 ± 2 (SEM) mm Hg) exhibiting normal values for end-diastolic dP/dV and dP/dV/V, for chamber stiffness constants (a, a') derived from P-V and normalized P-V relations, respectively, for end-diastolic myocardial elastic stiffness (E₀ or E₀), and for the myocardial stiffness constants (K₀ or K₀) of the circumferential stress-strain relation. Eight other patients with aortic stenosis (Group II, left ventricular end-diastolic pressure = 20 ± 3 (SEM) mm Hg) exhibited significant increases in end-diastolic dP/dV, dP/dV/V, E₀ and E₀ and a tendency for increase in the chamber stiffness constants (a, a') and myocardial stiffness constants (K₀, K₀). These observations suggest that concentric increase in muscle mass (increase in wall thickness/minor axis radius ratio and wall volume/chamber volume ratio) is an important determinant of elevated mid- and late diastolic pressures in patients with valvalur aortic stenosis, while concurrently mitigating increases in both systolic and diastolic wall stress. In some patients with aortic stenosis, however, diastolic filling pressures are elevated more severely, not only as a result of concentric hypertrophy, but also in response to augmented muscle stiffness. Reversibility of increased ventricular diastolic stiffness and elevated filling pressures was documented as concentric hypertrophy regressed post-aortic valve replacement in one patient, suggesting that fibrosis is not invariably the cause of enhanced myocardial stiffness in this secondary and compensatory form of hypertrophy.

INCREASED LEFT VENTRICULAR diastolic stiffness has been cited as a cause of elevated left ventricular diastolic pressure, pulmonary venous hypertension and associated symptoms of dyspnea, reduced exercise tolerance and syncope in patients with valvular aortic stenosis.1, 2, 3 However, quantitation of diastolic stiffness in this common clinical disorder, using both pressure-volume analysis of the ventricular chamber and stress-strain analysis of the myocardial wall, has not been accomplished, primarily due to technical obstacles in simultaneously measuring left ventricular volume, wall thickness and intracavitary pressure. A more complete and quantitative characterization of abnormal diastolic properties of the left ventricle, as well as their reversibility after aortic valve replacement, would provide an improved understanding of the pathogenesis of symptoms in individual patients and could have important implications with respect to the indication and timing for surgical intervention.

In this investigation we tried to obtain the relevant mechanical analyses in the cardiac catheterization laboratory using newer micromanometer-angio- graphic catheters and/or bimodal, simultaneous transseptal and retrograde catheterization of the left ventricle. We have then applied theories of elasticity and computed diastolic ventricular wall stress (force per unit area), strain (change in length per unit length), and instantaneous elastic stiffness (d-stress/d-strain) to approximate the stiffness properties of the myocardial fibers.4, 5 In addition, we have analyzed pressure-volume derived indices of stiffness in order to deduce whether abnormally elevated diastolic pressures may be explained by increased ventricular wall mass alone, free of the effects of intrinsic changes in myocardial stiffness.

Methods

Patients

Seventeen patients, four with normal left ventricular function and no evidence of myocardial hypertrophy, and 13 with moderate to severe aortic stenosis and unequivocal increase in wall thickness, mass, and/or ratio of wall volume to chamber volume, were investigated during the course of diagnostic right and left heart catheterization. The age range, standard hemodynamic and angiographic data, and other pertinent clinical features are listed in table 1. Three of the four subjects with normal left ventricular function were studied because of atypical chest pain and were found to have normal coronary arteriograms. One subject (GS) was found to have a secundum atrial sep-
tal defect with a small left-to-right shunt (Qp/Qs = 1.6/1). One subject (RW) had mild prolapse of the posterior leaflet of the mitral valve but had no segmental wall motion abnormalities. All patients with aortic valve stenosis and left ventricular hypertrophy were studied because of signs or symptoms suggesting significant outflow obstruction. One subject, DW, was studied both before and one year after valve replacement with a porcine heterograft.

Although five patients (JJ, TL, LO, HR, ES) with aortic stenosis had concomitant evidence of coronary artery disease on their coronary arteriograms, none had historical, electrocardiographic or ventriculographic evidence of a myocardial infarction, and they demonstrated no signs or symptoms of ischemia or regional wall motion abnormality when the pressure-volume measurements were being registered. Thus, coronary artery disease was not felt to influence the measurements of diastolic stiffness in any of these patients.

Data Collection and Processing

All studies were performed while the patients were under mild sedation (sodium pentobarbital, 100 mg). Local anesthesia (1% xylocaine) was also administered. All left heart catheters were inserted either via a right brachial arteriotomy or percutaneous puncture of the femoral vein with transseptal insertion of the catheter into the left ventricle. In 10 of the 18 studies simultaneous pressure-volume measurements were made utilizing a 5 F Millar micromanometer catheter passed retrograde across the aortic valve while contrast agent was injected via the transseptal catheter into the left ventricle. In the remaining eight instances, simultaneous pressure and volume data were obtained using a Millar Instruments 8 F micromanometer-angiographic catheter passed retrograde across the aortic valve.

**Ventricular Pressure**

The high-gain, high-fidelity left ventricular pressure tracing was calibrated by matching the signal with a simultaneous lumen pressure registered through the transeptal catheter or through the lumen of the Millar angiographic-micromanometer catheter. Zero level for fluid-filled catheter measurements was considered as 10 cm above the table top. The output of the micromanometer catheter was amplified using a

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*Patients in group 1, aortic stenosis.

Abbreviations: SP = systolic pressure; DP = diastolic pressure; HR = heart rate; CI = cardiac index; LVEDP = left ventricular end-diastolic pressure; RVEDP = right ventricular end-diastolic pressure; LA = left atrial pressure; RA = right atrial pressure; LVEDVI = left ventricular end-diastolic volume index; EF = ejection fraction; AVOA = aortic valve orifice area; AV grad. = aortic valve gradient; LVSP = left ventricular systolic pressure; RBC = red blood cells; Hg = mercury; mm Hg = millimeters of mercury; BSA = body surface area; ECG = electrocardiogram; M = male; F = female; ASD = atrial septal defect; Qp = pulmonary blood flow; Qs = systemic blood flow; CAD = coronary artery disease; RCA = right coronary artery; LAD = left anterior descending; LVH = left ventricular hypertrophy; RQCD = right ventricular conduction delay; MR = mitral regurgitation.
Table 1. (Continued)

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Aortic Stenosis

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P value NS

Postoperative Study

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Hewlett-Packard photographic recording system and synchronized with the cineangiographic frame exposures using a cinepulse time marker (fig. 1).

Ventricular Volume, Wall Thickness and Mass

Special effort was made to position the holes of the angiographic catheter directly in front of the mitral valve, thereby minimizing the stimulation of ventricular premature contractions during filming. Left ventricular volumes were measured frame by frame throughout diastole on a single plane cineangiogram, filmed during normal sinus rhythm in the 5-10 degree right anterior oblique projection, and performed in mid-inspiration by selective injection of 50-60 ml of Hypaque-75 into the left ventricle over three or four seconds. An x-y electromagnetic tablet and calculator digitizer (Hewlett-Packard 9830 A) were used to determine left ventricular dimensions and volume on sequential diastolic frames, using the area-length method and regression equation as described by Kasser and Kennedy for the direct anterior-posterior projection.7

Left ventricular free wall thickness measurements were made at end-diastole by tracing the endocardial and epicardial margins of the myocardium along the junction of the middle and lower thirds of the left ventricle (fig. 1), and corrected for distortion from non-parallel x-rays using a radiopaque cross-hatched grid. Left ventricular mass was then calculated at end-diastole using the average free wall thickness, the end-diastolic volume, and the regression equation of Rackley et al.8

In order to estimate wall thickness (h) during the remainder of diastole, we assumed a constant myocardial mass of uniform thickness and used the individual volume determinations to calculate the wall thickness obligatory to this mass for the respective geometric models (sphere and ellipsoid of revolution) used for the myocardial stress-strain analyses. We chose to back-calculate wall thickness for all cine frames other than that at end-diastole because of the well-recognized difficulty in estimating this dimension while the trabeculae of the left ventricle are infolded during mid-diastole.

Theoretical Considerations

A pressure-volume curve was constructed using the sequential volume determinations and their respective pressures, beginning at the end of the rapid filling phase and proceeding up through the peak of the a wave (fig. 2, upper panel). The interval during early diastole was excluded because of the non-exponentiality of the pressure-volume relations during this time frame, likely reflecting the occurrence of velocity-dependent or viscous effects during this phase.6, 9-11 Although inertial and viscous drag effects
may also be important during the "atrial kick." we did not observe consistent, significant deviations from the best exponential fit curve during this time frame in the patients in this study, although as shown in figure 2, lower panel, the stress-radius curve for the ellipsoidal model demonstrated generally the greatest scatter around the mathematical curve fit. The sequential pressure-volume coordinates were fitted by a non-linear least squares method to a monoexponential relation, \( P = C_1 + C_2 e^{C_3} \), where \( C_1, C_2 \) and \( C_3 \) are constants, \( P \) = pressure, \( V \) = volume, and \( e \) = the base of the natural logarithm (fig. 2, top panel). By differentiating the above exponential curve, a linear relationship is obtained between \( dP/dV \) and pressure (\( dP/dV = aP + b \)) and the calculated slope \( (a) \) then is equal to the chamber stiffness constant, (fig. 3, left upper panel). In addition, \( dP/dV \) was normalized to \( dP/dV/V \) (volume elasticity) at each pressure-volume coordinate to allow more appropriate comparisons of chamber stiffness between individual patients with variable ventricular sizes. A second stiffness rate constant \( (a') \) for this normalized relation was calculated by plotting the respective values for volume elasticity and intraventricular pressure, applying a linear least squares method, and finding the slope of the line of best fit (fig. 3, right upper panel).

For the diastolic stress-strain relation over the same time interval of diastole, we arbitrarily used natural strain, \( \ln (l/l_o) \), where \( l \) equals an instantaneous diastolic dimension and \( l_o \) = the initial or minimal diastolic dimension, because of its relative mathematical simplicity and the likelihood that it is more appropriate to biological elastic phenomena. Since \( l_o \) is a constant, d-strain is equal to \( dl/l \). Midwall circumferential stress was calculated assuming spherical and ellipsoidal geometry for the left ventricular chamber and using the formulae derived by Mirsky et al.,\(^4\) as follows:

\[
S_S = P \left( \frac{V}{V_w} \right) \left( 1 + \frac{b^2}{2R^3} \right) \quad (1)
\]

and

\[
S_E = P \left( \frac{R}{h} \right) \left( 1 - \frac{h}{2R} - \frac{R^2}{2A^2} \right) \quad (2)
\]

where \( S_S \) = stress for spherical model, \( S_E \) = stress for ellipsoidal model, \( P \) = pressure in g/cm\(^2\), \( V \) = ventricular volume, \( V_w \) = volume of the myocardial wall (assuming specific gravity of 1.05 for myocardium), \( b \) = the external radius of a thick-walled sphere, \( R \) = the radius at midwall of thick-walled sphere or ellipse, \( h \) = wall thickness, and \( A \) = semi-major axis at midwall of thick-walled ellipse.

The stress-radius curve for both spherical and ellipsoidal models was likewise assumed to be a monoexponential function whereby

\[
S_{S \text{ or } E} = C_1 + C_2 e^{C_3 R} \quad (3)
\]

where \( C_1, C_2, \) and \( C_3 \) are again constants obtained by non-linear least square fit, (fig. 2, middle and lower panels).

Differentiating this equation,

\[
dS/dR = C_2 d/dR \left[ e^{C_3 R} \right] = C_3 C_2 e^{C_3 R}
\]

By substitution, using equation (3)

\[
dS/dR = C_3 \left[ S - C_1 \right] \quad (4)
\]
Since natural strain \( (\text{St}) = \ln \left( \frac{R}{R_0} \right) \), \( d(\text{St}) = \frac{dR}{R} \). Thus, \( dS/d(\text{St}) \) or elastic stiffness \( (E) \) can be written as

\[
E = \frac{dS}{d(\text{St})} = RC_a[S - C_a].
\]  

(5)

The modulus of elasticity or stiffness constant \((K_S \text{ or } E)\) was then calculated from the values for elastic stiffness and wall stress by applying a linear least squares method to find the slope of the line of best fit (fig. 3, lower two panels).

We also report the theoretical calculation of elastic stiffness \((E_1)\) and stiffness constant \((K_E)\) for the spherical model using the equations derived by Mirsky and Parmley.4

All statistical evaluations were performed using the Student \( t \)-test for unpaired variables.

Results

Left Ventricular Systolic Pressure, Aortic Valve Gradient, and Aortic Valve Orifice Area

The 13 subjects with aortic stenosis all manifested left ventricular systolic pressures which ranged between 160–264 mm Hg and which averaged 209 ± 9 (SEM) mm Hg (table 1). The aortic valve systolic pressure gradient averaged 70 ± 5 mm Hg, and the aortic valve orifice area calculation averaged 0.62 ± 0.07 cm² for the subjects with aortic stenosis. Thus, most subjects demonstrated hemodynamic signs of severe aortic valve obstruction and a secondary left ventricular pressure overload at the time of the cardiac catheterization study.

Left Ventricular Free Wall Thickness, Left Ventricular Mass, Ratio of Wall Volume to End-Diastolic Volume and Ratio of Wall Thickness to Minor Axis Radius at End-Diastole

The significant amount of myocardial hypertrophy in the subjects with aortic stenosis was indicated by the average left ventricular free wall thickness of 1.19 ± 0.06 as opposed to a mean value of 0.79 ± 0.09 cm in the normal patients \((P = 0.005)\). Left ventricular mass averaged 76.1 ± 14.7 g/m² in the normal group and 134.0 ± 8.6 g/m² in patients with aortic stenosis, indicating the marked degree of hypertrophy in the latter group \((P = 0.005)\). The ratio of wall volume to chamber volume \((V_w/V)\) at end-diastole was significantly greater in the patients with aortic stenosis compared to the normal subjects, averaging 1.68 ± 0.10 and 1.23 ± 0.09, respectively \((P = 0.05)\). Similarly, the ratio of wall thickness to minor axis radius at end-diastole \((h/r)\) averaged 0.469 ± 0.027 in the patients with aortic stenosis and 0.330 ± 0.020 in the four normal subjects \((P = 0.025)\).

The patients with aortic stenosis were subdivided arbitrarily into two groups: group I consisted of patients with either high-normal or elevated end-diastolic pressure but normal chamber stiffness parameters (i.e., \(dP/dV, dp/dV/V, a, a'\)) and myocardial stiffness parameters (i.e., \(E_o, E_E, K_o, K_E\));
group II consisted of patients with elevated end-diastolic pressure and evidence of increase in all or most of the chamber and myocardial stiffness parameters (table 2). There were no significant differences in the averages of left ventricular wall thickness, left ventricular mass, ratio of wall volume to chamber volume, or ratio of wall thickness to minor axis radius at end-diastole between group I and II (table 2).

Left and Right Ventricular End-diastolic Pressures, and Left Ventricular End-diastolic Volume, End-diastolic Stress and Ejection Fraction

The end-diastolic pressure averaged 8 ± 1 mm Hg for the normal group, as compared to 18 ± 2 mm Hg for the total group of subjects with aortic stenosis, P = 0.05 (table 1). The left ventricular end-diastolic volume index (LVEDVI) averaged 66 ± 7 and 70 ± 6 cc/m² for the normal and aortic stenosis patients, respectively (P = NS) (table 1). Eight of 13 patients with aortic stenosis had left ventricular end-diastolic pressures greater than 14 mm Hg and six of these eight had normal LVEDVI determinations while two had mild (105 ± 110 cc/m²) increases in LVEDVI. Thus, in these subjects with aortic stenosis where elevated diastolic filling pressures are noted in association with a normal LVEDVI, either abnormal myocardial stiffness or increased chamber stiffness resulting from increased myocardial mass is suggested, or both.

End-diastolic stress (stress dia), using the spherical model, averaged 16.9 ± 3.4 g/cm² in the four normal subjects and averaged 33.5 ± 3.6 g/cm² in the total group of subjects with aortic stenosis (P = NS). The respective values using the ellipsoidal model were 27.5 ± 10.5 and 50.3 ± 5.4 g/cm² (P = NS). Patients in group I with aortic stenosis did not demonstrate significant increases (compared to normal group) in end-diastolic stress, averaging 22.2 ± 5.4 g/cm² for the spherical model and 34.4 ± 7.8 g/cm² for the ellipsoidal model while patients in group II manifested significant elevation of this same parameter, averaging 40.5 ± 2.8 and 60.4 ± 4.5 g/cm², for the respective models (P = 0.001) (fig. 4, table 2).

The right ventricular end-diastolic pressure (RVEDP) averaged 6.8 ± 0.8 and 9.1 ± 1.4 mm Hg for the normal patients and aortic stenosis patients,
respectively \((P = \text{NS})\) (table 1). The corresponding average right atrial mean pressures were lower at 5.3 \(\pm\) 0.5 and 6.4 \(\pm\) 1.0 mm Hg, reflecting dominant \(a\) waves in the right ventricular pressure pulses (table 1). The end-diastolic pressure gradient across the ventricular septum, left ventricular end-diastolic pressure (LVEDP)-RVEDP averaged 1.3 \(\pm\) 0.5 mm Hg for the normal subjects and 8.9 \(\pm\) 1.2 mm Hg for the patients with aortic stenosis.

The ejection fraction averaged 65 \(\pm\) 4% in the normal patients and 61 \(\pm\) 4% in the subjects with valvular aortic stenosis \((P = \text{NS})\) (table 1). Thus, there did not appear to be differences in extent of shortening (as reflected by the ejection fraction) or end-diastolic fiber-length (as reflected by end-diastolic volume index) which might contribute to differences in the operational levels of volume elasticity \((\text{dP/dV}_v)\) or elastic stiffness \((E_s\text{ or } s)\) between the normal subjects and subjects with aortic stenosis.

**Pressure-Volume Analysis of Chamber Stiffness**

Using a monoexponential, least squares curve fit of pressure-volume coordinates, the chamber stiffness constant \((a)\) was found to average 0.039 \(\pm\) 0.014 in the four normal patients, compared to 0.037 \(\pm\) 0.007 in the 13 subjects with aortic stenosis \((P = \text{NS})\). With the subgroups of patients with aortic stenosis, the chamber stiffness constant averaged 0.022 \(\pm\) 0.006 in group I and 0.047 \(\pm\) 0.010 in group II \((P = \text{NS})\) (table 2). As shown in figure 5, upper panel, the average chamber stiffness constant \((a)\) tended to be higher in group II than in the four normal subjects, but the average values for the two groups were not statistically different.

The chamber stiffness constant \((a')\) for volume elasticity averaged 3.94 \(\pm\) 1.04 for the normal subjects and 5.79 \(\pm\) 1.27 for the total group of subjects with aortic stenosis \((P = \text{NS})\). Subgroups I and II averaged 3.17 \(\pm\) 0.43 and 7.43 \(\pm\) 1.86, respectively \((P = \text{NS})\) (table 2). Neither subgroup was found to be significantly different from the normal subjects; however, Group II tended to have higher values for \(a'\), as shown in figure 5, lower panel.

Operational end-diastolic chamber stiffness \((\text{dP/dV}_{\text{med}})\) tended to be higher in the subjects with aortic stenosis, averaging 0.47 \(\pm\) 0.10 mm Hg/cm\(^3\), compared to the normal subjects who averaged 0.18 \(\pm\) 0.05, although the differences did not reach statistical significance \((P = \text{NS})\). In subgroup I, \(\text{dP/dV}_{\text{med}}\) averaged 0.16 \(\pm\) 0.02 and in subgroup II averaged 0.67 \(\pm\) 0.12 mm Hg/cm\(^3\), \(P = 0.01\). In addition, \(\text{dP/dV}_{\text{med}}\) in subgroup II was significantly different from the normal subjects \((P = 0.05)\) (table 2, fig. 5, upper panel).

Similarly, volume elasticity \((\text{dP/dV}_v)\) at end-diastole averaged 16.8 \(\pm\) 4.3 and 70.5 \(\pm\) 17.6 mm Hg/unit volume for the normal and aortic stenosis groups, respectively \((P = \text{NS})\). However, subgroup II was significantly increased as compared to both the normal patients and subgroup I \((P = 0.05)\) (table 2, fig. 3, lower panel).

**Stress-Strain Analysis of Myocardial Stiffness**

**Spherical Model**

Using a non-linear monoexponential least squares curve fit of the stress-radius coordinates the myocardial stiffness constant \((K_s)\) at the midwall of the minor axis circumference was calculated on the average as 15.9 \(\pm\) 2.8 ml\(^1\) for the normal subjects and 24.1 \(\pm\) 5.0 ml\(^1\) for the patients with aortic stenosis \((P = \text{NS})\).
Using the exact formula of Mirsky et al., to calculate $K_T$, the corresponding values were 16.4 ± 3.0 and 24.7 ± 5.1 m$^{-1}$ ($P = \text{NS}$). By contrast, $K_S$ in subgroup II averaged 30.7 ± 7.3 m$^{-1}$ which was not significantly different from the average value for the normal patients or subgroup I (fig. 4, table 2). $K_T$ demonstrated corresponding (essentially identical) differences between the various groups (table 2). The average myocardial elastic stiffness ($E_S$) at end-diastole for the normal group averaged 215 ± 55 mg/cm$^2$, and 628 ± 136 g/cm$^2$ for the total group with aortic stenosis ($P = \text{NS}$). $E_S$ in subgroup I of the patients with aortic stenosis averaged 234 ± 26 g/cm$^2$, which was not significantly different from the four normal subjects. However, in subgroup II $E_S$ averaged 880 ± 172 g/cm$^2$, which was significantly greater than subgroup I as well as the normal group ($P = 0.02$) (table 2, fig. 4).

**Ellipsoidal Model**

The myocardial stiffness constant, $K_E$, for the ellipsoidal minor axis stress-strain relation averaged 13.9 ± 3.7 and 19.0 ± 4.0 g/cm$^2$ for the normal group of patients with aortic stenosis, respectively ($P = \text{NS}$). Likewise, the average $K_E$ for groups I and II did not differ significantly from the average value for the normal subjects. However, elastic stiffness ($E_E$) at end-diastole was significantly higher in the subgroup II of patients with aortic stenosis (948 ± 205 g/cm$^2$) as compared to both the normal subjects (251 ± 74) and subgroup I (314 ± 57) (fig. 4, table 2) ($P = 0.05$ for II vs normal and II vs I).
**Table 2. (Continued)**

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**Comparison of Stiffness Constants Ks, Ks/ and KE**

The myocardial stiffness constant (Ks) and elastic stiffness at end-diastole (Es), derived from the monotransformation of stress-radius curve for the spherical model, demonstrated very high correlations (r = 0.99) with Ks/ and Es/ respectively (fig. 6). We take these correlations to indicate that the exponential curve fitting routine itself leads to minimal error in deriving Ks and Es. Moreover, it supports the use of a stress-mass axis curve fitted, using the ellipsoidal model, as the most appropriate method of deriving KE and Es, since no exact solution is possible assuming an ellipsoid of revolution. A similar linear regression analysis comparing Ks and KE for all patients likewise revealed the correlation to be high (r = 0.83), confirming similar results of other investigators. However, it is apparent that KE systematically overestimates Ks, likely due to an underestimation of circumferential wall stress and an overestimation of elastic stiffness with a spherical model.

**Discussion**

Although technically and conceptually a difficult clinical investigation, the characterization of left ventricular distensibility in the presence of valvular aortic stenosis has important implications for both medical and surgical treatment of this relatively common cardiac disorder. If secondary myocardial hypertrophy in aortic stenosis is associated invariably with an obligatory as well as irreversible increase in myocardial stiffness, then aggressive efforts to forestall this pathophysiologic adaptation would seem desirable. However, if increased ventricular chamber stiffness is related primarily to increased muscle mass with no increase in intrinsic muscle stiffness, one might expect that left ventricular distensibility would revert toward
normal as hypertrophy regressed in response to therapeutic measures to relieve the left ventricular pressure overload. Alternatively, if hypertrophy persists, without fibrosis, is associated with an increase in muscle stiffness, possibly due to architectural distortion and malalignment of myofibers, it is unpredictable whether regression of hypertrophy would lead to normalization of chamber distensibility. Hypertrophy with fibrosis, however, would be expected to cause irreversible changes in both myocardial and chamber stiffness.

Previous experimental data bearing on the above hypotheses are inconsistent and demonstrate interspecies variation. Using hypertrophied rat myocardium at muscle lengths which resulted in peak isometric tension, Bing et al. reported that there was a significant increase in resting tension (i.e., increased stiffness). Similarly, Alpert et al., using rabbit papillary muscle, reported that the modulus of elasticity (ratio of stress to strain) was greater in hypertrophied than in control muscle preparations even though the individual muscles were normalized for cross-sectional area. In contrast, Spann et al., Grimm et al., and Cooper et al. have all reported no significant differences in the resting length-tension curves of normal and hypertrophied cat papillary muscles. However, Mirsky reexamined the data of Spann et al., using the natural strain definition for dimensional change, and concluded that the passive stiffness constants are elevated in hypertrophy due to pressure overload.

In patients with pressure overload hypertrophic states, Grossman et al. studied the incremental change in late diastolic ventricular pressure (ΔP) related to the change in minor axis diameter (ΔD) and found that the severity of stiffness increase (ΔP/ΔD) correlated with wall thickness, suggesting that chamber stiffness was directly related to severity of hypertrophy. However, direct assessment of the passive stress-strain characteristics of the myocardium was not attempted in these patients. Mirsky subsequently presented an approximate analysis of the data of Grossman et al. in patients with chronic pressure overload by assuming fixed geometric relationships between an ultrasonically derived minor axis and ventricular volume; these calculations suggested that the myocardial stiffness constants were elevated significantly in patients with valvular aortic stenosis.

In this study we have attempted to define in man the elastic stiffness of the myocardial fibers by calculating, from direct pressure, volume and wall thickness measurements during mid- and late diastole, the passive stress-strain properties at the midwall of the minor axis circumference. Considering all 13 subjects with aortic stenosis, the percentage augmentation in normalized end-diastolic chamber stiffness (volume elasticity or dP/dV/V), as compared to the four normal subjects, was 300%, while the corresponding augmentation of myocardial elastic stiffness (d-stress/d-strain) was 189%. This comparison suggests that augmented myocardial stiffness contributes partially to observed levels of chamber stiffness, but concentric hypertrophy (increase in end-diastolic wall thickness/minor axis radius and wall volume/chamber volume ratio) itself must also play an important role. Further insight is given by inspection of the plots for the subgroups of patients with aortic stenosis in figure 5, which demonstrates that the average slope of the pressure-volume relationship (dP/dV versus P or dP/dV/V vs P) is not significantly different between the normal and aortic stenosis group I, although with the patients in the latter group the filling pressures are higher for any given diastolic “volume strain”
individual hypertrophied myofibers may not be stiffer. Our findings in subgroup I also imply that regression of hypertrophy (reduction in h/r and Vw/EDV ratios) post aortic valve replacement, a phenomenon which has been confirmed by serial left ventriculography and echocardiography, should be associated with reductions in left ventricular diastolic pressure.

By contrast, figure 5 also demonstrates that some patients with aortic stenosis and concentric hypertrophy (subgroup II) manifest a combination of high diastolic filling pressures, elevated diastolic stresses, and augmented KE and KE values, indicating inadequate hypertension to normalize diastolic stress and some intrinsic change in muscle stiffness. Thus, in these patients both concentric increases in myocardial mass and enhanced myocardial elastic stiffness contribute to the marked augmentation of mid- and late diastolic pressures. Prediction of total reversal of elevated filling pressures with aortic valve replacement in subgroup II is less certain. Nevertheless, patient DW demonstrated near-normalization of all chamber and myocardial stiffness parameters by one-year post aortic valve replacement (fig. 3, table 2). The return toward normal of diastolic distensibility in patient DW could be suspected from the reduced prominence of the “atrial kick” on the postoperative study (fig. 1). That the observed changes in stiffness in this patient were temporally related to regression of hypertrophy is supported by the observed changes in both ventriculographic as well as echocardiographic indices of wall thickness and mass (table 3). Further studies in more than one patient obviously will be necessary to confirm that chamber stiffness invariably reverts toward normal as hypertension regresses. Histologic confirmation of myocardial morphology is not available in patient DW; as hypothesized earlier, patients with myocardial fibrosis may be exceptions to the reversibility noted in patient DW.

Before accepting the validity of any of these conclusions, the limitations of measuring both chamber and myocardial elasticity should be considered. Since several investigators have noted that the in vivo diastolic pressure-volume curve departs from a simple monoexponential model during the rapid filling phase and is complicated by viscous effects, we purposefully excluded pressure-volume coordinates during this part of diastole. Both inertial and viscous effects may also complicate analysis of passive elasticity during atrial systole, but the measured pressure-volume coordinates in our patients showed minimal departure from the monoexponential curve fits during this time frame, and thus we arbitrarily chose to accept all data points up through the peak of the a wave. Glantz has

\[
E_T = 1021.1x + 58.231 \\
r = 0.998
\]

\[
E_S = 1023x + 0.0545 \\
r = 0.998
\]

**Figure 6.** Upper: Correlation of theoretical elastic stiffness constant (K$_T$) on vertical axis, and calculated elastic stiffness constant (K$_S$). Lower: Correlation of the elastic stiffness at end-diastole (E$_s$) on horizontal axis and elastic stiffness at end-diastole (E$_T$) using spherical model. K$_s$ and E$_s$ are derived from stress-radius monoexponential curve fit while K$_T$ and E$_T$ are based upon theoretical mathematical calculation (see text).
emphasized that in order for a stiffness parameter based upon a monoexponential analysis to be clinically useful, it must describe the whole pressure-volume curve from a short segment; or, a derived stiffness constant should not vary when it is computed from differing segmental portions of the same force-length curve. This contention is germane to our study, since none of the pressure-volume and stress-strain curves in the subjects reported herein demonstrated perfect monoexponentiality (fig. 2). Thus, it was anticipated that efforts to calculate individual stiffness coefficients from different segments of an already limited pressure-volume or stress-strain curve would be futile. Segmental curve fitting of only part of the measured raw pressure-volume and stress-strain coordinates will increase inappropriately the least squares weighting of those points which fall the furthest distance from the line of best fit for all the available data coordinates. It seems axiomatic that anything less than a perfect monoexponential function for the initial coordinates will lead to ever-greater variation in segmental stiffness constants as those portions of the whole curve with more scatter are isolated and curve-fitted. Thus, although the assumption of a monoexponential model for mid- and late diastole is imperfect, we feel that it best approximates the portion of the diastolic filling curve where passive elastic phenomena are primarily operative, and yet allows quantitative description of interpatient differences in the shape and steepness of the pressure-volume and stress-strain curves.

It would be desirable to be able to obtain a wider range of diastolic pressure and volume coordinates by altering the amount of venous return on individual beats. For example, intermittent vena caval occlusion has been useful in characterizing the static elastic properties in the canine experimental preparation. In patients with calcific aortic stenosis, however, sudden reduction in venous return by balloon occlusion of the inferior vena cava cannot be justified, and interventions such as slowing the heart rate by paired pacing or beta-adrenergic blockade might themselves alter diastolic stiffness. Moreover, acute volume loading potentially would provoke the external constraining effect of the pericardium (vida infra). Thus, study of the pressure-volume coordinates on individual cardiac cycles is the most practical and desirable mode of analysis of diastolic stiffness changes in pressure overload hypertrophy.

In addition to the questions of monoexponentiality and adequacy of pressure-volume coordinates, we are also concerned about the accuracy of wall thickness and mass measurements by left ventriculography. Since Rackley et al. found acceptable correlation between angiographic and postmortem determinations of left ventricular mass, we chose to utilize their formula and regression equation which assume a uniform wall thickness around the ellipsoidal shell. Any errors generated by this assumption are likely to be directionally the same for all patients reported here. The close correlation of posterior wall thickness by echocardiography and lateral free wall thickness by left ventriculography in patient DW, both before and after regression of hypertrophy, supports the accuracy of the wall thickness measurements (table 4).

Recently-reported observations on shifts of the basal left ventricular pressure-volume curve in response to pharmacologic interventions (e.g., nitroprusside, nitroglycerin and angiotensin) have raised important questions about the role of the pericardium and right ventricle in affecting the pressure-volume relationship, as well as the potential importance of using transmural rather than absolute intraventricular pressure measurements for assessment of left ventricular diastolic distensibility. While such considerations are of obvious importance with acute interventions, which cause acute changes in left ventricular volume, it is unlikely that chronic adaptations such as ventricular hypertrophy would significantly influence intrapericardial pressure or that the pericardium itself would be an additional external constraint on diastolic filling in our patients with valvular aortic stenosis without significant left ventricular dilatation. It is clear, however, that in the presence of an intact pericardium, the distensibility characteristics of the right ventricle influence those of the left ventricle. In our patients there was no clinical or electrocardiographic evidence of right ventricular dilatation or hypertrophy, although the right ventricular end-diastolic pressure measurements were elevated in nine of the 13 patients with aortic stenosis and left ventricular hypertrophy. In these subjects, therefore, it is likely that the elevation of the end-diastolic pressure and prominence of the a kick in the right ventricle represents the converse effect of left-sided distensibility properties influencing those of the right side of the heart.

In order to assess quantitatively the effects of either a positive or negative bias on left ventricular pressure due to external pericardial constraints, overestimated transmural pressure, or inaccurate pressure calibration, we arbitrarily subtracted and added 5 mm Hg to each of the pressure coordinates for the pressure-volume and stress-strain analysis of patient DW and repeated the monoexponential, least squares curve fit. As shown in table 4, hypothetical errors of diastolic pressure measurements of this magnitude have no effect on the chamber stiffness constant (a), end-diastolic stiffness (dP/dV) or volume elasticity (dP/dV/V). However, calculations of midwall myocardial stress are affected by the pressure bias, and errors ranging from ±7% were noted for calculations of Ks, ±6% for Ke, ±3 to + 0.7% for elastic stiffness (dS/dStr) for the spherical model and + 0.5% to + 0.7% for elastic stiffness in the ellipsoidal model. Thus, it appears that errors in pressure determination of this magnitude (±5 mm Hg) would change slightly, but not significantly, the myocardial stiffness parameters assessed in our patient groups.

In conclusion, we have found that detailed analysis of the pressure-volume and stress-strain relations of the left ventricle in patients with valvular aortic
stenosis has provided greater insight into the mechanisms responsible for elevation of diastolic filling pressures in association with myocardial hypertrophy. Concentric myocardial hypertrophy necessitates increased intraventricular force to displace the left chamber, although it serves concurrently to normalize average diastolic wall stress. However, in some subjects diastolic stress is not normalized (inactive hypertrophy) and increased myocardial stiffness can be demonstrated by circular and longitudinal wall stress-strain relations which thereby exaggerates further the elevation of diastolic filling pressure. Further pre- and postoperative studies will be necessary in order to define the morphologic and histologic characteristics which predict reversibility of abnormal diastolic mechanical properties once the pressure overload is relieved by cardiac surgery.

References


Table 4.

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*Values actually measured in patient DW, Group II.
Diastolic left ventricular pressure-volume and stress-strain relations in patients with valvular aortic stenosis and left ventricular hypertrophy.
K L Peterson, J Tsuji, A Johnson, J DiDonna and M LeWinter

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