Diastolic properties of the left ventricle in normal adults and in patients with third heart sounds

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ABSTRACT To explore the pathogenesis of the third heart sound (S₃), left ventricular hemodynamics in early diastole were studied during catheterization in normal adults without S₃s (group I, n = 12) and in cardiac patients with S₃s as the result of severe mitral regurgitation (group II, n = 11), dilated cardiomyopathy (group III, n = 24) or restricted left ventricular filling (group IV, n = 4). The height and steepness of the rise in left ventricular pressure after minimum diastolic pressure (the so-called rapid filling wave), maximum dV/dt, and the time constant of fall in isovolumetric pressure were measured. The completeness of relaxation was evaluated from the number of time constants elapsed at the time of minimum diastolic pressure. Pressure-volume data were fitted to simple elastic and viscoelastic models incorporating inflow rate into the equation. In all patients with S₃ a significantly higher and steeper rapid filling wave was found than in normal adults. Maximum dV/dt was significantly greater in group II (1084.9 ± 416 ml/sec; mean ± SD) than in the other groups (463.9 ± 177.1 ml/sec in group I, 448.8 ± 134.0 ml/sec in group III, and 709.9 ± 226.8 ml/sec in group IV). No significant differences in left ventricular chamber elastic properties in the different groups were found. However, intrapatient comparisons of the results of the use of elastic and viscoelastic equations revealed a significantly better curve fit (r = .930 vs .968, p < .005) and a much higher viscous constant for group III. Similar results were found in group IV. In patients with S₃ left ventricular relaxation was slower (time constant of 37.4 ± 3.7 msec in group I, 43.2 ± 10.0 msec in group II, 56.8 ± 15.4 msec in group III, and 41.8 ± 13.7 msec in group IV) and more incomplete (number of time constants elapsed at minimum diastolic pressure 3.08 ± 0.23 in group I, 2.58 ± 0.56 in group II, 2.15 ± 0.68 in group III, and 2.49 ± 1.12 in group IV) than in normal adults. In conclusion, the presence of an S₃ was associated with a higher and steeper rapid filling wave on the left ventricular pressure tracing. The increased rapid filling wave could be attributed mainly to an increased filling rate in patients with volume overload (group II) and to impaired relaxation or increased viscous resistance to filling in patients with myocardial dysfunction (groups III and IV). This increased rapid filling wave may play an important role in the pathogenesis of the S₃ since it causes more rapid deceleration of inflow and since the vibrations of the S₁ occur during this phase of left ventricular filling.


THE THIRD HEART SOUND (S₃) is an early diastolic low-frequency sound that may be present under different hemodynamic conditions. Over the years various theories have been advanced regarding the pathogenesis of the S₃, but so far none of the proposed mechanisms have been able to explain all the clinical aspects of this phenomenon. Although most of the theories attribute the S₃ to the termination of rapid filling by the left ventricular wall, the fundamental mechanism of this process, in terms of changes in relaxation rate, filling rate, diastolic pressures, and mechanical properties of the left ventricle, remain unknown. In this study left ventricular diastolic hemodynamics were studied in cardiac patients with S₃s and in normal adults without them.

Methods

Patients. Fifty-one patients (17 women and 34 men) were selected from a large population sample scheduled for diagnostic cardiac catheterization. Twelve patients (group I) with a mean age of 46.7 ± 4.3 (± SD) years were considered to have normal left ventricular function. Eight of them had no coronary lesions and four had insignificant coronary stenosis. These patients had no S₃s and served as control subjects.

Thirty-nine patients had cardiac diseases associated with definite S₃s. In all patients studied, the presence or absence of

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the S₃ was confirmed by a complete phonocardiographic examination (including recordings from the apical region in left recumbent lateral position). Eleven of these 39 patients with S₃ (mean age 45.2 ± 15.4 years) had severe mitral valve regurgitation with well-preserved left ventricular function and they comprised group II. Mitral stenosis was absent and the degree of regurgitation, estimated from the left ventricular angiogram, was severe in all patients (grade 3 or 4 on a scale of 0 to 4: the left atrium as intensely or more densely opacified than the left ventricle or aorta with slow clearing of contrast medium). Group III consisted of 24 patients (mean age 47.3 ± 14.5 years) with dilated cardiomyopathy. The cause of the left ventricular dilatation was either unknown (10 patients) or due to coronary disease (14 patients). In patients with ischemic cardiomyopathy significant coronary lesions had already caused one or more myocardial infarctions. In the latter small regional differences in wall motion were present, but patients with left ventricular aneurysms were excluded. Group IV consisted of four patients (mean age 54.3 ± 10.4 years) with restricted left ventricular filling due to either constrictive peri(epi)carditis with pericardial calcifications (three patients) or restrictive cardiomyopathy of unknown cause (one patient). In all four patients the typical dip-and-plateau filling pattern in the left ventricular diastolic pressure tracing and nearly normal left ventricular systolic function was observed.

With the exception of one patient who had a transient episode of atrial flutter (see below), all patients were in normal sinus rhythm during the experimental procedures.

When possible and depending on the clinical state, therapy with cardioactive medication was interrupted 3 days before the catheterization. In two patients in group II and five in group III the administration of vasodilators (nitrates, hyalurazine, and captopril) or antiarrhythmic drugs (quinidine, aprindine) was continued until 12 to 18 hr before catheterization to prevent deterioration of left ventricular function or to maintain sinus rhythm. Informed consent was obtained before catheterization and no complications attributable to the procedure were encountered.

Catheterization procedure. In 32 patients simultaneous pressure-volume measurements were obtained. This group included 11 patients from group I, six from group II, 13 from group III (nine with ischemic and four with idiopathic dilated cardiomyopathy), and two from group IV (one with constrictive pericarditis and one with restrictive myopathy). In these patients a dual catheter system was used according to the method of Ludbrook et al. to obtain both high-fidelity pressures and high-quality left ventricular angiograms. In the other 19 patients simultaneous insertion of pressure and angiographic catheters could not be done for various reasons. In these patients left ventricular angiography was performed after the pressure recording was obtained.

A No. 7 or No. 8F micromanometer with a fluid-filled side lumen (Gaeltec) was used and introduced via the left brachial artery. The micromanometer signal was split up for pressure, dP/dt, and internal phonoregistration. The external phonocardiogram was recorded by means of an acceleration-type microphone (Siemens) attached to the chest between the apical region and the left intercostal place. Mannheimer filters with nominal frequencies of 25 and 50 Hz were used for external and internal phonoregistrations.

Simultaneous recordings of the electrocardiogram, left ventricular pressures (micromanometer and fluid-filled system), dP/dt, and internal and external phonoregistrations were made on an 8-channel ink-jet recorder (Elema 82) and on magnetic tape (Honeywell 101). After pressure-phonoregistration recordings, an angiographic catheter (No. 8F pigtail) was introduced via the right brachial artery. Single-plane left ventricular angiography was then performed with the patient in the 30 degree right oblique position and during held submaximum inspiration. A cine frame pulse provided an electrical signal at the time of each frame exposure. Film was exposed at 90 frames/sec. During angiography pressures and phonorecording were continuously recorded. Figure 1 shows a recording from a patient with cardiomyopathy.

Measurements and calculations

Pressures. On the low-gain (scale 200 mm Hg/4 cm) tracings the following measurements were obtained: maximum systolic aortic pressure, diastolic aortic pressure, maximum positive left ventricular systolic dP/dt, maximum negative left ventricular systolic dP/dt, and the time constant of left ventricular relaxation (T). According to the method of Weiss et al. T was derived from the rate constant of the best exponential fit to the pressure data during isovolumetric relaxation (from maximum negative left ventricular systolic dP/dt to the level of left ventricular end-diastolic pressure) by the method of least squares. To study the completeness of relaxation the number of Ts elapsed after maximum negative dP/dt at the time of left ventricular minimum pressure was computed.

On the high-gain tracings (scale 40 mm Hg/4 cm) the following were measured (figure 1): heart rate, left ventricular minimum pressure in early diastole (0 point), height of the so-called rapid filling wave (from 0 to F), maximum dP/dt of the rapid filling wave, and left ventricular end-diastolic pressure (point C).

Volumes. With an ultrasonic pen (Science Accessories Corporation) the left ventricular silhouette of each frame was traced starting from end-systole to end-diastole. The first adequately opacified sinus beat was analyzed excluding premature beats and the first subsequent sinus beat. Correction for x-ray magnification was accomplished by filming a calibrated metal grid at the estimated height of the center of the heart. The computer program for calculating left ventricular volumes was based on the method of Kennedy et al. Depending on the length of diastole, a varying number of frames was analyzed per patient. Because of scatter in the primary volume data, the volume-time curve was smoothed by a polynomial approximation technique. Slightly different values were obtained depending on the degree of filtering. In accordance with Gaasch et al. a nine-point filter was selected for the calculations. After digitizing and filtering, the volumes were differentiated (dV/dt)

The following volumetric parameters were measured: end-systolic volume, end-diastolic volume, diastolic volume at the time of minimum left ventricular pressure (ODV), early filling volume (measured as ODV − end-systolic volume), early filling volume normalized for end-diastolic volume and expressed as a percentage of total diastolic filling (early filling fraction), maximum rate of dV/dt, maximum dV/dt normalized for end-diastolic volume, and ejection fraction.

Pressure-volume relationship. High-gain left ventricular diastolic pressures were measured serially at 11.11 msec intervals synchronously with each angiographic frame. To make more appropriate comparisons of viscoelastic properties between patients with different left ventricular sizes, left ventricular volumes were also normalized (Vm). Smoothed volumes (V) were divided by a constant volume (Vc) calculated as the mean diastolic volume between the OVD and end-diastole (Vc = ODV + EDV/2) so that Vn = V/Vc × 100.

Simultaneous left ventricular pressure-volume data from the ODV to end-diastole were fitted by a simple elastic monoexponential equation (P = be/angular + P = be/angular) and by a viscoelastic exponential equation taking into account inflow rate (dV/dt or dVn/dt) during diastole (P = be/angular + Y·dV/dt or P = be/angular + Yn·dVn/dt, where e = base of the natural logarithm; b, bn,
FIGURE 1. High-gain intracardiac pressure-phonoregistration recording during left ventriculographic examination in a patient with dilated cardiomyopathy. ECG = electrocardiogram; Ext Phono = external phonocardiogram; Int Phono = internal phonocardiogram; LVP (fluid) = left ventricular pressure from the fluid-filled system; LVP (tip) = left ventricular pressure from the micromanometer; max dP/dt RFW = maximum dP/dt of the rapid filling wave (from O to F); S1, S2, S3, S4 = first, second, third, and fourth heart sounds; A = A wave; C = end-diastole.

k, and kn = simple elastic variables to be fitted to the data; B, Bn, K, Kn, Y, and Yn = viscoelastic variables to be fitted to the data; dV/dt or dVn/dt = inflow rate). According to the method of Hess et al., these formulas were transformed to the semilogarithmic linear equation lnP = kV + lnB or lnP = knVn + lnBn and ln(P - Y·dV/dt) = kV + lnB or ln(P - Yn·dVn/dt) = KnVn + lnBn. Incremental values of Y or Yn ranging from 0.001 to 3.0 were inserted into the viscoelastic equation until the highest possible correlation coefficient was obtained. The value of Y or Yn giving the best correlation was considered a quantitative expression of the viscous resistance to filling and named the viscous constant. The rate constants k or kn and K or Kn represent the elastic and viscoelastic moduli of chamber stiffness, respectively.

Statistical analyses. Data are mean ± SD. To test the hypothesis that no difference existed between the means of groups, one-way analysis of variance was used. If the null hypothesis was rejected at the 5% level, Tukey’s multiple-comparison method was used to determine the specific differences among the population means. For each comparison between two groups the studentized range (q value) was calculated.

Results

Left ventricular pressures, volumes, and derived indexes. The mean heart rates during intracardiac recording of pressure-phonoregistrations in the different groups were: 82.2 ± 13.3, 77.3 ± 11.3, 92.7 ± 15.9, and 84.5 ± 12.7 beats/min in groups I through IV, respectively. Left ventricular pressures, volumes, and derived indexes are listed in tables 1A and 2A. Results of statistical analysis of the differences between the mean values for the groups are listed in tables 1B and 2B.

In all patients with S3 the height and the peak rate of the pressure increase after minimum diastolic pressure were significantly greater than in normal adults without S3. The importance of these findings is further illustrated in figure 2: in a patient with cardiomyopathy we were able to record intracardiac pressures and phonoregistrations during a transient episode of atrial flutter. In this patient the speed of the pressure increase after minimum diastolic pressure varied from beat to beat depending on the amount of atrial contribution to early filling. Accordingly, the intensity of the internally and externally recorded S1 was clearly correlated with the height and speed of rise of the rapid filling wave. Determination of the exact onset of the S3 on the
**PATHOPHYSIOLOGY AND NATURAL HISTORY—VENTRICULAR PERFORMANCE**

![Image]

**TABLE 1A**

Left ventricular pressures and derived indexes in the different groups (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>AOSP (mm Hg)</th>
<th>AODP (mm Hg)</th>
<th>max dp/dt S pos (mm Hg/sec)</th>
<th>max dp/dt S neg (mm Hg/sec)</th>
<th>T (msec)</th>
<th>nT</th>
<th>LVPmin (mm Hg)</th>
<th>RFW (mm Hg)</th>
<th>max dp/dt RFW (mm Hg/sec)</th>
<th>LVEDP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>115.6</td>
<td>71.1</td>
<td>1914.7</td>
<td>2295.5</td>
<td>37.4^</td>
<td>3.08</td>
<td>1.88</td>
<td>1.64</td>
<td>28.9</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>±16.0</td>
<td>±10.6</td>
<td>±409.7</td>
<td>±530.3</td>
<td>±3.7</td>
<td>±0.23</td>
<td>±1.73</td>
<td>±1.52</td>
<td>±29.1</td>
<td>±3.5</td>
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<tr>
<td>Group II</td>
<td>98.1</td>
<td>62.8</td>
<td>1649.9</td>
<td>1225.8</td>
<td>43.2</td>
<td>2.58</td>
<td>3.10</td>
<td>5.55</td>
<td>170.7</td>
<td>13.3</td>
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<td></td>
<td>±11.1</td>
<td>±9.3</td>
<td>±557.5</td>
<td>±418.6</td>
<td>±10.0</td>
<td>±0.56</td>
<td>±3.0</td>
<td>±2.19</td>
<td>±123.3</td>
<td>±6.2</td>
</tr>
<tr>
<td>Group III</td>
<td>103.0</td>
<td>68.6</td>
<td>1278.1</td>
<td>1172.7</td>
<td>56.8</td>
<td>2.15</td>
<td>7.88</td>
<td>5.64</td>
<td>155.2</td>
<td>19.3</td>
</tr>
<tr>
<td></td>
<td>±14.5</td>
<td>±10.0</td>
<td>±502.0</td>
<td>±465.9</td>
<td>±15.4</td>
<td>±0.68</td>
<td>±5.62</td>
<td>±4.02</td>
<td>±133.4</td>
<td>±9.9</td>
</tr>
<tr>
<td>Group IV</td>
<td>109.2</td>
<td>67.9</td>
<td>1427.8</td>
<td>1527.8</td>
<td>41.8</td>
<td>2.49</td>
<td>6.04</td>
<td>6.55</td>
<td>116.3</td>
<td>16.4</td>
</tr>
<tr>
<td></td>
<td>±9.3</td>
<td>±5.2</td>
<td>±230.6</td>
<td>±281.8</td>
<td>±13.7</td>
<td>±1.12</td>
<td>±4.95</td>
<td>±1.08</td>
<td>±58.2</td>
<td>±4.8</td>
</tr>
<tr>
<td></td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(4)</td>
<td>(4)</td>
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<td>(4)</td>
</tr>
</tbody>
</table>

Values in parentheses are numbers of values for each parameter.

AOSP = maximum systolic aortic pressure; AODP = diastolic aortic pressure; max dp/dt S pos = maximum positive left ventricular systolic dp/dt; max dp/dt S neg = maximum negative left ventricular systolic pressure; nT = number of Ts elapsed at the time of minimum diastolic pressure; LVPmin = minimum left ventricular diastolic pressure; RFW = height of the rapid filling wave; max dp/dt RFW = maximum dp/dt of the rapid filling wave; LVEDP = left ventricular end-diastolic pressure.

^Correlation coefficient ranges for exponential left ventricular pressure fall: .992 to .998 (group I), .973 to .995 (group II), .959 to .997 (group III), .992 to .996 (group IV).

pressure-phonoregistration recording during catheterization was not always possible. However, in all patients the vibrations of the S wave clearly occurred during the ascending slope of the rapid filling wave.

Minimum diastolic pressure was significantly higher in patients with cardiomyopathy. Left ventricular end-diastolic pressure was highest in groups III and IV. Contractile function, as estimated by maximum positive systolic dp/dt, was slightly depressed in groups II and IV, but severely impaired in group III. Left ventricular relaxation, as measured by maximum negative systolic dp/dt and T, was significantly slower in patients in groups II and III. Completeness of relaxation was evaluated from the number of Ts elapsed by the time of minimum diastolic pressure. As per Weisfeld et al.,^15 relaxation was assumed to be complete at 3.5 Ts after maximum negative systolic dp/dt. By this criterion, left ventricular relaxation in the resting state was incomplete in all subjects studied (including the normal adults), but patients with cardiomyopathy clearly had the greatest relaxation abnormalities.

Left ventricular volumes (end-systolic and diastolic volumes and ODV) were significantly greater in groups II and III than in group I. In group IV somewhat greater volumes were also found. Due to the presence of mitral regurgitation, early filling volume and maximum dV/dt were significantly greater in group II than in the other groups. However, when these early filling parameters were normalized for end-diastolic volume very similar results were obtained in groups I, II, and

**TABLE 1B**

Statistical analysis of differences between means: pressure indexes

<table>
<thead>
<tr>
<th></th>
<th>AOSP</th>
<th>AODP</th>
<th>max dp/dt S pos</th>
<th>max dp/dt S neg</th>
<th>T</th>
<th>nT</th>
<th>LVPmin</th>
<th>RFW</th>
<th>max dp/dt RFW</th>
<th>LVEDP</th>
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</thead>
<tbody>
<tr>
<td>I vs II</td>
<td>4.2^a</td>
<td>—</td>
<td>NS</td>
<td>7.5^d</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>4.2^b</td>
<td>4.2^b</td>
<td>NS</td>
</tr>
<tr>
<td>I vs III</td>
<td>3.5^b</td>
<td>—</td>
<td>5.1^c</td>
<td>9.2^o</td>
<td>6.1^d</td>
<td>6.3^d</td>
<td>5.5^c</td>
<td>5.0^e</td>
<td>4.4^c</td>
<td>6.1^p</td>
</tr>
<tr>
<td>II vs III</td>
<td>NS</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>4.3^b</td>
<td>NS</td>
<td>4.2^b</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>F value</td>
<td>4.85^b</td>
<td>2.12(NS)</td>
<td>6.95^c</td>
<td>22.89^o</td>
<td>10.87^d</td>
<td>10.12^o</td>
<td>9.12^d</td>
<td>6.97^c</td>
<td>6.02^c</td>
<td>9.67^p</td>
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<tr>
<td>n_ave</td>
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<td>46</td>
<td>46</td>
<td>47</td>
<td>47</td>
<td>46</td>
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</tbody>
</table>

n_ave = total number of observations. Other abbreviations are as in table 1A.

^aStudentized range (q) value.

^p < .05; ^p < .01; ^p < .001.

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IV; the values in group III were definitely smaller. Ejection fraction was severely reduced in patients with cardiomyopathy. Values somewhat smaller than those in the normal subjects were found in groups II and IV. Within group III no significant differences between patients with ischemic or idiopathic dilated cardiomyopathy were found with respect to any of the angiographic parameters used in this study.

**Pressure-volume relationships.** The mean number of pressure-volume coordinates in diastole used for the calculations was nearly identical in groups I, II, and III, but smaller in group IV (22.5 in group I, 21.2 in group II, 21.6 in group III, and 15.5 in group IV).

The elastic and viscoelastic parameters obtained with nonnormalized and normalized volumes are given in table 3A. Results of statistical analysis of the differences between the groups are shown in table 3B.

The nonnormalized elastic and viscoelastic moduli of chamber stiffness (k, K) did not differ significantly among the groups. The normalized elastic and viscoelastic moduli of chamber stiffness (kn, Kn) were greater in groups II and III than in group I, although the differences were statistically significant only for Kn. The differences in pressure intercepts (b, bn, B, Bn) were statistically insignificant.

The introduction of dV/dt or dVn/dt into the pressure-volume equation only slightly improved the correlation coefficient for data from groups I and II, but it significantly improved the correlation for data from group III (figure 3). Accordingly, the viscous constants (Y and Yn) were much larger in group III. In addition, with the introduction of inflow rate into the equation, the rate constants significantly increased in group III (t = 2.57, p < .05 for k vs K; and t = 3.74, p < .005 for kn vs Kn), but not in groups I and II. There was also a marked improvement in the correlation of

**TABLE 2A**

Left ventricular volumes and derived indexes in the different groups (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>ESV (ml)</th>
<th>ODV (ml)</th>
<th>EDV (ml)</th>
<th>EFV (ml)</th>
<th>EFV/EDV (%)</th>
<th>EFR (%)</th>
<th>EF (%)</th>
<th>max DV/dt (ml/sec)</th>
<th>max dV/dt/EDV (sec⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>37.6</td>
<td>72.1</td>
<td>131.0</td>
<td>34.5</td>
<td>0.26</td>
<td>36.5</td>
<td>71.3</td>
<td>463.9</td>
<td>3.61</td>
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<tr>
<td></td>
<td>±16.0</td>
<td>±22.7</td>
<td>±39.5</td>
<td>±16.3</td>
<td>±0.08</td>
<td>±8.2</td>
<td>±7.6</td>
<td>±177.1</td>
<td>±1.44</td>
</tr>
<tr>
<td>Group II</td>
<td>118.4</td>
<td>168.8</td>
<td>298.3</td>
<td>69.1</td>
<td>0.28</td>
<td>46.3</td>
<td>61.3</td>
<td>1084.9</td>
<td>3.85</td>
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<tr>
<td></td>
<td>±70.8</td>
<td>±64.5</td>
<td>±122.0</td>
<td>±31.9</td>
<td>±0.09</td>
<td>±8.7</td>
<td>±15.5</td>
<td>±416.5</td>
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<tr>
<td></td>
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<tr>
<td>Group III</td>
<td>200.1</td>
<td>247.4</td>
<td>274.9</td>
<td>39.4</td>
<td>0.15</td>
<td>52.2</td>
<td>28.5</td>
<td>448.8</td>
<td>1.70</td>
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<td></td>
<td>±68.3</td>
<td>±66.0</td>
<td>±68.8</td>
<td>±10.9</td>
<td>±0.05</td>
<td>±15.7</td>
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<tr>
<td></td>
<td>(21)</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
<td>(13)</td>
<td>(21)</td>
<td>(21)</td>
<td>(21)</td>
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<tr>
<td>Group IV</td>
<td>66.5</td>
<td>77.3</td>
<td>159.4</td>
<td>32.2</td>
<td>0.28</td>
<td>44.2</td>
<td>62.3</td>
<td>709.9</td>
<td>4.61</td>
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<tr>
<td></td>
<td>±30.8</td>
<td>±15.9</td>
<td>±49.7</td>
<td>±0.3</td>
<td>±0.08</td>
<td>±11.0</td>
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<td>±226.8</td>
<td>±1.23</td>
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</tbody>
</table>

Values in parentheses are numbers of values for each parameter.

ESV = endystolic volume; ODV = diastolic volume at the time of minimum diastolic pressure; EDV = end-diastolic volume; EFV = early filling volume; EFV/EDV = early filling volume normalized for the end-diastolic volume; EFR = early filling fraction; max dV/dt = maximum filling rate in early diastole; max dV/dt/EDV = maximum filling rate in early diastole normalized for the enddiastolic volume.

**TABLE 2B**

Statistical analysis of differences between means: volume indexes

<table>
<thead>
<tr>
<th></th>
<th>ESV</th>
<th>ODV</th>
<th>EDV</th>
<th>EFV</th>
<th>EFV/EDV</th>
<th>EFR</th>
<th>EF</th>
<th>max dV/dt</th>
<th>max dV/dt/EDV</th>
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<tr>
<td>I vs II</td>
<td>4.3a</td>
<td>5.0b</td>
<td>6.8c</td>
<td>5.2a</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
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<td>11.2c</td>
<td>7.0c</td>
<td>NS</td>
<td>5.1b</td>
<td>4.4a</td>
<td>15.1c</td>
<td>NS</td>
<td>6.9c</td>
</tr>
<tr>
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<td>4.8a</td>
<td>4.2a</td>
<td>NS</td>
<td>4.6b</td>
<td>5.2a</td>
<td>NS</td>
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<td>7.3c</td>
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<tr>
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<td>30</td>
<td>30</td>
<td>30</td>
<td>41</td>
<td>41</td>
<td>41</td>
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</tbody>
</table>

Abbreviations are as in table 2A; statistical analyses as in table 1B.

*p < .05; b p < .01; c p < .001.
FIGURE 2. Intracardiac pressure-phonoregistration recording during an episode of atrial flutter in a patient with dilated cardiomyopathy. The height and steepness of the pressure rise after minimum diastolic pressure (the so-called rapid filling wave) is different from beat to beat and depends on the coincidence of early "passive" filling with active filling due to atrial (flutter) contraction. Accordingly, the intensity of both the internally and externally $S_3$ is strikingly correlated with the height and steepness of this pressure rise. Abbreviations are as in figure 1.

data from the two patients in group IV after the introduction of $dV/dt$ or $dVn/dt$ (figure 3) into the equation and their viscous constants were also high.

Discussion

In this study, filling dynamics and diastolic pressure-volume relationships were evaluated in patients with different cardiac diseases and presenting with $S_3$s and in normal adults without $S_3$s.

TABLE 3A

| Elastic and viscoelastic parameters in the different groups (mean ± SD) |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                            | $k$ (mm Hg/ml)              | $k$ (mm Hg/ml)              | $K$ (mm Hg/ml)              | $K_n$ (mm Hg/ml)             |
|                            | volume unit                 | b or bn (mm Hg)             | volume unit                 | B or Bn (mm Hg)              |
|                            |                             |                             |                             | Y (mm Hg)                   | Yn (mm Hg/sec)              |
|                            |                             |                             |                             | volume unit                 |                             |
| Group I (n = 11)           | 0.024 ± 0.014               | 0.027 ± 0.018               | 1.889 ± 0.017               | 0.030 ± 0.017               | 0.028 ± 0.019               | 1.743 ± 0.119               | 0.045 ± 0.013               | 0.036 ± 0.019               |
| Group II (n = 6)           | 0.024 ± 0.017               | 0.048 ± 0.018               | 2.855 ± 0.017               | 0.030 ± 0.017               | 0.028 ± 0.019               | 2.673 ± 0.119               | 0.045 ± 0.013               | 0.090 ± 0.019               |
| Group III (n = 13)         | 0.021 ± 0.017               | 0.052 ± 0.030               | 0.276 ± 0.016               | 0.026 ± 0.017               | 0.053 ± 0.019               | 0.138 ± 0.125               | 0.013 ± 0.019               | 0.283 ± 0.019               |
| Group IV (n = 2)           | 0.012 ± 0.009               | 0.013 ± 0.017               | 7.682 ± 0.017               | 0.043 ± 0.017               | 0.015 ± 0.017               | 0.024 ± 0.019               | 0.156 ± 0.125               | 0.382 ± 0.019               |

$k$ or $kn$ = elastic modulus of chamber stiffness using nonnormalized or normalized volumes; $K$ or $Kn$ = viscoelastic modulus of chamber stiffness using nonnormalized or normalized volumes; $b$, $bn$, $B$, or $Bn$ = pressure intercepts; $Y$ or $Yn$ = viscous constant obtained with nonnormalized or normalized volumes.

Method. In accordance with Ludbrook et al. we used a dual catheter system with a micromanometer for pressure recording and an angiographic catheter for contrast injection. Reasons for the use of a separate angiographic catheter were the marked dilatation of the left ventricular cavity in many patients and the need for high injection rates (>20 ml/sec) to obtain adequate opacification. Furthermore, the side lumen of the catheter allowed continuous zeroing of the micromanometer pressure during left ventriculographic examination (figure 1). Together with the high sampling rate (pressure-volume coordinates every 11.11 msec) and the adequate smoothing technique of the volumes (compensating for the time lag of the filter) this had to improve the reliability of the pressure-volume measurements.

On the other hand, it has to be recognized that volume measurements derived from single-plane cineangiography in patients with marked spherical left ventricular dilation and segmental wall motion abnormalities might be somewhat inaccurate.

Left ventricular pressures, volumes, and derived indexes. Recently it has been suggested that intracardiac pressure fluctuations cannot explain the origin of the $S_3$.

In our study we found a higher and steeper pressure rise after minimum diastolic pressure (so-called rapid filling wave) in patients with $S_3$s compared with in normal adults without them. Figure 2 illustrates a striking relationship between the intensity of the $S_3$ and the height and steepness of the rapid filling wave. Previous studies have shown that left ventricular pressure is the most important determinant of the morphology of the left apexcardiogram, especially in diastole. In a comparative study between the calibrated left apexcardiogram and left ventricular micromanometer pressure...
TABLE 3B
Statistical analysis of differences between means: elastic and viscoelastic parameters

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>kn</th>
<th>b or bn</th>
<th>K</th>
<th>Kn</th>
<th>B or Bn</th>
<th>Y</th>
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<tr>
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</tr>
<tr>
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<td>1.97</td>
<td>2.11</td>
<td>1.07</td>
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<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations are as in table 3A, statistical analyses as in table 1B.

*p < .01; **p < .001.

in 28 cardiac patients we found significant linear correlations between the height and peak dP/dt of the rapid filling wave of both tracings (r = .55, p < .01 and r = .80, p < .001, respectively).* Therefore, the present results can explain the well-known association of the S3 with a pronounced rapid filling wave on the left apexcardiogram (which is considered to be the subaortic counterpart of the S3). On the other hand, Prewitt et al.24 could not demonstrate a consistent relationship between filling rate, rapid filling wave of the apexcardiogram, and the S3. This lack of correlation could be explained by the fact that the pressure rise of the rapid filling wave occurs after maximum inflow and in fact represents the delayed pressure response of the ventricle to filling.25-28 This pressure response is dependent not only on the inflow rate but also on the completeness of relaxation and the viscoelastic properties of the left ventricular wall (see below).

As expected, left ventricular volumes (end-systolic, end-diastolic, and ODV) were significantly greater in patients with cardiac diseases than in normal adults. Due to the presence of mitral regurgitation, maximum dV/dt and early filling volume were significantly higher in group II than in the other groups. However, when these early filling parameters were normalized for end-diastolic volume, similar results were found in groups I, II, and IV, but definitely smaller values were found in group III. Although early filling volume/end-diastolic volume was significantly smaller in patients with cardiomyopathy, this early filling volume (occurring before minimum diastolic pressure) represents 52% of total diastolic filling, emphasizing the importance of the early filling process in patients in a low-output state.

The present results and the observation of a decreased atrial contribution to filling in patients with cardiomyopathy by Greenberg et al.29 together with the opposite findings reported in the literature in patients with left ventricular hypertrophy,30-33 are very consonant with the clinical phonocardiographic picture. Indeed, a fourth heart sound without an S3 is commonly found in patients with hypertrophic ventricles of normal or decreased cavity size, while a fourth heart sound in addition to a more prominent S3 is usually present in patients with dilated ventricles.

Diastolic properties of the left ventricle. Left ventricular properties were analyzed in terms of the pressure-volume relationship. As suggested by Mirsky,34 we also used normalized volumes in the calculations to allow more appropriate comparisons between ventricles of different sizes.

FIGURE 3. Intrapatient comparisons of the correlation coefficients from the simple elastic (r) and viscoelastic (R) equations in the different groups (I, II, III, and IV). Heavy lines indicate mean values for each group. NS = not significant.
Among the different groups no significant differences were found in k, the elastic modulus of chamber stiffness. When the normalized moduli of chamber stiffness (kn) were compared, somewhat higher values were found in groups II and III, although the differences did not reach statistical significance. From these results it appears that in patients with compensated volume overload and in those with cardiomyopathy the increase in intrinsic chamber stiffness is rather small and statistically insignificant when compared with that in normal adults.

Since it has been demonstrated that left ventricular diastolic properties are characterized more precisely by a viscoelastic than a simple elastic model,19,37 we adapted such a model from Hess et al.19 By introducing inflow rate into the exponential equation a viscous constant was calculated that expressed and quantified the flow-dependent influences on left ventricular pressure in diastole. With this approach we found that the viscous constant was definitely higher in patients with cardiomyopathy than in normal adults or in patients with mitral regurgitation. The correlation coefficients and the rate constants of the exponential equations significantly increased in this group, which was not observed in normal adults or in patients with mitral regurgitation. Although simultaneous pressure-volume data were available in only two patients with restricted left ventricular filling, the results were very similar to those in the group with cardiomyopathy. From these data it seems that in the latter groups increased viscous forces are acting in early diastole, which may partly explain the increased and steeper pressure rise at that time.

Since diastolic pressures in patients with mitral regurgitation were definitely higher, apparently without a significant increase in the elastic or viscoelastic modulus of chamber stiffness, one may suppose that in this patient group the ventricle is shifted to a steeper part of the pressure-volume curve (preload-dependent change in chamber stiffness36). This preload-induced increase in operative chamber stiffness seems to be a major mechanism in this group and to be responsible for the elevated pressures during diastole and more specifically for the steeper pressure rise of the rapid filling wave.

Delayed relaxation from the preceding systole may affect early diastolic pressures. We therefore studied left ventricular relaxation rate and the completeness of relaxation at the time of minimum diastolic pressure. In patients with cardiac diseases and S3s relaxation was slower and more incomplete than in normal adults. Patients with cardiomyopathy clearly showed the greatest relaxation abnormalities. Comparable results were reported by Hirota.37 From these data it may be assumed that impaired relaxation contributes to the increased pressure rise after minimum diastolic pressure, especially in patients with cardiomyopathy. Although from our data it is impossible to separate the influences of myocardial viscoelasticity and incomplete relaxation on early diastolic pressures, it is of interest to note that the patients with the highest viscous constants also had the most delayed relaxation. It therefore may be supposed that incomplete relaxation of the ventricle also represents a higher viscous resistance during early filling.

Conclusions: pathogenesis of the S3. Several findings from this study may give new insights into the pathogenesis of the S3. Regardless of the nature of their cardiac disease, all patients with S3s had increased rapid filling waves that were nearly of the same magnitude on the left ventricular pressure tracings. We recently demonstrated that the pressure rise of the rapid filling wave in dogs is responsible for rapid deceleration of left ventricular inflow by reversal of the transmitral pressure gradient and that the vibrations of the S3 occur during this phase of pressure rise and deceleration of flow.28 The results of the present study together with the occurrence of the S3 during the E-F closing slope of the mitral valve on the echocardiogram38 confirm these experimental findings.

In previous studies in patients with constrictive pericarditis the onset of the S3 has been placed at the nadir of the early diastolic dip.4,39 However, we found that in all patients the vibrations of the S3 occurred after minimum diastolic pressure, during the ascending slope of the rapid filling wave. The use of fluid-filled systems for pressure recordings in the above-mentioned studies may explain the small differences in temporal relationships. On the other hand, we also observed that, in patients with constrictive pericarditis, both the onset of the rapid filling wave and of the S3 occur closer to the second heart sound than in the other groups, probably indicating an earlier and more sudden halting of left ventricular filling. In one patient in our study with restrictive myopathy the same pressure-sound relationships were observed, but the S3 occurred somewhat later after minimum diastolic pressure.

In summary, our findings postulate a mechanism of production of the S3 that explains its presence under different hemodynamic conditions. The steep left ventricular pressure increase in early diastole (so-called rapid filling wave) causes a reversal of the transmitral pressure gradient and hence a more rapid deceleration of inflow. Since the vibrations of the S3 occur during this phase of deceleration of flow, a conversion of
kinetic into vibratory energy may be supposed. These vibrations (recent studies indicate that the left ventricular wall is probably the major cardiac structure that is set into vibrations\(^\text{10, 28}\)) will become audible and recordable from the chest if they are transmitted with sufficient intensity. The higher the inflow rate (valvular regurgitation, high-output states) and the steeper the rapid filling wave (high filling rates, incomplete relaxation, increased viscous resistance to filling, pericardial constriction) the greater the amount of deceleration and the more likely an \(S\), will be generated.

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