Diastolic Simple Elastic and Viscoelastic Properties of the Left Ventricle in Man

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SUMMARY We performed simultaneous high-fidelity left ventricular pressure and echocardiographic dimension measurements in 30 patients with normal left ventricular function (group 1; n = 6), moderate-to-severe aortic regurgitation (group 2; n = 14) or congestive cardiomyopathy (group 3; n = 10). We determined diastolic stress, strain and strain rate in all 30 patients and fitted the data to a simple elastic and a viscoelastic stress-strain model.

The inpatient analysis of the simple elastic and viscoelastic stress-strain relationship showed a significantly better curve fitting ($r = 0.93$ vs $0.96$) for the viscoelastic model. The correction by the viscoelastic model occurred mainly during the highly filling-rate dependent early diastole, whereas the correction during atrial filling was low. Early diastolic deviations from the simple elastic stress-strain relationship were especially pronounced in the patients with myocardial hypertrophy. The viscoelastic constants of myocardial stiffness, B and K, were significantly different from the corresponding simple elastic constants, b and k, indicating that the simple elastic stiffness constants include both elastic and viscous forces.

Normalized stress-strain data are mandatory for interpatient comparison. We attempted normalization by using a diastolic circumferential reference length at a common wall stress of 15 dyn x 10$^5$/cm$^2$. However, in 17 of the 30 patients, stress values of 15 dyn x 10$^5$/cm$^2$ were either too high (controls) or too low (congestive cardiomyopathy). Another limiting factor was the loss of data points during early diastole by normalization, which resulted in an underestimation of viscous forces.

The non-normalized and the normalized viscoelastic stress-strain relationships clearly have limitations — the first is preload dependent, the second underestimates viscous forces. However, the viscoelastic constants of myocardial stiffness, K, as assessed by both methods, were increased in patients with congestive cardiomyopathy, but normal in patients with aortic regurgitation. The enhanced diastolic viscoelastic stiffness in cardiomyopathy does not seem to be related to muscle mass, because the angiocardiographically determined left ventricular muscle mass was similar in both groups of patients with myocardial hypertrophy.

FOR MANY YEARS, attempts to quantify the functional state of the left ventricular myocardium have focused on the systolic events of cardiac contraction. Recently, there has been an increasing interest in the assessment of left ventricular diastolic function and the role of altered diastolic function in the deterioration of myocardial contractile function.1, 2

According to the traditional concept, heart muscle behaves as a nonhookean elastic material with an exponential relationship between pressure and volume during the phase of passive left ventricular filling.3,4 However, the true exponential nature of the diastolic pressure-volume and pressure-dimension relationship has been questioned, because in animals5, 7 and in man,8, 9 experimentally determined diastolic pressure-volume relations deviated markedly from an exponential curve. Therefore, it was suggested that the diastolic mechanical properties of the left ventricle should be described by a viscoelastic rather than by a true elastic model.8, 7

We evaluated left ventricular diastolic function with special reference to viscoelastic properties in patients with normal left ventricular function and in patients with aortic insufficiency and congestive cardiomyopathy. Our aim was to distinguish between elastic and viscous properties in patients with myocardial hypertrophy and to determine the influence of viscous elements during passive diastolic filling.

Material and Methods

Patients

Thirty patients (eight females and 22 males) with an average age of 38 years (range 19–68 years) who underwent diagnostic catheterization were included in the study. We divided the patients into three groups.

Group 1 consisted of six control patients with normal left ventricular function. One patient had minimal pulmonic stenosis, one idiopathic dilatation of the ascending aorta and one Leriche syndrome. The other three patients were catheterized because they complained of atypical chest pain; the coronary arteries were normal in all three.

Group 2 consisted of 14 patients with severe aortic regurgitation. Eight of them had a slight aortic stenosis and eight had slight-to-moderate mitral insufficiency.

Group 3 consisted of 10 patients with congestive cardiomyopathy; four had slight-to-moderate mitral insufficiency.

Cardiac Catheterization

We performed right- and left-heart catheterization in all 30 patients after they gave informed consent. Premedication consisted of 10 mg Librium (chlordiazepoxide hydrochloride) given orally 1 hour before
the procedure. We performed standard pressure measurements using fluid-filled catheters and recorded the results on an oscillograph (Electronics for Medicine DR/16). We assessed aortic and mitral regurgitation quantitatively by thermodilution techniques.\textsuperscript{10} When the diagnostic catheterization was completed, we introduced a Millar 7F micromanometer into the left ventricle through a 11.5F Brockenbrough catheter which had been advanced to the left ventricle by the transseptal route.\textsuperscript{11} We calibrated the micromanometer by superposing the micromanometer tracing on the conventional pressure tracing. Before insertion, the manometer was balanced and zeroed at 37°C. The frequency response of the recording system including the tiptransducer and the DC amplifier was flat to 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.

We performed the left ventricular pressure measurements simultaneously with the left ventricular echocardiogram at a paper speed of 100 mm/sec. We obtained the echocardiograms (single-beam method; Ekoline 20A, Smith-Kline Instruments) with the patient in the anteroposterior or slight right anterior decubitus position. The recordings were made with a 2.25 MHz, 3/8-inch diameter transducer which transmitted 1-\textmu sec ultrasound pulses at a rate of 1000/sec. We used the gain, damping and reject controls to obtain the best possible M-mode display of the interventricular septum and the left ventricular posterior wall just below the mitral valve. For the quantitative evaluation, we assessed the echocardiographic left ventricular endocardial diameter from the septum to the posterior wall and the left ventricular pressure every 20 msec during one heart cycle (fig. 1). We determined wall thickness at end-diastole, which corresponded to the end of the "a" wave of the left ventricular pressure tracing or to a point 20 msec before the peak of the R wave on the ECG. 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.\textsuperscript{12, 13} Moreover, the measured echocardiographic diameter does not necessarily correspond to the true minor axis\textsuperscript{14} of the ventricular ellipsoid, especially in enlarged left ventricles. The error of not measuring the same topographic diameter during the heart cycle appears to be small, because our measurements were started at the end of active relaxation, when the systolic tilting movement of the heart was practically completed.\textsuperscript{15} We excluded eight of 38 patients (22%) because of unsatisfactory echocardiograms.

The cardiac cycle from which our measurements were made was selected from all cycles of one respiratory cycle. 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 cycle. We considered this heart cycle to be the most representative one because it generally occurred midway between the extremes of inspiration and expiration.

We performed left ventricular cineangiography with the patient in the right anterior oblique (RAO) position, according to our standard technique.\textsuperscript{16} We quantitatively analyzed the left ventricular cineangiograms according to the area-length method.\textsuperscript{17} We calculated end-diastolic and end-systolic volumes of the left ventricle in each patient and derived left ventricular ejection fraction as the angiographic stroke volume divided by the end-diastolic volume × 100. We determined end-diastolic wall thickness from the RAO silhouette of the left ventricle in nine cases and from a second contrast dye injection in the anteroposterior projection in 21 cases. The end-diastolic wall thickness determined by cineangiography was slightly but not significantly higher (0.05 ± 0.2 cm) than the end-diastolic wall thickness measured by echocardiography.

After completing ventriculography, we performed selective coronary arteriography in three patients in group 1 and in all patients in groups 2 and 3. All coronary arteriograms were normal.

**Calculations**

Every 20 msec throughout diastole, starting at the lowest diastolic pressure (≥3 mm Hg) up to the end-diastolic pressure, we calculated wall thickness, meridional wall stress, midwall minor axis circumference, midwall strain, internal left ventricular diameter lengthening rate and midwall strain rate in each patient.

For calculating instantaneous wall thickness, we assumed that the cross-sectional area of the myocardial wall, determined at end-diastole from the echocardiographic measurement of the internal left ventricular diameter and the wall thickness, was constant. However, this assumption is not entirely valid because it assumes no motion in the long-axis dimension. Since long-axis deformation is in fact small,\textsuperscript{18} the resultant error is not great. We did not measure wall thickness directly from the echocardiogram throughout diastole because the thickness changes at 20-msec intervals were below the axial resolution of the echo technique. Therefore, we calculated instantaneous wall thickness (h) as

\[
h = -\frac{D}{2} + \sqrt{\frac{D^2}{4} + \frac{A_c}{\pi}},
\]

where D is the internal left ventricular diameter and \( A_c \) the end-diastolic cross-sectional wall area.

\[
A_c = \pi \cdot (h_{ed}^2 + h_{ed} \cdot D_{ed}),
\]

where \( h_{ed} \) is the end-diastolic wall thickness and \( D_{ed} \) the end-diastolic internal left ventricular diameter.

We calculated the diastolic meridional wall stress
LEFT VENTRICULAR PRESSURE-DIMENSION RELATIONSHIP

![Graph showing left ventricular pressure-dimension relationship](image)

We evaluated left ventricular diastolic function by the logarithmic pressure and linear dimension relationship, starting at the lowest diastolic pressure and ending at the end-diastolic pressure. PCG = phonocardiogram, AoP = aortic pressure; LVP = left ventricular pressure; dP/dt = first derivative of the left ventricular pressure; dP/dt/P = first derivative of the left ventricular pressure divided by total pressure; IVS = interventricular septum; ECG = electrocardiogram; PW = posterior wall; D = left ventricular minor axis diameter.

(S) acting at the circumference of the left ventricular minor axis from the equation:

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

where \( P \) equals the actual diastolic pressure.

We calculated the midwall minor axis circumference (l) from the equation:

\[ l = \pi \cdot (D + h) \]

Using the Lagrangian strain definition, we obtained the midwall strain (E) by the equation:

\[ E = \frac{1 - L_o}{L_o} \]

where \( L_o \) is the diastolic midwall circumference measured at the lowest diastolic pressure. This is not the true \( L_o \) at a transmural pressure of 0 mm Hg which would be the best reference length to use. However, it is not possible to obtain the true \( L_o \) in man at catheterization. The intrapatient comparison of simple elastic and viscoelastic stress-strain relationships is not invalidated by the use of \( L_o \). For the interpatient comparison, however, we calculated a diastolic midwall circumference at a constant stress of 15 dyn \( \times \) \( 10^5 \)/cm² (normalized midwall axis circumference) and obtained a normalized strain (\( E_n \)).

\[ E_n = \frac{1 - L_{15}}{L_{15}} \]

where \( L_{15} \) is the preloaded midwall axis circumference at a stress of 15 dyn \( \times \) \( 10^5 \)/cm².

The strain rate (\( \dot{E} \)) was obtained as:

\[ \dot{E} = \frac{dE}{dt} \]
where \( dE \) is the instantaneous difference of strain and 
\( dt \) the instantaneous difference of time; i.e., \( \dot{E} \) equals 
the first derivative of strain.

We obtained the normalized strain rate \( (\dot{E}_n) \) from 
the equation:

\[
\dot{E}_n = \frac{dE_n}{dt}.
\]

An example of all calculated parameters is given in 
figure 2.

Curve Fitting

We evaluated two different models of mechanical 
properties of the diastolic heart muscle: first, a simple 
elastic stress-strain relationship, and second, a 
viscoelastic stress-strain relationship incorporating a 
parallel viscous element. We used both models 
to assess left ventricular diastolic properties. Rankin 
and co-workers\(^7\) determined left ventricular diastolic func-
tion experimentally in chronically instrumented 
dogs by using these two models. In all of our 30 
patients, the stress-strain data were fitted to an equation for a 
simple elastic model:

\[
S = b \cdot e^k \cdot E
\]

and for a viscoelastic model:

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

where \( b \) and \( k \) are the simple elastic constants of 
myocardial stiffness, \( B \) and \( K \) the viscoelastic con-
stants of myocardial stiffness, and \( y \) is the viscoelastic 
constant of myocardial viscosity.

We fitted the stress-strain data to a linear regression 
function, \( y = a \cdot x + b \). The semilogarithmic linear 
equation of the simple elastic model was \( \ln S = k \cdot E + \ln b \), and the corresponding linear equation of the 
viscoelastic model \( \ln (S - y \cdot \dot{E}) = K \cdot E + \ln B \).

We determined the semilogarithmic linear regres-
sion formula of the viscoelastic model by inserting 
assumed values of \( y \) into the equation and varying 
them from 0.01-15.0 until we obtained the best 
curve fit, i.e., the highest possible correlation coefficient. 
A sample calculation is given in table 1.

Statistics

We made the statistical comparison of the simple 
estastic and the viscoelastic relationship (intrapatient 
comparison) using the Wilcoxon signed rank sum test.

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**Figure 2.** Calculated diastolic parameters in a patient with severe aortic regurgitation. The non-
normalized data are given on the left, the normalized data on the right. We normalized data using a 
reference midwall circumferential length at a constant stress of 15 dyn \( \times \) \( 10^6 \) cm\(^2\). The first point of the non-
normalized data represents the data at the lowest diastolic pressure, the last point, the data at the end-
diastolic pressure. The normalized data start at a diastolic stress of 15 dyn \( \times \) \( 10^6 \) cm\(^2\) (dashed lines).
TABLE 1. Sample Calculation for the Evaluation of the Viscoelastic Stress-Strain Relationship

<table>
<thead>
<tr>
<th>k</th>
<th>b</th>
<th>r</th>
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<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Simple elastic relationship

0.09 9.75 — 0.90

K B y r

Viscoelastic relationship

8.7 7.61 15.0 0.53
8.0 10.91 10.0 0.66
7.8 11.00 7.0 0.79
7.4 11.47 5.0 0.84
7.3 12.06 3.0 0.88
7.3 12.30 2.0 0.89
7.2 12.55 1.0 0.90
7.2 12.81 0.5 0.91
→ 7.2 12.85 0.1 0.93 ←
6.1 16.12 0.01 0.86

Sample calculation for the evaluation of the viscoelastic stress-strain relationship. The stress and strain data are fitted to the linear regression function \(\ln (S-y-E) = K\cdot E + \ln B\). We varied one (y) of the three constants (K, B, y) from 0.01-15.00 until we obtained the best curve fit, i.e., the highest possible correlation coefficient r. The best curve fit is indicated by arrows.

Abbreviations: S = diastolic stress; E = diastolic strain; \(\dot{E}\) = diastolic strain rate; y = viscoelastic constant of myocardial viscosity; K, B, y = viscoelastic constants of myocardial stiffness; k, b = simple elastic constants of myocardial stiffness; ln = natural logarithm.

For the interpatient comparison, we used the Wilcoxon rank sum test.

Results

Hemodynamics

The aortic regurgitation fraction in group 2 averaged 61% (range 30–83%). In addition to the aortic regurgitation, eight patients of group 2 had a mitral regurgitation (average 13%; range 5–52%). Four patients in group 3 had slight-to-moderate mitral insufficiency (average 32%; range 17–50%). In eight patients of group 2 with an additional aortic stenosis, the mean systolic pressure gradient across the aortic valve was 32 mm Hg (range 14–56 mm Hg). The hemodynamic data for all three groups are listed in Table 2. Heart rate and right ventricular end-diastolic pressure were not significantly different in the three groups. Left ventricular end-diastolic pressure was increased to 19 mm Hg in group 2 and to 23 mm Hg in group 3.

The assessment of the left ventricular angiographic parameters showed a slightly decreased ejection fraction in group 2 (60%) and a significantly \((p < 0.005)\) decreased ejection fraction in group 3 (35%). Left ventricular end-diastolic volume was significantly increased in group 2\((p < 0.001)\) and group 3\((p < 0.02)\). Left ventricular muscle mass was significantly enhanced in group 2\((160 g/m^2; p < 0.005)\) and in group 3\((137 g/m^2; p < 0.025)\). The volume/mass ratio was slightly but not significantly increased in groups 2 and 3 compared with group 1.

Diastolic Properties

Simple Elastic Relationship

We found a linear simple elastic stress-strain relationship, defined by a correlation coefficient between diastolic stress and strain \(\geq 0.90\), in 22 patients. All six control patients, 11 patients with aortic regurgitations and five patients with congestive cardiomyopathy had a linear simple elastic relationship.

However, in group 2 there was a nonlinear, biphasic relationship \((r = 0.86–0.89)\) in three patients with a flat portion during early and a steep portion during late diastole. In group 3, we found a biphasic relationship \((r = 0.68–0.89)\) in five patients.

TABLE 2. Hemodynamic Findings in Control Patients (Group 1), Patients with Aortic Regurgitation (Group 2) and Congestive Cardiomyopathy (Group 3)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 6)</th>
<th>Group 2 (n = 14)</th>
<th>Group 3 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>70 ± 10</td>
<td>78 ± 12</td>
<td>82 ± 16</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>7 ± 2</td>
<td>8 ± 4</td>
<td>9 ± 4</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>13 ± 2</td>
<td>19 ± 10</td>
<td>*</td>
</tr>
<tr>
<td>EF (%)</td>
<td>*</td>
<td>*</td>
<td>23 ± 10</td>
</tr>
<tr>
<td>EF (%)</td>
<td>70 ± 5</td>
<td>60 ± 10</td>
<td>35 ± 20</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>87 ± 26</td>
<td>190 ± 47</td>
<td>182 ± 64</td>
</tr>
<tr>
<td>LMMI (g/m²)</td>
<td>92 ± 33</td>
<td>160 ± 33</td>
<td>137 ± 35</td>
</tr>
</tbody>
</table>

Values are mean ± sd.

*\(p < 0.05\).

†\(p < 0.025\).

‡\(p < 0.001\).

Abbreviations: HR = heart rate; RVEDP = right ventricular end-diastolic pressure; LVEDP = left ventricular end-diastolic pressure; EF = left ventricular systolic ejection fraction; EDVI = left ventricular end-diastolic volume index; LMMI = left ventricular muscle mass index.
Viscoelastic Relationship

A linear viscoelastic stress-strain relationship was present in 26 patients. All six control patients, 13 patients with aortic regurgitation and seven patients with congestive cardiomyopathy had a linear viscoelastic relationship. However, despite correction for the dynamic viscous influences, we found a non-linear, biphasic relationship in one patient with aortic regurgitation (r = 0.88) and three patients with congestive cardiomyopathy (r = 0.75-0.89). The stiffness and viscosity constants of the three groups are listed in Table 3.

Simple Elastic vs Viscoelastic Properties

The intrapatient comparison of the simple elastic and viscoelastic stress-strain relationships showed significantly higher correlation coefficients for the viscoelastic than for the simple elastic relationship (r = 0.96 and 0.93, respectively). Figure 3, from a patient with aortic regurgitation, shows that the diastolic stress-strain relationship is strengthened after correction for the viscous influences and that the correlation coefficient is increased from 0.96 to 0.99. Correction occurred mainly during early diastolic filling; the viscous influences during atrial filling were small. This is also evident from Figure 2, which shows a high strain rate during early diastole and a low strain rate during late diastole. The early diastolic deviation from the simple elastic stress-strain relationship was especially pronounced in the patients with myocardial hypertrophy (groups 2 and 3).

In all 30 patients, the viscoelastic constant of myocardial stiffness, K, was significantly (p < 0.005) higher than the simple elastic constant, k, and the viscoelastic constant, B, was significantly (p < 0.001) smaller than the simple elastic constant, b (Table 4).

Normalized Simple Elastic Relationship

We obtained normalized data in only one control patient because the diastolic stress values in the other five control patients were lower than the stress of 15 dyn x 10^5/cm^2, which was chosen for normalization. We obtained normalized data in nine patients with aortic regurgitation and found a linear normalized simple elastic stress-strain relationship in eight of them. We did not evaluate five patients because the diastolic stress values were lower than 15 dyn x 10^5/cm^2 in four and higher in one. We obtained normalized data in only three patients with congestive cardiomyopathy and found a linear normalized simple elastic stress-strain relationship (r > 0.90) in one of them. We did not evaluate seven patients because the diastolic stress values were higher than 15 dyn x 10^5/cm^2 in five and lower in two. Normalization to a constant wall stress of 15 dyn x 10^5/cm^2 caused a loss of data points during early diastole. Patients in whom less than five data points remained were excluded from normalization.

Normalized Viscoelastic Relationship

We obtained normalized data in one control patient, nine patients with aortic regurgitation and three patients with congestive cardiomyopathy. We found a linear normalized viscoelastic stress-strain relationship in the control patient, in eight patients with aortic regurgitation and in one patient with congestive cardiomyopathy. No patient had a substantial improvement of the correlation coefficient after correction for the viscous influences. The diastolic viscoelastic stiffness constants of the three evaluated groups are listed in Table 3. We made no statistical comparisons between the three groups because the number of patients in groups 1 and 3 was too small.

Non-normalized vs Normalized Data

The intrapatient comparison of the non-normalized and the normalized stress-strain data in 13 patients (Table 5) showed no significant difference for the simple elastic relationship. The viscoelastic stress-strain relationship, however, showed a significantly higher constant of myocardial stiffness, B, and a significantly lower constant of myocardial viscosity, y, for normalized compared with the non-normalized data. This is probably because normalization is accompanied by a loss of data points during early diastole, which is particularly rate dependent.

Discussion

Until recently, it was generally accepted that an exponential relationship exists between left ventricular diastolic stress and strain. However, several authors have suggested that deviations from the exponential

| TABLE 3. Non-normalized and Normalized Viscoelastic Stress-Strain Data |
|--------------------------|--------------------------|--------------------------|
|                         | Non-normalized data      | Normalized data          |
|                         | Group 1 (n = 6)          | Group 2 (n = 14)         | Group 3 (n = 10)         |
| B                       | 2.89                     | 2.86                     | 11.64                    |
| K                       | 11.8                     | 16.4                     | 30.6                     |
| y                       | 0.67                     | *                        | 3.16                     | 3.50                     |
|                         | Group 1 (n = 1)          | Group 2 (n = 9)          | Group 3 (n = 3)          |
| B                       | 13.61                    | 12.09                    | 13.74                    |
| K                       | 9.7                      | 12.1                     | 30.0                     |
| y                       | 0.10                     | 0.45                     | 0.45                     |

*p < 0.05.

The non-normalized data show significantly increased constants of myocardial stiffness (K, B) in group 3, whereas myocardial stiffness is normal in patients with aortic regurgitation. Myocardial viscosity (y) is significantly higher in patients with aortic regurgitation than in control patients and is increased, although not significantly, in patients with congestive cardiomyopathy. Normalized stress-strain data were available in only 13 of the 30 evaluated patients, because the common wall stress used for normalization in the others was either too high (controls) or too low (patients with congestive cardiomyopathy). Therefore, statistical evaluation of the normalized data was not possible.
relationship may occur and that parallel viscous properties are important determinants of left ventricular diastolic mechanics.9-9 Rankin and co-workers9 demonstrated in chronically instrumented dogs that left ventricular diastolic stress during early diastole and atrial filling was higher than would have been predicted by a simple elastic model, and that dynamic influences are responsible for the deviations from the real elastic relationship. Therefore, the present study sought to determine left ventricular diastolic properties by a simple elastic and a viscoelastic stress-strain relationship in 30 patients with normal or enlarged and hypertrophied left ventricles.

Intrapatent Comparison

The intrapatent comparison of the simple elastic and the viscoelastic stress-strain relationship showed that the diastolic stress and strain data fitted better to the viscoelastic than to the simple elastic regression formula, and the correlation coefficients for the viscoelastic model were significantly higher than for the simple elastic model. This finding confirms that viscous properties are important determinants of left ventricular diastolic function, and that diastolic filling characteristics are determined by both elastic and viscous elements.

The diastolic stress-strain relationships were mainly improved by correction of the viscous influences during early diastole, which is particularly filling-rate dependent; the correction during atrial filling was a minor contribution to the improvement of the simple elastic stress-strain relationship because diastolic filling rate during atrial systole was generally low.

The diastolic constants of myocardial stiffness were significantly different for the simple elastic (k and b) and the viscoelastic (K and B) stress-strain relationship (table 4). The simple elastic constant, k, was significantly lower and the simple elastic constant, b, significantly higher than the corresponding viscoelastic constants, K and B. This difference between the simple elastic and the viscoelastic constant of myocardial stiffness was small in the control patients (table 4), but significant in patients with myocardial hypertrophy (groups 2 and 3). Therefore, it is important for the assessment of diastolic myocardial stiffness to evaluate the viscous influences during filling, because the simple elastic constants reflect a composite of elastic and viscous forces and may be misleading, especially in patients with myocardial hypertrophy.

Interpatent Comparison

For the interpatent comparison, normalized diastolic stress-strain data are needed because

Figure 3. Left ventricular diastolic stress-strain relationship in a patient with severe aortic regurgitation (same patient as in figure 2). The simple elastic relationship on the left side shows appreciable deviation during early diastolic filling from the monoexponential diastolic stress-strain relationship (circles are non-normalized data; triangles are normalized data). After correction for the viscous influences, the viscoelastic stress-strain relationship is more linear and the correlation coefficient for the regression equation increases from 0.96 to 0.99 and from 0.90 to 0.93, respectively. S = left ventricular diastolic stress; E = left ventricular diastolic strain; S = (y \cdot \dot{E}) = left ventricular diastolic stress minus the product of myocardial viscous constant (y) and diastolic strain rate (E).
diastolic strain is dependent on the diastolic reference midwall minor-axis circumference, i.e., on the preloaded reference muscle length. Therefore, we calculated a diastolic midwall minor-axis circumference at a common wall stress of 15 dyn x 10^3/cm^2 and used this reference length to calculate diastolic strain data. However, stress values of 15 dyn x 10^3/cm^2 were generally too high in control patients and too low in patients with congestive cardiomyopathy. Thus, normalized stress-strain data could be obtained only in 13 of the 30 evaluated patients (43%), i.e., one control patient, nine patients with aortic regurgitation and three patients with congestive cardiomyopathy.

Another limiting factor was that normalization in most patients with a common reference wall stress of 15 dyn x 10^3/cm^2 was accompanied by a loss of data points during the highly filling-rate dependent early diastole, when diastolic viscous influences were most pronounced. The normalized viscoelastic stress-strain data showed significantly higher values for the diastolic constant of myocardial stiffness, B, and lower values for the diastolic constant of myocardial viscosity, y (table 5), than for the non-normalized viscoelastic stress-strain data. However, the stiffness constants, K, were not significantly different.

For the interpatient comparison, normalized stress-strain data are theoretically needed, but a common diastolic reference wall stress is obtained only in a minority of patients. Moreover, in some patients with a common diastolic reference wall stress, normalization leads to an underestimation of diastolic viscous properties due to the loss of data points during early diastolic filling.

### Clinical Implications

For the interpatient comparison, normalized viscoelastic stress-strain data are preferable. However, normalization to a reference length at a transmural pressure of 0 mm Hg is not possible in man at catheterization and normalization to a common stress of 15 dyn x 10^3/cm^2 is complicated by other methodological problems (vide supra); thus, the use of normalized data for the interpatient comparison has limitations. Non-normalized data are theoretically not valid for interpatient comparisons because the diastolic stress-strain data are preload dependent.

Therefore, both methods have limitations, but the results are similar. The non-normalized data (table 3) showed an increased myocardial stiffness constant, K, in patients with congestive cardiomyopathy, whereas K was normal in patients with aortic regurgitation. However, the extent of myocardial hypertrophy, as evaluated by angiocardiology, was similar or even smaller in patients with congestive cardiomyopathy (137 g/m^2) than in patients with aortic regurgitation (160 g/m^2) (table 2). The interpatient comparison by normalized stress-strain data showed that in two patients with congestive cardiomyopathy the constants of myocardial stiffness, K, were higher than in the control patient or the patients with aortic

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**Table 4. Simple Elastic vs Viscoelastic Parameters (Intra-patient Comparison)**

<table>
<thead>
<tr>
<th>Simple elastic relationship</th>
<th>Viscoelastic relationship</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>r</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>k</td>
<td>K</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>b</td>
<td>B</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single groups</td>
<td></td>
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<tr>
<td>Group 1 (Controls)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>r</td>
<td>NS</td>
</tr>
<tr>
<td>k</td>
<td>K</td>
<td>NS</td>
</tr>
<tr>
<td>b</td>
<td>B</td>
<td>NS</td>
</tr>
<tr>
<td>Group 2 (Aortic regurgitation)</td>
<td></td>
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<tr>
<td>r</td>
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<tr>
<td>k</td>
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<tr>
<td>b</td>
<td>B</td>
<td>&lt;0.01</td>
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<tr>
<td>Group 3 (Congestive cardiomyopathy)</td>
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<tr>
<td>r</td>
<td>r</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>k</td>
<td>K</td>
<td>NS</td>
</tr>
<tr>
<td>b</td>
<td>B</td>
<td>NS</td>
</tr>
</tbody>
</table>

For all patients there is a significant difference between the simple elastic and the viscoelastic parameters; in the control group there was no significant difference, but in groups 2 and 3 the correlation coefficients were significantly different between the simple elastic and the viscoelastic relationship, as were the stiffness constants in group 2.

Abbreviations: r = correlation coefficient for the semilogarithmic linear regression equation; k, b = simple elastic constants of myocardial stiffness; K, B = viscoelastic constants of myocardial stiffness.

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**Table 5. Non-Normalized vs Normalized Stress-Strain Data (Intrapatient Comparison)**

<table>
<thead>
<tr>
<th>Simple elastic relationship</th>
<th>Normalized data</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-normalized</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.93</td>
<td>NS</td>
</tr>
<tr>
<td>k</td>
<td>10.1</td>
<td>NS</td>
</tr>
<tr>
<td>b</td>
<td>9.15</td>
<td>NS</td>
</tr>
<tr>
<td>Viscoelastic relationship</td>
<td></td>
<td></td>
</tr>
<tr>
<td>r</td>
<td>0.97</td>
<td>NS</td>
</tr>
<tr>
<td>K</td>
<td>20.8</td>
<td>NS</td>
</tr>
<tr>
<td>B</td>
<td>5.89</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>y</td>
<td>3.37</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

The simple elastic non-normalized and normalized data are not significantly different; however, the viscoelastic normalized stress-strain data show significantly higher B (viscoelastic constant of myocardial stiffness) and significantly lower y (viscoelastic constant of myocardial viscosity) values than the non-normalized stress-strain data. The correlation coefficients (r) and the viscoelastic constant of myocardial stiffness, K, are similar with both methods.

Abbreviation: k = simple elastic constants of myocardial stiffness.
regurgitation (fig. 4). When we used normalized data to evaluate the three patients with congestive cardiomyopathy and the nine patients with aortic regurgitation, the extent of myocardial hypertrophy was similar, 169 g/m² vs 172 g/m², respectively. It is likely, therefore that the increased slope of the viscoelastic stress-strain relationship in patients with congestive cardiomyopathy, regardless of whether normalized or non-normalized data were used, is due to structural changes, probably consisting of an increased admixture of fibrous tissue. In contrast, stiffness constants are normal in patients with aortic regurgitation despite considerable myocardial hypertrophy. Myocardial viscosity evaluated by non-normalized stress-strain data is increased in patients with congestive cardiomyopathy and aortic regurgitation. Viscous forces seem to be enhanced in patients with myocardial hypertrophy, whether or not structural changes — in contrast to elastic forces — are present.

Other determinants of left ventricular diastolic function include inertial properties, left ventricular relaxation, left ventricular cavity shape and extrinsic influences such as right ventricular loading conditions, pericardial and pleural pressure, and coronary artery perfusion. Inertial components and left ventricular relaxation seem to contribute little to diastolic stiffness; changes in left ventricular cavity shape consequent to chronic elevation of filling pressure and dilatation of the right ventricle can, however, lead to definite alterations of left ventricular diastolic filling. The right ventricular end-diastolic pressure was not significantly different in our three groups and does not seem to be responsible for the deviations from the exponential diastolic stress-strain relationship. Whether pleural pressure was comparable in our patients cannot be ascertained, but no patient had emphysema. Pericardial restriction during the late phase of diastolic filling was suggested in two patients with congestive cardiomyopathy who had marked late diastolic deviations from the linear viscoelastic stress-strain relationship. Both patients had a severe distension of the left ventricle (end-diastolic volume index 187 and 225 ml/m²; upper limit of the normal range 121 ml/m²) due to advanced congestive cardiomyopathy. Changes in coronary artery perfusion may alter diastolic properties in patients with acute myocardial ischemia. However, all patients in groups 2 and 3 had normal coronary arteries and there were no signs of acute myocardial ischemia.

In summary, viscous properties are important determinants of left ventricular diastolic function, especially in patients with myocardial hypertrophy. Normalization of strain to a reference circumferential

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**Figure 4.** Normalized (N) and non-normalized (NN) stress-strain data in patients with normal left ventricular function, aortic regurgitation or congestive cardiomyopathy. Normalized stress-strain data were available in 13 patients; the lines connecting the non-normalized and the normalized data indicate the 13 patients for whom both data are present. The normalized viscoelastic constant, B, of myocardial stiffness is somewhat higher than the non-normalized constant. In contrast, the viscoelastic constant, K, shows similar values for the normalized and the non-normalized data. Two of the three patients with congestive cardiomyopathy have increased K values by both methods. The viscoelastic constant, y, of myocardial viscosity shows, however, a considerable difference between the normalized and the non-normalized data, because normalization is accompanied by a loss of data points during the highly filling-rate dependent early diastole, when viscous forces are most pronounced.
wall length at a constant wall stress of 15 dyn \times 10^3/cm^2 permits interpatient comparison for the assessment of myocardial wall stiffness in patients with different heart diseases. At similarly elevated muscle mass, myocardial stiffness seems to be higher in patients with congestive cardiomyopathy than in patients with aortic regurgitation.

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