Diastolic Function and Myocardial Structure
in Patients with Myocardial Hypertrophy

Special Reference to Normalized Viscoelastic Data

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SUMMARY Diastolic myocardial stiffness and viscosity were determined in 40 patients with myocardial hypertrophy by combined echo-pressure measurements. These diastolic measurements were compared with left ventricular muscle fiber diameter and interstitial fibrosis as obtained from left ventricular endomyocardial biopsies at catheterization.

The patients were divided into four groups: group 1 — eight control patients; group 2 — 10 patients with moderate-to-severe aortic stenosis; group 3 — 10 patients with moderate-to-severe aortic insufficiency; and group 4 — 12 patients with congestive cardiomyopathy. Myocardial stiffness and viscosity were assessed using a viscoelastic stress-strain model. For the interpatient comparison, a normalization of the stress-strain relationship was performed by calculating a reference midwall circumference (1) at a transmural stress of 1000 dyn/cm². The light microscopic evaluation of the left ventricular biopsies included the quantitative assessment of interstitial fibrosis by the point-counting system and of muscle fiber diameter by direct measurement.

The normalized viscoelastic constant of myocardial stiffness (Kw) was slightly, but not significantly, increased in patients with aortic stenosis and insufficiency (13.3 and 13.0), whereas K, was significantly (p < 0.05) higher in patients with congestive cardiomyopathy (33.8) than in the control subjects (8.8). The constant of myocardial viscosity (Yw) was elevated slightly in patients with aortic valve disease and moderately in patients with congestive cardiomyopathy. In contrast, 1, was significantly increased in all three groups with myoccardial hypertrophy compared with group 1.

Left ventricular interstitial fibrosis amounted to 2% in seven control patients, 15% in patients with aortic stenosis, 11% in patients with aortic insufficiency and 28% in patients with congestive cardiomyopathy. Muscle fiber diameter (control patients 13.7 μ) was largest in patients with aortic stenosis (26.8 μ) and was somewhat smaller in patients with aortic insufficiency (21.7 μ) or congestive cardiomyopathy (23.6 μ). The comparison of functional and structural properties of the left ventricle showed a significant correlation between myocardial stiffness and interstitial fibrosis (r = 0.59; p < 0.001), whereas there was no correlation between myocardial stiffness and angiographic muscle mass or muscle fiber size.

In summary, normalized myocardial stiffness is normal in most patients with aortic valve disease, but is significantly higher in patients with congestive cardiomyopathy. Myocardial stiffness appears not to be influenced by left ventricular muscle mass or muscle fiber size, but is increased in the presence of massive left ventricular interstitial fibrosis. These findings suggest that diastolic myocardial stiffness in myocardial hypertrophy is related more to the interstitial than to the muscular tissue.

IN CHRONIC HEART DISEASE, changes in myocardial mechanical properties are thought to be the consequence of changes in myocardial structure and morphology.1,2 The relationship between these mechanical properties and myocardial morphology is not clear, and several authors3-8 have suggested that the increase in myocardial muscle stiffness may be caused by an increase in muscle mass or muscle fiber size. In the present study we evaluated the diastolic myocardial stiffness, with special reference to normalized viscoelastic data, in patients with myocardial hypertrophy of varying etiology and compared the stiffness measurements with angiographic muscle mass, muscle fiber diameter and the extent of interstitial fibrosis determined by left ventricular endomyocardial biopsies.

Material and Methods

Patients

Forty patients, nine females and 31 males, average age 41 years (range 19–65 years), who underwent diagnostic heart catheterization were studied. The patients were divided into four groups.

Group 1 included eight control patients with normal left ventricular function. Two patients had a minimal pulmonic stenosis, one an idiopathic dilatation of the ascending aorta and one a small atrial septal defect. The other four patients were catheterized because they complained of atypical chest pain. Their coronary arteries were, however, normal.

Group 2 included 10 patients with moderate-to-severe pure or predominant aortic stenosis. Five had slight-to-moderate aortic insufficiency and three had slight-to-moderate mitral insufficiency.

Group 3 included 10 patients with moderate-to-severe pure or predominant aortic insufficiency. Five

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Supported by the Swiss National Science Foundation.

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Received July 3, 1979; revision accepted June 20, 1980.

Circulation 63, No. 2, 1981.

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had slight-to-moderate aortic stenosis and four had slight mitral insufficiency.

Group 4 included 12 patients with congestive cardiomyopathy. Four had slight-to-moderate mitral insufficiency.

Cardiac Catheterization

Right- and left-heart catheterization was performed in all 40 patients. Before catheterization all patients gave informed consent. Premedication consisted of 10 mg of chlordiazepoxide hydrochloride (Librium) given orally 1 hour before the procedure. Standard pressure measurements were carried out by fluid-filled catheters and were recorded on an oscillograph (Electronics for Medicine DR/16). Aortic and mitral regurgitation were assessed quantitatively by thermodilution.\(^6\) When the diagnostic part of the catheterization procedure was completed, a Millar \#8F micromanometer was introduced into the left ventricle through a \#11.5F Brockenbrough catheter, which had been advanced to the left ventricle by the transseptal route.\(^7\) The patients were then given i.v. heparin in a dose of 10,000 units. The micromanometer was calibrated by superposing the micromanometer tracing with the conventional pressure tracing. Before insertion, the manometer was balanced and zeroed at 37°C. The frequency response of the recording system, including the tip-transducer and the DC amplifier, was flat beyond 100 Hz. The resonant frequency of the Millar micromanometer is 25–35 kHz. The left ventricular high-fidelity pressure curve was differentiated by a circuit with a time constant of 0.8 msec.

The left ventricular pressure measurements were carried out simultaneously with the left ventricular echocardiogram at a paper speed of 100 mm/sec. The echocardiograms (single-beam method; Ekoline 20A, Smith Kline Instruments) were obtained in the anteroposterior position or in a slight right anterior decubitus position according to our standard technique.\(^8\) The quantitative evaluation included the assessment of the left ventricular endocardial diameter from the septum to the posterior wall, the posterior wall thickness and the left ventricular pressure by a computer-assisted system using an electronic digitizer (Numonics). The measurements were made during one heart cycle, which was selected from all cycles of one respiratory swing. The criterion of selection was an end-diastolic pressure representing the arithmetic mean of the highest and the lowest end-diastolic pressure during the respiratory swing.

The echocardiographic technique has limitations in determining left ventricular dimensions. The axial resolution is defined by the wavelength and is considered to be 0.68 mm at 2.25 MHz.\(^9\) Moreover, the measured echocardiographic diameter does not necessarily correspond to the true minor axis\(^10\) of the ventricular ellipsoid, especially in enlarged left ventricles. The error of not measuring the same topographic diameter during the heart cycle appears, however, to be small, because our measurements were started at the end of active relaxation, when the systolic tilting movement of the heart was almost completed.\(^11\)

The validation of the echocardiographic dimension measurements was made by calculating the left ventricular reference volume at a common wall stress of 1000 dyn/cm\(^2\) and the left ventricular volume at end-diastole. Left ventricular volume was calculated by the area-length method\(^12\)–\(^14\): \(V = \frac{\pi}{6} \cdot L \cdot D^2\), where \(V\) = left ventricular volume, \(L\) = major and \(D\) = minor left ventricular axis. The minor axis was determined by echocardiography and the long axis by multiplying the minor axis by the angiographic major/minor axis ratio obtained at end-systole for the volume calculation at 1000 dyn/cm\(^2\) and at end-diastole for the volume calculation at end-diastole. The results for the echo- and angiographic volume determinations are given in table 1. The echocardiographic left ventricular volume at 1000 dyn/cm\(^2\) and

<table>
<thead>
<tr>
<th>Table 1. Echocardiographic and Angiographic Data</th>
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<tr>
<td><strong>Group 1</strong></td>
</tr>
<tr>
<td>ESVI (ml/m(^2))</td>
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<tr>
<td>VI (ml/m(^2))</td>
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<td>EDVI (ml/m(^2))</td>
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<td>EDVI (ml/m(^2))</td>
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<tr>
<td>EF (%)</td>
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<tr>
<td>Δ%</td>
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<tr>
<td>D(int) (cm)</td>
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<td>D(int) (cm)</td>
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</tbody>
</table>

Values are mean ± SEM.

\(^*p < 0.05,
\(†p < 0.025.

Abbreviations: ESVI = end-systolic volume index; VI = reference volume at 1000 dyn/cm\(^2\); EDVI = end-diastolic volume index; EF = ejection fraction; Δ% = percent ejected volume; D(int) = end-diastolic internal diameter; A = angiocardiography; E = echocardiography.
end-diastole corresponded well with the angiographic volumes at end-systole and end-diastole in group 1 and 2; however, at larger volumes, echocardiography underestimated the angiographic volumes in group 3 and 4 at end-systole and at end-diastole (table 1). The angiographic method tends to overestimate left ventricular volume, especially in enlarged ventricles, whereas echocardiography tends to underestimate left ventricular volume. The relative change (i.e., angiographic ejection fraction and echocardiographic percent ejected volume), however, corresponded reasonably well between the two methods. These data show that echocardiography is a valid method for measuring left ventricular dimensions and parameters in assessing diastolic myocardial function.

Left ventricular cineangiography was performed in the right anterior oblique position according to our standard technique. Quantitative analysis of the left ventricular cineangiograms was carried out according to the area-length method. End-diastolic and end-systolic volumes of the left ventricle were calculated in each patient, as well as systolic ejection fraction. End-diastolic wall thickness was determined from a second angiogram obtained in the anteroposterior projection. In 13 patients in whom a second angiogram was not available, wall thickness was determined from the right anterior oblique projection. Left ventricular muscle mass was calculated by the technique of Rackley et al.

After ventriculography, selective coronary arteriography was carried out in six group 1 patients, in all group 2 and 4 patients and in eight group 3 patients. All coronary arteriograms were normal.

At the end of the catheterization a percutaneous transseptal left ventricular endomyocardial biopsy was performed in all patients in groups 2, 3 and 4 using the King's College biop tome, which was introduced into the left ventricle through the #11.5F Brockenbrough catheter (fig. 1). In each patient three biopsies were taken, mainly from the lateral portion of the left ventricle. Usually, some premature ventricular complexes occurred during the biopsy, but there were no complications in any of the 32 patients. Immediately after biopsy the material was fixed in Bouin's solution for light microscopy and in glutaraldehyde for electron microscopy. Then, the biopsies were embedded in paraffin for light and in epon for electron microscopy.

Quantitative evaluation of left ventricular endomyocardial biopsies was carried out by morphometry. Muscle fiber diameter was determined by direct measurements using a special ocular with a scale (fig. 2A). With this scale, 50–150 muscle fibers were measured and an average muscle fiber diameter was calculated in all patients. Interstitial fibrosis was evaluated by using the point-counting system. A special ocular with a grid with vertical and horizontal lines providing 100 intersection points was used to determine the amount of fibrous tissue (fig. 2B). Counting the number of points overlying fibrous tissue was used for quantitative assessment of interstitial fibrosis. The total number of points, i.e., 100, was regarded as 100% and the points counted in the fibrotic areas were expressed as percent of the entire tissue within the limits of the grid. To assess both muscle fiber diameter and interstitial fibrosis, only cross sections at a magnification of ×500 were evaluated, and in each patient two biopsies were examined. The average muscle fiber diameter was calculated from 12 sections with six stains (hematoxylin-eosin, van Gieson, elastic fiber, Masson-trichome, periodic acid Schiff and reticulum fiber stain), and in each section five to 10 measurements were carried out. Interstitial fibrosis was determined from four sections with two stains (Masson-trichome and van Gieson stain), and in each section five to eight measurements were performed. In group 1, no endomyocardial biopsies were performed. In group 1, no endomyocardial biopsies were performed.
myocardial biopsies is limited because only small pieces of left ventricular myocardium (approximately one-tenth of the left ventricular wall thickness) can be evaluated.

Schwarz and co-workers\textsuperscript{25} have determined the endo-epicardial ratio of myocardial interstitial fibrosis in patients with aortic stenosis (endo-epicardial ratio 1.46) and aortic insufficiency (endo-epicardial ratio 1.05) using transmural biopsies obtained at open heart surgery and found a predilection of interstitial fibrosis in the endocardium of patients with aortic stenosis, whereas fibrosis was diffuse in patients with aortic insufficiency. Roberts and Ferrans\textsuperscript{21} demonstrated in 64 patients with congestive cardiomyopathy a transmural scarring, sometimes focal and sometimes diffuse, of all four heart chambers. Thus, in patients with aortic insufficiency and congestive cardiomyopathy, it seems reasonable to expect that the endocardial specimen is representative for the whole left ventricular myocardium. In contrast, in patients with aortic stenosis there is a certain overestimation of interstitial fibrosis by left ventricular endomyocardial biopsies.

Calculations

In each patient the following measurements were calculated during one heart cycle by using a computer-assisted system (DEC PDP 11) with a program originally developed by Gibson and Brown\textsuperscript{22}. Left ventricular internal dimension, its first derivative, velocity of shortening of midwall circumference, normalized velocity of shortening of midwall circumference, first derivative of pressure and meridional wall stress according to the equation

\[ S = \frac{D}{4h} \cdot \frac{P \cdot D}{(1 + h/D)} \]

where

\( S = \) meridional wall stress, \( P = \) left ventricular pressure, \( D = \) internal left ventricular diameter and \( h = \) left ventricular wall thickness.

Meridional wall stress was used in the present study because all variables in the above stress equation were directly measured in each patient. The meridional wall stress is in a different plane (longitudinal plane) from the minor-axis strain (circumferential plane). However, instead of using a circumferential stress model assuming that the left ventricular major axis is equal to the minor axis (spherical model) or that the major axis is in given relation to the minor axis using a regression equation to calculate the major left ventricular axis (ellipsoidal model), we preferred to use the meridional wall stress, because it was demonstrated in five chronically instrumented dogs\textsuperscript{*} that the measured left ventricular meridional and measured left ventricular circumferential wall stress are highly correlated (fig. 3). Meridional and circumferential wall stress was calculated in these five dogs at 5-msec intervals using ultrasonic crystals for the measurement of the minor and major left ventricular axis.\textsuperscript{17} All measurements

\*Unpublished data from the Department of Medicine, Seaweed Canyon, University of California, San Diego, La Jolla, California 92033.
were carried out in the resting state using 68 cardiac cycles in the five dogs (average 13.6 per dog), representing 8980 data pairs for the meridional \(S_m\) and circumferential left ventricular wall stress \(S_c\). The correlation between the two wall stresses (fig. 3) was excellent (average correlation coefficient 0.997) and a linear relationship \(S_m = 0.472 \cdot S_c + 0.011\) was demonstrated. Thus, left ventricular meridional and circumferential wall stress in the conscious dog are closely correlated, and demonstrate that the circumferential wall stress is 2.12 times higher than the meridional wall stress. These data confirm that the left ventricular meridional wall stress is a valid measurement for the assessment of left ventricular wall stress, although the theoretical concept for the assessment of left ventricular diastolic mechanical properties using longitudinal wall stress and circumferential wall stress is not entirely valid.

Left ventricular midwall circumference\(^1\) was calculated according to the equation \(L = \pi \left( D + h \right) \). Using the midwall circumference the midwall strain \((E)\), the normalized midwall strain \((E_n)\), the strain rate \((\dot{E})\) and the normalized strain rate \((\dot{E}_n)\) were calculated. The midwall strain using the Lagrangian strain definition\(^1\) was obtained by the equation \(E = \frac{1 - L_{po}}{L_{po}}\), where \(L_{po}\) is the diastolic midwall circumference measured at the lowest diastolic pressure. This is not the true \(L_0\) at a transmural pressure of 0 mm Hg, which would be the best reference circumference. However, \(L_0\) cannot be measured in the intact human heart, and a method of dimension normalization is needed for interpatient comparison. To approximate unloaded muscle circumference, we determined by extrapolation the left ventricular midwall circumference at the very low wall stress of 1000 dyn/cm\(^2\), which corresponds to a distending pressure of 0.8 mm Hg (fig. 4). This circumference was termed \(L_1\) for the purpose of the present study. It served to calculate normalized midwall strain: \(E_n = \frac{1 - L_1}{L_1}\).

Clearly, there is potentially some error in the extrapolation procedure of \(L_1\). However the extrapolated range is generally low (2000–5000 dyn/cm\(^2\)) and the curve fit of the stress-strain relationship is high in most patients (range 0.79–0.99). Thus, the error of the normalization procedure is small, but the advantage of dimension normalization is obvious. The strain rate was obtained as \(\dot{E} = dE/dt\), where \(\dot{E}\) is the first derivative of strain. The normalized strain rate was obtained from the equation \(\dot{E}_n = dE_n/dt\).

### Curve Fitting

The diastolic function measurements were determined by using a viscoelastic model proposed by Rankin and co-workers,\(^1\) which incorporates a parallel elastic and a parallel viscous element. The following equation was used:

\[
S = C + B \cdot e^K \cdot \dot{x} + y \cdot \dot{E},
\]

where \(S\) = meridional wall stress, \(B, C\) and \(K\) = viscoelastic constants of myocardial stiffness, \(e = \text{base of}\)
Therefore, constant viscosity and myocardial viscosity and \( E \) = strain rate.

Using the extrapolation to a midwall circumference at 1000 dyn/cm\(^2\) as a method of dimension normalization, the stress-strain equation could be rewritten as

\[
S = B_n \cdot e^{K_n \cdot E_n} + y_n \cdot E_n.
\]

Thus, when normalized strain \( E_n \) is used, the viscoelastic constant \( B_n \) is always 1000 dyn/cm\(^2\) and \( C \) is 0. Therefore, myocardial stiffness can be evaluated by only the viscoelastic constant \( K_n \).

To evaluate the diastolic stress-strain relationship, all data were fitted to a linear regression function

\[
y = a \cdot x + b.
\]

The corresponding regression function of the normalized viscoelastic model was therefore

\[
\ln (S - y_n \cdot E_n) = K_n \cdot E_n + \ln B_n.
\]

This equation was solved by using an iteration procedure\(^a\) in which for one constant \( (y_n) \), assumed values were inserted into the equation, and these values were varied until the best curve fit was obtained.

**Statistics**

The statistical comparison was performed by using the Wilcoxon rank-sum test.

**Results**

**Hemodynamics**

In group 2, diagnostic heart catheterization revealed a mean systolic pressure gradient across the aortic valve of 62 mm Hg and additional aortic regurgitation in five patients of 30%. The average aortic valve area was 0.85 cm\(^2\) in the patients with aortic stenosis. Three patients of group 2 had mild-to-moderate mitral insufficiency (average 22%). In group 3 the aortic regurgitation fraction averaged 51% and the aortic valve area 2.05 cm\(^2\). In addition to aortic regurgitation, five patients of group 3 had aortic stenosis, with a mean systolic pressure gradient of 33 mm Hg, and four patients mild mitral regurgitation of 10%. Four group 4 patients had slight-to-moderate mitral insufficiency (average 31%).

Hemodynamic data are listed in table 2. Heart rate was not significantly different among the four groups, but left ventricular end-diastolic pressure was increased in group 4 (\( p < 0.05 \)). Left ventricular systolic pressure was significantly increased in groups 2 and 3, but was normal in group 4. Right ventricular end-diastolic pressure was not significantly different in any group. The angiographic function measurements revealed a slightly decreased ejection fraction in group 2, but a significantly decreased ejection fraction in groups 3 and 4. Left ventricular end-diastolic volume and muscle mass were significantly higher in groups 2, 3 and 4. Peak systolic and end-diastolic meridional wall stresses as evaluated by the echo-pressure measurements were significantly higher in groups 2, 3 and 4 than in group 1.

**Diastolic Properties**

The assessment of normalized viscoelastic properties in the four groups showed a good correlation between linear strain and logarithmic stress. The correlation coefficients were similar in all four groups (table 3) and did not differ significantly. The calculated diastolic reference midwall circumference was significantly higher in groups 2, 3 and 4 than in group 1. The normalized viscoelastic constant of myocardial stiffness \( K_n \) was slightly increased in groups 2 and 3, but was significantly higher in group 4 than in group 1 (figs. 5 and 6). The constant of myocardial viscosity was slightly increased in groups 2 and 3. Group 4 had the highest viscous resistance, although it was not significantly different from that in group 1.

**Morphologic Data**

The quantitative evaluation of left ventricular endomyocardial biopsies showed the largest muscle fiber diameter in patients with aortic stenosis (table 4). Average muscle fiber diameter was lower in patients with aortic insufficiency and congestive cardio-
### TABLE 2. Hemodynamic Data

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>78 ± 3</td>
<td>74 ± 6</td>
<td>82 ± 5</td>
<td>89 ± 5</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>6 ± 1</td>
<td>4 ± 1</td>
<td>5 ± 1</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>12 ± 1</td>
<td>18 ± 3</td>
<td>20 ± 3</td>
<td>*</td>
</tr>
<tr>
<td>RVSP (mm Hg)</td>
<td>25 ± 2</td>
<td>30 ± 4</td>
<td>29 ± 3</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
<td>116 ± 3</td>
<td>196 ± 11</td>
<td>163 ± 7</td>
<td>108 ± 5</td>
</tr>
<tr>
<td>EF (%)</td>
<td>69 ± 4</td>
<td>62 ± 5</td>
<td>53 ± 4</td>
<td>33 ± 3</td>
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<tr>
<td>EDVI (ml/m²)</td>
<td>89 ± 8</td>
<td>129 ± 11</td>
<td>240 ± 19</td>
<td>212 ± 16</td>
</tr>
<tr>
<td>LMMI (g/m²)</td>
<td>79 ± 5</td>
<td>171 ± 16</td>
<td>217 ± 19</td>
<td>163 ± 13</td>
</tr>
<tr>
<td>PS (dyn·10⁶/cm²)</td>
<td>115 ± 14</td>
<td>290 ± 30</td>
<td>263 ± 25</td>
<td>196 ± 14</td>
</tr>
<tr>
<td>ES (dyn·10⁶/cm²)</td>
<td>12 ± 2</td>
<td>31 ± 6</td>
<td>35 ± 6</td>
<td>36 ± 6</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05.
† p < 0.02.
‡ p < 0.005.

Abbreviations: HR = heart rate; RVEDP = right ventricular end-diastolic pressure; LVEDP = left ventricular end-diastolic pressure; RVSP = right ventricular peak systolic pressure; LVSP = left ventricular peak systolic pressure; EF = left ventricular systolic ejection fraction; EDVI = left ventricular end-diastolic volume index; LMMI = left ventricular muscle mass index; PS = peak systolic meridional wall stress; ES = end-diastolic meridional wall stress.

### TABLE 3. Normalized Viscoelastic Stress-Strain Data

<table>
<thead>
<tr>
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<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>r</td>
<td>0.95 ± 0.01</td>
<td>0.94 ± 0.02</td>
<td>0.96 ± 0.01</td>
<td>0.91 ± 0.02</td>
</tr>
<tr>
<td>l₁ (cm)</td>
<td>12.5 ± 1.1</td>
<td>18.2 ± 0.8</td>
<td>19.2 ± 1.1</td>
<td>20.0 ± 1.3</td>
</tr>
<tr>
<td>Kₙ</td>
<td>8.8 ± 1.9</td>
<td>13.3 ± 1.9</td>
<td>13.0 ± 2.5</td>
<td>33.8 ± 8.2</td>
</tr>
<tr>
<td>Yₙ (dyn·10⁶/cm²/sec)</td>
<td>0.2 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>2.5 ± 1.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
* p < 0.05.
† p < 0.005.

Abbreviations: l₁ = diastolic reference midwall circumference at a wall stress of 1000 dyn/cm²; Kₙ = normalized viscoelastic constant of myocardial stiffness; Yₙ = normalized viscoelastic constant of myocardial viscosity.
myopathy, but was significantly thicker than in our postmortem control group. The assessment of left ventricular interstitial fibrosis showed similar results in patients with aortic stenosis and aortic insufficiency. However, patients with congestive cardiomyopathy had significantly more interstitial fibrosis than the other two groups or than the postmortem control group, and it was considered to be severe.

### Diastolic Function and Myocardial Structure

The comparison of the diastolic function measurements (reference midwall circumference, normalized viscoelastic constant of myocardial stiffness, normalized viscoelastic constant of myocardial viscosity) with the morphologic measurements (left ventricular muscle mass index [LMMI], average muscle fiber diameter) showed similar results. However, patients with congestive cardiomyopathy had significantly more interstitial fibrosis than the other two groups or than the postmortem control group, and it was considered to be severe.

**Table 4. Morphologic Data**

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<thead>
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<th>Group 4</th>
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<tbody>
<tr>
<td>MFD (µ)</td>
<td>13.7 ± 1.0</td>
<td>26.8 ± 1.7</td>
<td>21.7 ± 0.9</td>
<td>23.6 ± 1.1</td>
</tr>
<tr>
<td>IF (%)</td>
<td>2 ± 1</td>
<td>15 ± 1</td>
<td>11 ± 2</td>
<td>28 ± 4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.

* *p < 0.005.
† *p < 0.02.

Abbreviations: MFD = muscle fiber diameter; IF = interstitial fibrosis; n = number of measurements performed for the assessment of average muscle fiber diameter.

**Figure 5.** Normalized diastolic viscoelastic stress-strain relationship in four selected patients. The slope of the stress-strain relationship in the patients with aortic stenosis (AS) and aortic insufficiency (AI) is slightly increased, but in the patient with congestive cardiomyopathy (COCM) it is clearly increased. The intercept of the normalized stress-strain relationship is by definition constant at 1000 dyn/cm² in all four patients. CO = control patient; $E_n$ = normalized strain; $S - y_n \cdot E_n$ = meridional wall stress ($S$) minus the product of normalized viscoelastic constant of myocardial viscosity ($y_n$) and normalized strain rate ($E_n$).
The diameter [MFD], left ventricular interstitial fibrosis [IF]) showed the following significant correlations: $I_1$ and LMMI ($r = 0.36, p < 0.025$), $K_n$ and IF ($r = 0.59, p < 0.001$), $Y_n$ and IF ($r = 0.43, p < 0.02$). The relationship between myocardial stiffness and left ventricular interstitial fibrosis is shown in figure 7.

**Discussion**

The myocardial structure that determines the diastolic properties of the left ventricle is not known; it has been suggested, however, that an increase in muscle mass during myocardial hypertrophy may alter the elastic properties of the left ventricle. Schwarz and co-workers showed in patients with aortic stenosis that diastolic wall stiffness was increased with an increase in wall thickness. However, the stiffness parameters they used were, for theoretical reasons, not adequate for correctly assessing diastolic myocardial wall stiffness.

The purpose of this study was to evaluate the diastolic myocardial wall stiffness, with special reference to normalized viscoelastic data in patients with myocardial hypertrophy and to determine the effect of muscle mass, muscle fiber size and interstitial fibrosis on myocardial stiffness.

**Diastolic Stress-Strain Data**

Traditionally, the diastolic stress-strain relationship is considered exponential. Recently, it has been demonstrated that the diastolic stress-strain relationship is characterized more adequately by a viscoelastic than a simple elastic relationship with a mon-exponential curve fit. The viscous properties play an important role, particularly during the filling-rate-dependent early diastole, but are negligible at low filling rates during mid- and late diastole. In chronically instrumented dogs it was shown that the viscous properties are both filling-rate-dependent and length-dependent, which means viscous influences are more prominent in larger ventricles at high filling rates. Our clinical data confirm this finding because viscous resistance was small in control patients despite high filling rates, but was high in patients with congestive cardiomyopathy despite low filling rates. Thus, for the correct assessment of left ventricular diastolic properties, the viscous influences have to be considered.

Another problem in the assessment of left ventricular diastolic properties in man is the method of normalization, because non-normalized stress-strain data are preload-dependent and theoretically not valid for interpatient comparisons. Hess et al. proposed strain normalization to a common wall stress of $15 \pm 10$ dyn/cm$^2$; however, this method of normalization was limited because in only about 50% of all patients was a common wall stress found, and normalization was accompanied by a data loss, especially during the particularly filling-rate-dependent early diastole, when viscous influences were most pronounced. Therefore, a
new method of normalization was evaluated by calculating a reference wall circumference at the very low wall stress of 1000 dyn/cm² (0.8 mm Hg). This technique provided adequate data in all patients (fig. 5). Moreover, the diastolic stress-strain equation was simplified by keeping the viscoelastic constant $B_\infty$ (intercept = 1000 dyn/cm² in all patients) constant so that diastolic wall stiffness was determined only by the viscoelastic constant $K_n$. One potential error of the normalization procedure may originate from the extrapolation to reference wall circumference $L_1$. However, the error is generally small because the extrapolated range is small and the correlation coefficient of the diastolic stress-circumference relationship is usually high.

Diastolic myocardial wall stiffness was normal in patients with aortic stenosis and aortic insufficiency despite a considerable increase in muscle mass of 216% and 275%, respectively. Therefore, the increased end-diastolic pressure in these two groups is not the result of increased muscle stiffness, but is needed to distend more muscle with a normal myocardial stiffness. In contrast to these findings, diastolic myocardial wall stiffness is significantly higher in patients with congestive cardiomyopathy, although the increase in muscle mass (206%) is less than in the patients with aortic valve disease. Apparently, a qualitative change of heart muscle tissue must have occurred in patients with congestive cardiomyopathy, and the increase in end-diastolic pressure is the result of both higher muscle mass and increased myocardial stiffness.

Diastolic myocardial viscosity showed no significant differences in the four groups, but was slightly higher in patients with aortic stenosis and aortic insufficiency and clearly more enhanced in patients with congestive cardiomyopathy. Thus, myocardial viscosity appears to be increased parallel to the increase in myocardial wall stiffness.

**Morphologic Data**

Left ventricular morphology and structure are the basic determinants of the diastolic mechanical properties of the left ventricle. Thus, the purpose of the present study was to evaluate quantitatively left ventricular muscle fiber diameter and interstitial fibrosis from left ventricular endomyocardial biopsies in patients with aortic valve disease and interstitial fibrosis. Moreover, the technique provided adequate data in all patients (fig. 5). Moreover, the diastolic stress-strain equation was simplified by keeping the viscoelastic constant $B_\infty$ (intercept = 1000 dyn/cm² in all patients) constant so that diastolic wall stiffness was determined only by the viscoelastic constant $K_n$. One potential error of the normalization procedure may originate from the extrapolation to reference wall circumference $L_1$. However, the error is generally small because the extrapolated range is small and the correlation coefficient of the diastolic stress-circumference relationship is usually high.

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cardial viscosity and interstitial fibrosis ($r = 0.43$). Thus, the diastolic viscoelastic constants of myocardial stiffness and viscosity are elevated, with an increase in interstitial fibrosis. However, mild-to-moderate interstitial fibrosis ($\leq 20\%$) causes only minor changes in diastolic mechanical properties, whereas severe interstitial fibrosis causes significant changes in diastolic myocardial stiffness. The correlation between the diastolic viscoelastic constant of myocardial stiffness and left ventricular mass index was not significant, and despite a considerable increase in muscle mass in the patients with aortic stenosis and aortic insufficiency, the stiffness measurements remained essentially normal. Thus, a simple increase in mass does not necessarily cause an increase in stiffness if myocardial structure does not show an increase in fibrous tissue content. However, in patients with increased mass and normal myocardial stiffness, an enhanced filling pressure is needed to distend the hypertrophied muscle with an increased muscle mass.

Other determinants that might affect diastolic myocardial stiffness and viscosity regardless of the actual amount of interstitial fibers are inertial properties,26 left ventricular relaxation,27 left ventricular cavity shape,28 right ventricular loading conditions,29 pericardial and pleural pressure30 and coronary artery perfusion.31 Inertial components play a certain role during the fast left ventricular filling phase, but seem to contribute little to the left ventricular stress-strain relationship.32 Left ventricular relaxation might influence the diastolic stress-strain relationship during acute myocardial ischemia with a significant increase in relaxation time, but in the absence of coronary artery disease, left ventricular relaxation seems to play a minor role for changes in diastolic stiffness.37 Changes in left ventricular cavity shape consequent to right ventricular pressure overload with thickening of the interventricular septum28 might influence left ventricular filling, but in our four groups the right ventricular end-diastolic and peak systolic pressures did not differ significantly. Pericardial and pleural pressures cannot be measured during cardiac catheterization in man, but no patient had hemodynamic features of pericardial constriction or emphysema. Changes in coronary artery perfusion can alter diastolic wall thickness and might therefore influence diastolic myocardial wall stiffness during acute myocardial ischemia.31 However, none of the 40 patients had signs of acute myocardial ischemia.

We conclude that normalized viscoelastic myocardial stiffness is normal in most patients with aortic stenosis and aortic insufficiency, but is significantly increased in patients with congestive cardiomyopathy. The increase in myocardial stiffness seems not to be the result of an increase in left ventricular muscle mass or muscle fiber size, but due to an increase in left ventricular interstitial fibrosis. These findings suggest that myocardial stiffness in myocardial hypertrophy is related more to the interstitial than to the muscular tissue.

Acknowledgment

The authors express their appreciation to J. Mohacsi and K. Barben for the secretarial help.

References

12. McDonald IG: The shape and movements of the human left ventricle during systole. Am J Cardiol 26: 221, 1970
Effects of Atropine on Diastolic Time

KENNETH A. CONRAD, M.D.

SUMMARY Atropine was given intravenously to 10 normal volunteers in increments of 0.01 mg/kg to a total dose of 0.04 mg/kg. This produced an increase in heart rate from 65 ± 11 to 112 ± 14 beats/min, a decrease in diastolic time from 534 ± 131 to 180 ± 65 msec, and a decrease in percent diastole from 55.6 ± 5.3% to 32.4 ± 7.2% (p < 0.001). Administration of isoproterenol in doses that increased heart rate from 69 ± 9 to 99 ± 12 beats/min produced a decrease in diastolic time from 485 ± 98 to 312 ± 47 msec and only a slight decrease in percent diastole, from 54.2 ± 4.3% to 50.6 ± 3.9%. Atropine, in doses commonly used clinically, may significantly reduce diastolic time and the percent diastole. Because diastolic time is an important determinant of coronary perfusion, administration of atropine to patients with coronary artery disease may increase myocardial ischemia.

DIASTOLIC TIME is an important determinant of subendocardial perfusion and, therefore, of myocardial oxygenation. The effects of various pharmacologic agents on diastolic time and on percent diastole have been described recently. A significant increase in percent diastole occurs after administration of propranolol, dobutamine and cedilanid; isoproterenol significantly reduces percent diastole. Atropine is frequently used in patients who have acute myocardial infarction. This study was conducted because the effects of this drug upon diastolic time have not been assessed. The effects of propranolol and isoproterenol on diastole were also studied to confirm the work of other investigators and to compare the effects of these drugs, particularly isoproterenol, with those of atropine.

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Received January 25, 1980; revision accepted June 26, 1980.
Circulation 63, No. 2, 1981.

Methods

Twenty-one normal subjects, 16 males and five females, ages 22–33 years, were selected for participation in the study. Serial systolic time intervals (STIs) were measured before and after the administration of atropine, propranolol or isoproterenol as outlined below.

Group 1 consisted of five male and five female volunteers who received i.v. atropine in increments of 0.01 mg/kg to a total dose of 0.04 mg/kg. STIs were measured 5 minutes after administration of each dose of atropine.

Group 2 consisted of 11 male volunteers who were given a standard isoproterenol test, consisting of administration of increments of isoproterenol as follows: 0.5, 1, 2, 5, 10, 20, 50, 100 and 200 μg until the heart rate increased by at least 25 beats/min. STIs were measured after each dose of isoproterenol. The volunteers returned for another study no earlier than 2 weeks after the isoproterenol test. At that time, resting STIs were measured and propranolol, 40 mg by mouth four times a day, was given. The next day, the STIs were measured one more time.
Diastolic function and myocardial structure in patients with myocardial hypertrophy.

Special reference to normalized viscoelastic data.

O M Hess, J Schneider, R Koch, C Bamert, J Grimm and H P Krayenbuehl

Circulation. 1981;63:360-371
doi: 10.1161/01.CIR.63.2.360

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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