Serial changes in left ventricular relaxation and chamber stiffness after large myocardial infarction in rats

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ABSTRACT  To determine the time course of changes in left ventricular diastolic properties after a large myocardial infarction, we serially measured left ventricular relaxation, chamber stiffness, and the ratio of left ventricular cavity to wall volume (V/Vw) after coronary artery ligation in rats. Left ventricular relaxation was measured during the occlusion and then both relaxation and chamber stiffness were measured at 3 hr, 24 hr, and 3, 5, and more than 22 days after infarction. Left ventricular pressures and left ventricular dP/dt were recorded with micromanometer-tipped catheters. Left ventricular relaxation was measured by computer digitization of the left ventricular pressure tracings and averaged over 100 to 150 cardiac cycles. Five chamber stiffness constants were calculated from pressure-volume curves that were obtained ex vivo. We found ventricular relaxation prolonged for the first hour after coronary occlusion; relaxation was maximally prolonged at 10 to 15 min after onset of occlusion. After 1 hr relaxation returned to normal. However, by 5 days ventricular relaxation was again prolonged. Left ventricular stiffness constants were increased at 3 and 24 hr, resulting in a shift of the left ventricular pressure-volume relation to the left. At 3 days after coronary artery ligation, all stiffness constants and the pressure-volume relation returned to normal. At more than 22 days the pressure-volume relation was shifted to the right and the stiffness constant for low filling pressures was decreased. V/Vw was significantly decreased from 0.603 ± 0.021 at 3 and 24 hr to 0.379 ± 0.024 and 0.362 ± 0.032, respectively. V/Vw was significantly increased at more than 22 days (0.921 ± 0.094). We conclude that left ventricular diastolic function in rats is dynamic during the acute and healing phases of myocardial infarction. Left ventricular relaxation is prolonged at 10 to 15 min after coronary occlusion, then returns to normal, and by 5 days is again prolonged. Changes in left ventricular chamber stiffness are biphasic, first increasing then decreasing. These observed changes in chamber stiffness are related in part to changes in V/Vw.


TRANSIENT PERIODS of myocardial ischemia that are relatively brief and do not result in infarction prolong left ventricular relaxation and shift the diastolic pressure-volume relation leftward toward the pressure axis.1–5 When diastolic function has been examined after myocardial ischemia of sufficient duration to produce infarction, conflicting results have been reported. For example, early after acute infarction in dogs, left ventricular compliance has been found to be both increased6 and decreased.7–9

In rats studied 3 weeks or longer after myocardial infarction, left ventricular chamber stiffness is decreased and the pressure-volume relation is shifted to the right for that portion of pressure-volume relation that is linear, i.e., over the range of low distending pressures10 and higher filling pressures.11 The reason for the apparent differences in the pressure-volume relationship in studies of acute and chronic infarction is not clear. Miskey et al.12 postulated that left ventricular chamber stiffness, which is a function of muscle stiffness, left ventricular geometry, and the ratio of ventricular cavity to wall volume (V/Vw), may be continuously changing during the first hours or days after myocardial infarction.13 Furthermore, infarct expansion,14 which may greatly contribute to changes in V/Vw, has not been carefully studied in relation to observed changes in diastolic properties.15

The purpose of this study was: (1) to study the serial
effects of healing acute and chronic myocardial infarction on diastolic properties of the left ventricle, (2) to study independently the abnormalities of active relaxation and passive-elastic properties, and (3) to determine the possible role of left ventricular remodeling due to infarct expansion on the changes in the pressure-volume relation that were observed.

Methods

Experimental infarction. Male Sprague-Dawley rats (200 to 300 g) were subjected to coronary artery ligation by techniques previously described. Briefly, the rats were anesthetized with ether, a left lateral thoracotomy was performed, and the heart was expressed from the chest cavity. A ligature was placed in the region of the intramyocardial location of the left coronary artery and tied. The heart was returned to the chest cavity and the rat was allowed to recover until time for catheter placement for hemodynamic testing. The rats with infarction were divided into five groups based on time elapsed from coronary ligation to procedure but the suture was placed and not tied. Of these rats, seven were studied at 2 hr, six at 24 hr, six at 3 days, six at 5 days, and seven at more than 22 days (range 22 to 32 days) after myocardial infarction.

The control group consisted of 14 unoperated, normal rats with no evidence of myocardial infarction and 32 sham-operated rats. The sham-operated rats underwent an identical surgical procedure but the suture was placed and not tied. Of these 32 rats, seven were studied at 2 hr, six at 24 hr, six at 3 days, six at 5 days, and seven at more than 22 days after the sham procedure.

In open-chest rats (n = 6), the effects of acute coronary artery occlusion on left ventricular relaxation were determined by measuring T (the exponential time constant of left ventricular pressure decay) immediately before and every 10 to 15 min for 2 hr after coronary artery ligation. Coronary artery ligation was performed as above after tracheotomy, with the rat ventilated with a Harvard positive-pressure ventilator and under ether anesthesia. Control rats (n = 5) underwent an identical surgical procedure, except a suture was not placed.

Hemodynamic studies. Electrocardiograms were recorded with use of a nine-lead system. If electrocardiographic criteria for a large myocardial infarction were found, the rats were selected for hemodynamic study. During ether anesthesia the right carotid artery was cannulated with a 1 mm micromanometer-tipped catheter that was passed under constant pressure monitoring into the left ventricle. Left ventricular dp/dt was obtained from a differentiating circuit in the physiological recorder (Gould 2400). The signal was filtered with use of a high-frequency filter at 100 Hz. All data were also recorded onto an FM tape recorder (Gould 6500). The femoral vein was cannulated with silicone rubber tubing. Both catheters were then secured and exteriorized to the dorsal cervical region. Rats were allowed to recover from anesthesia for 2.5 to 3 hr before hemodynamic data were recorded. Then, with stable pressure in conscious animals, 100 to 150 consecutive beats of left ventricular pressure were recorded on magnetic tape for subsequent computer-assisted analysis. In the open-chest studies of the effects of acute coronary occlusion, the catheter was inserted as above and remained in the ventricle after coronary ligation for up to 2 hr for the determination of pressure and T.

To obtain zero reference pressure, the catheter tip transducer was placed in warmed (99°F) saline before all hemodynamic studies. After 30 min pressure was zeroed to atmospheric pressure. At the conclusion of all studies, the catheter tip was again placed in warmed saline to determine the magnitude of baseline drift. Maximum drift recorded in this way was 2 mm Hg.

Pressure-volume relation. Pressure-volume data were determined by methods described previously. Briefly, after recording left ventricular pressures in conscious animals, the rats were anesthetized and potassium chloride was injected via the femoral vein catheter to arrest the heart in diastole. The lungs and great vessels were dissected free and the heart was rapidly removed. The right ventricle was incised and the atrioventricular groove was isolated by a ligature. The left ventricle was cannulated in retrograde fashion with a double-lumen polyethylene catheter (PE 50 within PE 200). One lumen of the catheter was attached to a pressure transducer (Statham 23D) and calibrated with a mercury manometer. The other lumen was attached to an infusion pump (Sage 341). Gentle aspiration of the left ventricular cavity was performed to remove residual blood and to reduce the pressure to −5 mm Hg. Normal saline was then infused at 0.70 ml/min into the suspended left ventricle and pressures were recorded until the pressure increased to 30 mm Hg. The infusion was stopped and the saline was aspirated. The procedure was performed a minimum of two and a maximum of three times. No pressure-volume data were obtained after 10 min from the time of cardiac arrest.

Pathologic studies. Myocardial infarct size was measured in all animals, except those studied after 3 and 24 hr, by techniques previously described. To determine infarct size in the rats studied and in 24 hr after coronary artery ligation the ventricles were cut into four slices and stained with triphenyltetrazolium. Each slice was photographed and then magnified 250 times and infarct size was determined as before. The slices were then processed for histologic study. Rats with infarct sizes less than 40% were excluded from further analysis and are not reported in Results.

Calculations

Left ventricular relaxation. The decay of left ventricular pressure with time can be closely approximated by the exponential relationship:

\[ P = P_a e^{-T} + P_A \]

where \( P_a + P_A \) is ventricular pressure at maximum negative dp/dt, \( P_A \) is left ventricular asymptote pressure, assuming left ventricular pressure decays to infinity, and \( a \) is the constant of the exponential relationship. Left ventricular relaxation was calculated by use of a modification of the methods described by Weiss et al. and Martin et al. Left ventricular pressure of 100 to 150 consecutive cardiac cycles was digitized with an IBM AT computer at a frequency of 1000 Hz. For each cardiac cycle maximum positive and maximum negative dp/dt, and peak systolic and end-diastolic pressure points were identified. The value of end-diastolic pressure for each cycle was subtracted from each pressure point on the pressure decay curve of that cycle beginning at maximum negative dp/dt and ending at a point equal to the end-diastolic pressure. The resulting values were then fit to the relation

\[ dp/dt = -a(P - P_a) \]

where \( a \) is calculated by the least squares method (mean correlation coefficient \( r = .993 \)) and \( T = -1/a \). An example of the analysis of 1 beat is shown in figure 1.

Chamber stiffness. From the pressure-volume data recorded ex vivo, the stiffness constants \( K_0, K_1, K_2, K_3 \), and \( K_4 \) were determined by a modification of a previously described method. Briefly, pairs of simultaneous pressure-volume points (15 pairs for each pressure interval) were recorded, digitized, and stored. For pressures from 0 to +3.0 mm Hg, the relation between pressure and volume was linear and the slope of the
The pressure-volume relation was designated \( K_1 \). For pressure from 3 to 10 mm Hg, the relation
\[
P = P_0 e^{K_1 V}
\]
was found to best describe the pressure-volume relation. Thus, in \( P = P_0 = K_2 V \), and when in \( P \) is plotted vs volume (\( V \)), \( K_2 \) is the slope of this relation. \( K_3 \) and \( K_4 \) were calculated from the same exponential relation as \( K_2 \), but the pressure intervals chosen were from 10 to 20 and 20 to 30 mm Hg, respectively. Finally, \( K_0 \), the overall chamber stiffness constant, was also calculated from the same exponential relation, but the entire range (3 to 30 mm Hg) of pressure was chosen.

Left ventricular \( V/V_W \). Ventricular cavity volume at a distending pressure of 10 mm Hg was determined from the passive pressure-volume relation. Left ventricular wall volume was determined from the mass of the left ventricle, such that \( V_W = \text{left ventricular mass (g)} \times 1.05 \) (the density of muscle). This relation assumes that ventricular muscle is incompressible. 30

Statistical analysis. Results are expressed as the mean \( \pm \) SEM. Comparisons between the infarcted and sham-operated rats were performed with use of Student’s t test for unpaired data. For comparisons of infarcted and sham-operated rats with control, Dunnett’s analysis for multiple comparisons against a single control was used. The values for stiffness constants and \( T \) were determined by regression analysis with the method of least squares for each pressure-volume and pressure-time relation.

Results

Baseline measurements. There were 10 rats at 3 hr, six rats at 24 hr, six rats at 3 days, five rats at 5 days, and 10 rats at more than 22 days that had myocardial infarctions of greater than 40% of the left ventricle and those results are reported here. Three rats with electrocardiographic evidence of acute myocardial infarctions were subsequently found to have infarcts of less than 40% of the left ventricle and were excluded from analysis. Although rats had generally uniform left ventricular weight/body weight ratios, left ventricular volumes were indexed to body weight. The mean values for body weight, left ventricular weight, and left ventricular weight/body weight for all rats are listed in table 1. When the control group was compared with the five infarct groups, there were significant differences in left ventricular weight in rats studied at 5 and more than 22 days, and in body weight in rats studied at more than 22 days. However, left ventricular weight/body weight was uniform except for a small but significant increase in the left ventricular weight/body weight in the 3 day cohort. Mean values for conscious heart rate, left ventricular systolic pressure, positive peak left ventricular dP/dt, left ventricular end-diastolic pressure, and \( T \) are listed in table 2. Heart rate was unchanged, while left ventricular systolic pressure and left ventricular dP/dt were decreased (\( p < .01 \)) in all infarct groups compared with control, and left ventricular end-diastolic pressure in all groups of infarcted rats was higher (\( p < .01 \)) than control.

Tables 1 and 2 also show baseline measurements and hemodynamic data for the sham-operated rats. Left ventricular weight and body weight were significantly different in the sham-operated rats studied at more than 22 days than in controls, again reflecting the slight increase in growth of rats studied after 22 days. There were no significant differences in the left ventricular weight/body weight ratio of the sham-operated rats vs control, or in any hemodynamic measurement vs control. When sham-operated rats were compared with those with infarction, left ventricular systolic pressure and positive peak left ventricular dP/dt were significantly decreased (\( p < .005 \) or .001) and left ventricular end-diastolic pressure was significantly increased (\( p < .001 \)) in the infarction groups at all times after coronary occlusion.

Left ventricular relaxation. In the open-chest rats \( T \) was 14.1 \( \pm \) 0.6 msec before coronary occlusion. At
10 to 15 min after coronary occlusion T was prolonged (p < .01) to 18.1 ± 0.7 msec; it had returned to the control value at 1 hr. In open-chest rats in which the coronary artery was not ligated the initial T was 13.9 ± 0.9 msec and it did not change over the next 2 hr (13.0 ± 0.2 at 2 hr).

In the conscious studies at 3 hr after coronary artery ligation T was normal, and it remained unchanged until 5 days after infarction (table 2). At that time T was prolonged (p < .01). T remained significantly prolonged (p < .01) in rats with infarction studies at more than 22 days.

There were no significant differences in T in any sham-operated cohort and that in the control group. However, when rats with infarction were compared with their respective sham-operated controls, T was very significantly prolonged (p < .001) at 5 days. T remained significantly prolonged in the rats with infarction at more than 22 days compared with the corresponding sham control value.

**Pressure-volume relations and chamber stiffness constants.** The left ventricular pressure-volume relations in the control and different experimental groups are shown in figure 2. With acute infarction there was a

### TABLE 1

Left ventricular weight, body weight, and left ventricular weight/body weight in control rats, sham-operated rats, and rats with large myocardial infarctions after coronary ligation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3 hr</th>
<th>24 hr</th>
<th>3 days</th>
<th>5 days</th>
<th>&gt;22 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV wt [g]</td>
<td>4.58 ± 0.20</td>
<td>5.38 ± 0.26</td>
<td>6.61 ± 0.18</td>
<td>4.90 ± 0.50</td>
<td>6.40 ± 0.27</td>
<td></td>
</tr>
<tr>
<td>(p &lt; .01)</td>
<td>(5.51 ± 0.12)</td>
<td>(5.24 ± 0.18)</td>
<td>(5.62 ± 0.15)</td>
<td>(5.18 ± 0.14)</td>
<td>(6.55 ± 0.19)</td>
<td></td>
</tr>
<tr>
<td>BW [kg]</td>
<td>2.56 ± 0.07</td>
<td>2.41 ± 0.09</td>
<td>2.13 ± 0.11</td>
<td>2.66 ± 0.08</td>
<td>2.29 ± 0.20</td>
<td></td>
</tr>
<tr>
<td>(T10 ± 0.9)</td>
<td>(2.25 ± 0.09)</td>
<td>(2.49 ± 0.06)</td>
<td>(2.45 ± 0.02)</td>
<td>(2.48 ± 0.07)</td>
<td>(3.02 ± 0.16)</td>
<td></td>
</tr>
<tr>
<td>LV wt/BW</td>
<td>2.13 ± 0.06</td>
<td>2.31 ± 0.10</td>
<td>2.36 ± 0.05</td>
<td>2.49 ± 0.06^b</td>
<td>2.12 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>(2.25 ± 0.03)</td>
<td>(2.12 ± 0.07)</td>
<td>(2.20 ± 0.03^c)</td>
<td>(2.09 ± 0.04)</td>
<td>(2.14 ± 0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Values in parentheses are those obtained from sham-operated animals. LV = left ventricular; BW = body weight; wt = weight.

^p < .05, infarction and sham-operated groups vs control.

^p < .05, rats with infarction compared with corresponding sham-operated rats.

### TABLE 2

Hemodynamics and T in conscious control rats, sham-operated rats, and rats with large myocardial infarctions after coronary ligation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>3 hr</th>
<th>24 hr</th>
<th>3 days</th>
<th>5 days</th>
<th>&gt;22 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>410 ± 8</td>
<td>415 ± 7</td>
<td>424 ± 6</td>
<td>412 ± 9</td>
<td>390 ± 20</td>
<td>392 ± 7</td>
</tr>
<tr>
<td></td>
<td>(405 ± 6)</td>
<td>(395 ± 17)</td>
<td>(384 ± 12)</td>
<td>(387 ± 9)</td>
<td>(377 ± 15)</td>
<td></td>
</tr>
<tr>
<td>LV SP (mm Hg)</td>
<td>144 ± 3</td>
<td>120 ± 1^a</td>
<td>119 ± 2^a</td>
<td>116 ± 4^a</td>
<td>118 ± 1^a</td>
<td>122 ± 4^a</td>
</tr>
<tr>
<td></td>
<td>(145 ± 3^c)</td>
<td>(142 ± 8^c)</td>
<td>(140 ± 6^c)</td>
<td>(147 ± 12^c)</td>
<td>(137 ± 3^c)</td>
<td>(137 ± 3^c)</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>8530 ± 400</td>
<td>6340 ± 300^a</td>
<td>5980 ± 280^c</td>
<td>5760 ± 610^a</td>
<td>4540 ± 290^a</td>
<td>5920 ± 330^a</td>
</tr>
<tr>
<td></td>
<td>(8290 ± 427^p)</td>
<td>(8677 ± 510^p)</td>
<td>(8878 ± 511^p)</td>
<td>(9504 ± 311^p)</td>
<td>(8556 ± 332^p)</td>
<td></td>
</tr>
<tr>
<td>LV EDP (mm Hg)</td>
<td>6 ± 1</td>
<td>21 ± 2^a</td>
<td>20 ± 2^a</td>
<td>16 ± 2^a</td>
<td>28 ± 4^a</td>
<td>31 ± 3^a</td>
</tr>
<tr>
<td></td>
<td>(8 ± 1^b)</td>
<td>(6 ± 1^b)</td>
<td>(8 ± 2^b)</td>
<td>(8 ± 2^b)</td>
<td>(6 ± 1^b)</td>
<td>(6 ± 1^b)</td>
</tr>
<tr>
<td>T (sec)</td>
<td>12.9 ± 0.8</td>
<td>15.4 ± 0.9</td>
<td>15.2 ± 0.5</td>
<td>16.7 ± 1.0</td>
<td>18.5 ± 0.6 ^a</td>
<td>19.8 ± 1.3 ^a</td>
</tr>
<tr>
<td></td>
<td>(12.9 ± 0.4)</td>
<td>(14.3 ± 0.4)</td>
<td>(15.0 ± 0.7)</td>
<td>(13.5 ± 0.3^p)</td>
<td>(14.3 ± 0.3^p)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>14</td>
<td>8</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Values in parentheses are those obtained from sham-operated animals.

HR = heart rate; EDP = end-diastolic pressure; LV = left ventricular; SP = systolic pressure; T = time constant of LV pressure decay.

^p < .01, infarction and sham-operated groups compared with control.

^p < .01; ^p < .005; ^p < .001, rats with infarction compared with corresponding sham-operated rats.
FIGURE 2. Mean left ventricular pressure-volume relation in control rats (●) and in rats 3 hr (○), 24 hr (△), 3 days (●), 5 days (●), and more than 22 days (▲) after infarction. With acute infarction there is a shift of the pressure-volume relation to the left. In the healing stages there is progressive rightward displacement of the pressure-volume relation.

The values for the chamber stiffness constants (K), the slope of the log pressure vs volume per kilogram relation) were as follows (table 3). K₀, the overall stiffness constant, was increased at 3 (p < .05) and 24 (p < .01) hr. K₀ returned to normal on day 3 and remained normal at 5 and more than 22 days.

K₁, the stiffness constant at low filling pressures, was increased (p < .01) at 3 and 24 hr compared with the control value and returned to normal on day 3. At day 5, K₁ showed a tendency to be decreased. K₁ was significantly decreased (p < .05) by greater than 22 days.

K₂, the stiffness constant at moderate filling pressures, was increased (p < .01) compared with the control value at 3 and 24 hr. K₂ returned to normal on day 3 and remained normal through day 22 after infarction.

K₃ and K₄, the chamber stiffness constants at high filling pressures did not change significantly from their control values of 2.42 ± 0.13 and 2.44 ± 0.10, respectively, at any time after acute myocardial infarction.

There were no significant differences with respect to any of the chamber stiffness constants between sham-operated rats and control. Differences between sham-operated rats and their corresponding cohort with infarction generally paralleled those already described for rats with infarction and controls. For example, compared with sham-operated controls, K₀ and K₁ were very significantly increased (p < .001) at 3 hr and 24 hr and very significantly decreased (p < .001) at more than 22 days in rats with infarction. K₂ likewise

TABLE 3
Left ventricular chamber stiffness constants and V/V₇ in control rats, sham-operated rats, and rats with large myocardial infarctions after coronary ligation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Time after infarction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K₀</td>
<td>3 hr</td>
</tr>
<tr>
<td></td>
<td>2.64 ± 0.14</td>
<td>(2.69 ± 0.09)^a</td>
</tr>
<tr>
<td></td>
<td>K₁</td>
<td>7.17 ± 0.43</td>
</tr>
<tr>
<td></td>
<td>K₂</td>
<td>2.23 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>K₃</td>
<td>2.42 ± 0.13</td>
</tr>
<tr>
<td></td>
<td>K₄</td>
<td>2.29 ± 0.14</td>
</tr>
<tr>
<td>V/V₇</td>
<td>0.603 ± 0.021</td>
<td>(0.598 ± 0.029)^p</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. Values in parentheses are those obtained from sham-operated animals.

^p < .05; ^b < .01, infarct group vs control.

^c p < .01; ^d p < .001 rats with infarction compared with sham-operated rats.
was significantly increased (p < .01) at 3 hr and 24 hr in the animals with infarction. However, $K_o$ measured at 3 days was significantly increased in the infarction group compared with the sham-operated control group.

\[ V/V_w \] This ratio was decreased (p < .05) from the control value of 0.603 ± 0.021 at 3 and 24 hr, and returned to normal on day 3. $V/V_w$ was significantly increased at day 5 (p < .05) and more than 22 days (p < .01) after infarction. There were no significant differences in $V/V_w$ in sham-operated rats and controls. However, when rats with infarction were compared with their sham-operated controls, the ratio was significantly decreased (p < .001) at 3 and 24 hr, and significantly increased (p < .001) at 5 days and more than 22 days in the former. These differences closely paralleled those between rats with infarction and the unoperated controls.

**Pathology.** Hearts studied 3 to 24 hr after coronary ligation demonstrated changes associated with hyperacute myocardial infarction with at least two of the following findings: (1) minimal to mild dilatation of the left ventricle, patchy congestion, patchy hemorrhage, hypereosinophilic muscle fibers, and contraction band necrosis, (2) dilatation of the left ventricle and unequivocal necrotic muscle fibers in a well-defined vascular distribution, edema, and congestion, and (3) a lack of inflammatory infiltrate. Hearts studied 3 days after coronary ligation had a brisk neutrophilic inflammatory infiltrate in addition to the findings described in the 3 to 24 hr group. Findings in rat hearts studied at 5 days after myocardial infarction were similar to those in the 3 day group but at 5 days there was significant granulation tissue with early fibrosis and less inflammatory cell infiltrate. All these hearts had wall thinning consistent with infarct expansion.\(^\text{14, 34}\) The last group was composed of rat hearts studied more than 22 days after myocardial infarction. These hearts had a portion of the left ventricle replaced by dense fibrous tissue, a dilated ventricular cavity, and wall thinning in the fibrous portion.

Percent infarct sizes in the groups were: 48 ± 3, 46 ± 3, 44 ± 4, 54 ± 2, and 44 ± 2 for 3 hr, 24 hr, 3 day, 5 day, and greater than 22 day cohorts, respectively. Percent infarct size in open-chest rats studied immediately after coronary occlusion was 44 ± 3.

**Discussion**

**Effects of acute coronary occlusion on left ventricular relaxation.** Our study is the first investigation to document the influence of progressive ischemia, acute myocardial infarction, and chronic myocardial infarction on left ventricular relaxation. Left ventricular relaxation was prolonged after 10 to 15 min of coronary artery occlusion and then returned to normal by 1 hr. Previous studies of left ventricular relaxation during myocardial ischemia induced by temporary coronary occlusion followed by reperfusion have generally found prolongation of global relaxation and return to normal relaxation with release of the ligation.\(^\text{2}\) We also found that acute coronary occlusion resulted in prolongation of left ventricular relaxation. With the evolution of established transmural myocardial infarction at 1 hr after coronary occlusion, relaxation returned to normal. This is consistent with the previous studies that demonstrated that left ventricular isovolumetric relaxation was not significantly prolonged 5 hr after coronary ligation produced myocardial infarction in dogs.\(^\text{25}\) The explanation for the bimodal behavior and changes over time in left ventricular relaxation after coronary ligation is unclear, but we speculate that myocardium with complete transmural necrosis no longer contributes to or has negligible influence on global relaxation, while relaxation in nonischemic myocardium is normal. In addition, infarcted myocardium may produce effects on loading conditions of the nonischemic myocardium adjacent to infarcted muscle, in which case there may be a shift to load dependency of relaxation.\(^\text{26}\)

**Effects of long-term coronary ligation on left ventricular relaxation.** Although T was dramatically prolonged shortly after coronary ligation, left ventricular relaxation measured in conscious rats returned to normal during the early healing phase after myocardial infarction. This normalization of relaxation occurred despite the changes in mean left ventricular peak systolic pressure, maximum dP/dt, and left ventricular end-diastolic pressure. However, after 5 days in rats with healing myocardial infarction and evidence of cardiac failure, left ventricular relaxation became significantly prolonged. This is in agreement with an earlier clinical study that demonstrated prolongation of left ventricular relaxation in patients with congestive heart failure secondary to coronary artery disease.\(^\text{27}\) The reasons for this are unclear. However, left ventricular hypertrophy in noninfarcted myocardium has been seen in patients with coronary artery disease.\(^\text{28}\) Since abnormal relaxation has been demonstrated in pathologic hypertrophy, it is possible that the development of compensatory hypertrophy in noninfarcted myocardium might exhibit the same relaxation abnormalities as those found in other states of pathologic hypertrophy.
pressure-volume relation after myocardial infarction. Using five chamber stiffness constants to characterize the passive pressure-volume relation, we were able to observe that progressive ischemia, acute infarction, and chronic healed infarction had no influence on the slope of the pressure-volume relation at distending pressures greater than 10 mm Hg. However, significant differences in the chamber stiffness constants at low (<10 mm Hg) filling pressures were responsible for a shift in the pressure-volume relation (figure 2).

Because we studied the time sequence of changes in the left ventricular pressure-volume relation, quantitated the relation by several stiffness constants, and used uniformly large myocardial infarctions, our results differ in certain respects from those of previous studies. For example, Forrester et al. reported a significant increase in left ventricular compliance measured 1 hr after acute myocardial infarction in dogs. The methods used by these investigators produced infarctions involving approximately 25% of the ventricle. In a later study, these same investigators showed that patients with acute myocardial infarction had decreased left ventricular compliance. In another earlier study, a significant decrease in ventricular volumes in vitro at normal (3 to 7 mm Hg) and elevated (10 to 40 mm Hg) left ventricular filling pressures was found in dogs 3 to 7 days after infarction. The decrease in ventricular compliance was inferred from the pressure-volume data since volume stiffness constants were not calculated. Average infarct size also was not reported by these investigators. In dogs studied at 3 to 4 weeks and then again at 6 to 8 weeks after infarction the left ventricular end-diastolic pressure was elevated, despite normal end-diastolic volumes. Thus, the pressure-volume relation was shifted to the left. Chamber stiffness constants were not calculated and average infarct size was only 11%. In patients with chronic healed myocardial infarction, Bleifeld et al. concluded that chamber stiffness was increased, although they did not analyze complete pressure-volume relations, while Fletcher et al. showed increased ventricular volumes and elevated filling pressures in rats with large (>45%) infarctions studied at 22 days after infarction. These later investigators also calculated linear and exponential volume stiffness constants and found that compliance increased at low distending pressures.

It is likely that the factors that contribute to the final passive-elastic properties of the damaged left ventricle are amplified differently during the various stages of ischemia and infarction. This point can be best illustrated by a semiquantitative analysis. Mirsky et al. suggest that a relationship exists between left ventricular chamber stiffness (dP/dV), muscle stiffness (EINV), and the V/Vw and have derived the following relation from a spherical model of the left ventricle:

\[
\frac{dP}{dV} = \frac{4}{9} \frac{E_{INV}}{V}/(1 + \frac{V}{V_w})
\]

According to this formulation, chamber stiffness is directly proportional to muscle stiffness and varies inversely with left ventricular volume and the V/Vw. In the present study, we found a decrease in V/Vw at 3 and 24 hr after acute myocardial infarction. This was associated with a leftward and upward shift in the pressure-volume relation (figure 2). This indicates an increase in chamber stiffness, a result predicted by the equation above.

Effect of infarct expansion on the pressure-volume relation. Recent morphologic data from human and animal studies have defined the anatomic and pathologic substrates of infarct expansion. In particular, studies in rats suggest that infarct expansion begins at 3 to 4 days, with the majority of rats with large infarctions demonstrating expansion at 5 to 7 days. Infarct expansion, since it increases left ventricular volume and V/Vw, would thus be expected to exert an influence on the pressure-volume relation at this time. Furthermore, according to Mirsky's formulation, it would influence the pressure-volume relation in a manner that opposes the effects of a possible increase in muscle stiffness. Thus, if the volume effects of left ventricular remodeling after infarction predominate over changes in myocardial stiffness, the changes in the pressure-volume relation will be largely a function of altered left ventricular size and will begin to be manifest precisely at the time that infarct expansion is evolving.

The direction and time course of change in the pressure-volume relation that we report conforms to this hypothesis. The data from our study further suggest that these influences begin between 24 hr and 3 days after large infarctions and continue into the late healing phase (>5 days). Finally, differences in whole ventricle passive-elastic properties of normal and infarcted myocardium are apparent primarily at low distending pressures, as shown by the steady decline in K1, the chamber stiffness constant from 0 to 3 mm Hg.

Despite the dynamic behavior of the pressure-volume relation in acute and healing large infarctions, it can be seen in figure 2 that operating chamber stiffness (dP/dV = KP at P = left ventricular end-diastolic pressure) is abnormally increased at all stages after myocardial infarction. This is true since left ventricular end-diastolic pressure is elevated at all stages after
large infarctions, and $K_s$ and $K_a$, the chamber stiffness constants for filling pressures of 10 to 30 mm Hg, are unchanged. Thus, in rat left ventricles that have sustained large infarctions, that portion of diastolic filling which contributes to stroke volume probably always occurs on the 'stiff' portion of the pressure-volume relation.

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References

24. Weisse AB, Soffa RS, Levinson GE, Jacobson WW, Regan T: Left ventricular function during the early and late stages of scar formation following experimental myocardial infarction. Am Heart J 79: 370, 1970
Serial changes in left ventricular relaxation and chamber stiffness after large myocardial infarction in rats.
T E Raya, R G Gay, L Lancaster, M Aguirre, C Moffett and S Goldman

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