Left Ventricular Diastolic Pressure-Volume Relations in Rats with Healed Myocardial Infarction

Effects on Systolic Function

Peter J. Fletcher, Janice M. Pfeffer, Marc A. Pfeffer, and Eugene Braunwald

SUMMARY To determine the effects of healed myocardial infarction on the diastolic compliance of the left ventricle, we studied 36 rats 26 days after left coronary artery ligation. Peak cardiac output and stroke volume were measured under ether anesthesia during volume loading, and peak left ventricular developed pressure was determined during occlusion of the ascending aorta. During a slow infusion of saline into the potassium-arrested left ventricle, diastolic pressure and volume were measured continuously over the pressure range —5 to 30 mm Hg. Infarct size was determined by planimetry of serial sections taken from each heart at 1-mm intervals from apex to base. In rats with healed infarcts, left ventricular volume was increased in proportion to infarct size and the diastolic pressure-volume relationship was shifted so that at pressures below 2.5 mm Hg volume was increased, resulting in an increased ventricular compliance in this low pressure range. Above this pressure, the slopes of the pressure-volume curves were similar in rats with and without infarctions. Peak cardiac output and pressure-generating capacity were impaired in proportion to infarct size. This impairment of cardiac performance correlated with the infarct size-related increase in diastolic volume, which served to offset the reduction in flow generating capacity caused by systolic dysfunction, while contributing directly to the impairment of pressure generating capacity. Circ Res 49: 618-626, 1981

THE development of left ventricular dysfunction is a well-recognized complication of myocardial infarction which has been observed to occur both in the acute phase and following recovery and which has been shown to exert an adverse effect on prognosis (Feild et al., 1974; Forrester et al., 1977, Weber et al., 1978). Changes in the curve relating left ventricular diastolic pressure and volume, i.e., in compliance (a change in volume relative to a change in pressure) have also been well-documented in patients with acute and healed infarction (Diamond and Forrester, 1972; Bleifeld et al., 1974; Smith et al., 1974a; Bertrand et al., 1978; Bertrand et al., 1979). The nature and degree of these changes in the diastolic properties of the left ventricle have been related to the site and extent of myocardial damage (Swan et al., 1972; Smith et al., 1974b; Bertrand et al., 1978; Bertrand et al., 1979).

Because measurement of the relationship between pressure and volume throughout diastole is difficult in humans, many investigators have had to rely on a limited segment of the diastolic pressure-volume relationship to characterize the diastolic properties of the left ventricle. However, the information derived from such measurements may be limited, since diastolic properties change as a function of end-diastolic pressure (Mirsky, 1976; Glantz, 1976).

In dogs, an increase in compliance occurs 1 hour after experimental myocardial infarction (Forrester et al., 1972) and is followed by a reduction in compliance in the healing phase, i.e., 3 to 5 days later (Hood et al., 1970). The latter has been demonstrated to be associated with an improvement in systolic function (Kumar et al., 1970). Since the infarcts produced in canine studies were relatively small, hemodynamic abnormalities were minor (Weisse et al., 1970; Kumar et al., 1970). Ligation of the left coronary artery in the rat can produce not only infarcts of a wide range of sizes, but after healing has occurred, a correspondingly wide spectrum of left ventricular dysfunction, from barely detectable impairment with infarcts up to 30% of the left ventricle to overt congestive heart failure with infarcts constituting greater than 46% of the left ventricle (Pfeffer et al., 1979). The purpose of the present study was to analyze the changes in the diastolic pressure-volume relations in the rat with

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healed myocardial infarctions ranging widely in size and to determine the relation between the observed changes in the diastolic properties and the systolic function of the left ventricle.

**Methods**

Thirty-six female normotensive American Wistar rats (West Jersey Biological Supply), ranging in age from 19 to 47 weeks and averaging 25 weeks, were studied. They were fed standard rat chow (Purina) and water ad libitum, housed in polyethylene cages, and maintained in a 12-hour light-dark cycle. During a preliminary operation, rats were anesthetized with ether, intubated, and placed on positive pressure ventilation (Harvard Rodent Respirator). The left coronary artery was ligated to produce myocardial infarction (23 rats) or a sham operation was performed (13 rats) as described previously (Maclean et al., 1978; Pfeffer et al., 1979).

Hemodynamic studies were performed 22-29 days (average 25 days) after coronary ligation or sham operation; by this time necrotic myocardium has been completely replaced by fibrous scar tissue in rats subjected to coronary ligation (Fishbein et al., 1978a). Under ether anesthesia, polyethylene cannulas were inserted into the trachea, the right carotid artery and jugular vein, and a femoral vein. Pressures were measured through a short segment of fluid-filled PE 50 tubing connected to a catheter tip manometer (Millar) via a three-way stopcock, with zero adjusted to mid-chest level. The undamped natural frequency of this catheter-transducer system was approximately 100 Hz. The carotid cannula was briefly advanced to the left ventricle, then withdrawn to the aortic arch. The jugular vein cannula was advanced to the right ventricle when possible, then withdrawn to the right atrium. Measurements were made, under light ether anesthesia and spontaneous respiration, of left ventricular systolic and end-diastolic pressures (LVEDP) and heart rate (HR), right ventricular systolic and end-diastolic pressures, and mean right atrial pressure (RAP).

Under positive pressure ventilation, a small anterior thoracotomy was performed and a calibrated flow probe (2.0 or 2.5 mm i.d.; Statham, Inc.) was placed around the ascending aorta for the measurement of phasic aortic blood flow and flow acceleration. With zero flow adjusted to end-diastole, mean aortic blood flow was obtained electronically and taken as cardiac output (CO), neglecting the coronary blood flow (Pfeffer and Frohlich, 1972). Cardiac output measured in this way agreed closely with that measured simultaneously with the radioactive microsphere reference sample technique in a separate group of rats. The relationship was: CO (microsphere) in ml/min = 0.68 CO (flowmeter) in ml/min + 0.094, r = +0.99. Systemic vascular resistance (SVR) was calculated as (MAP - RAP)/CO and was expressed as mm Hg/ml per min. Stroke work in gm.·m/beat was calculated as SV in ml x (MAP - RAP) in mm Hg x 0.0136.

After baseline measurements had been carried out over a 10-minute period to establish a stable state, warmed Tyrode’s solution was infused into a femoral vein at a rate of 40 ml/kg per min for 30 to 45 seconds. This infusion at first produces a rise in cardiac output followed by a plateau, despite further elevations in right atrial pressure (Pfeffer et al., 1976). Maximum pumping ability of each heart was defined as peak values of cardiac output (pCO) and stroke volume (pSV).

Fifteen minutes after the volume load, when all hemodynamic variables had returned to baseline levels, the flow probe was removed and the arterial catheter advanced into the left ventricle. The ascending aorta was briefly occluded around the catheter by a suture to produce contractions which were isovolumic except for coronary flow. Measurements were made of left ventricular peak systolic, end-diastolic, and developed pressures (peak systolic minus end-diastolic) from the first isovolumic beat and from the average of the six or seven cardiac cycles during the first second of aortic occlusion (Pfeffer et al., 1979). These measurements defined the maximum pressure-generating ability of the left ventricle. After completion of the afterload stress, we gave a second infusion of Tyrode’s solution while recording left ventricular and right atrial pressures to determine the maximum left ventricular end-diastolic pressure corresponding to the peak cardiac output and stroke volume. The diastolic volume which corresponded to this maximum end-diastolic pressure was obtained from the in vitro pressure-volume curve and in conjunction with the in vivo peak stroke volume attained during volume loading was used to derive an index of the ejection fraction, termed the ejection fraction index.

To define the passive pressure-volume characteristics of the left ventricle, the heart was arrested in diastole with potassium chloride and a double lumen catheter (PE 50 inside PE 200) was inserted 6 mm into the left ventricle via the aorta. The right ventricular free wall was incised to avoid fluid accumulation and a variable compressive force on the interventricular septum. The atrioventricular groove was ligated and the ventricle was compressed manually to expell blood and create a negative pressure of −5 mm Hg, which was taken as zero volume. Physiological saline was infused at 0.68 ml/min via one lumen while intraventricular pressure was continually recorded through the other lumen over the pressure range −5 to 30 mm Hg (Fig. 1). At least three reproducible pressure-volume curves were obtained within 10 minutes of cardiac arrest, well before the onset of rigor mortis. Ventricular volumes at pressures of 0, 2.5, 5, 10, 15, 20, and 30 mm Hg were determined from the pressure-volume curve. The pressure-volume curve was
linear from 0 to 2.5 mm Hg, and the pressure stiffness constant, $k_1$, was obtained from this portion of the curve. Above 2.5 mm Hg, pressure increased exponentially with volume, and stiffness constants, $k_2$, $k_j$, were calculated by fitting one exponential function of the form $P = b e^{kV}$ to the data from the intermediate pressure range (2.5 to 10 mm Hg) and a second exponential to the upper pressure range (15 to 30 mm Hg) (Fig. 1). Left ventricular chamber stiffness was derived as $dP/dV = kP$ from these exponential functions.

The method used to process the hearts for the measurement of infarct size differed slightly from that described previously (Fishbein et al., 1978a; Pfeffer et al., 1979). After the pressure-volume data had been recorded, the hearts were fixed in the distended form in 10% buffered formalin for 24 hours, then dissected into left ventricle plus interventricular septum and right ventricular free wall which were weighed separately. The whole left ventricle was dehydrated in alcohol, cleared in xylene, and embedded in paraffin. Transverse serial sections 50 μm thick were cut and every 20th section from apex to base (approximately every 1 mm) was mounted and stained with Masson’s trichrome from which hematoxylin was omitted to provide maximum discrimination between fibrous infarct and muscle (Fig. 2). Between 10 and 13 sections were obtained from each heart. The slides were projected with a magnification of 12X and the lengths of infarct and total left ventricle on both epicardial and endocardial surfaces of each section were measured with a planimeter (Numonics Corp.). Infarct size was calculated by dividing the sum of the planimetered endocardial and epicardial circumferences occupied by the infarct by the sum of the total epicardial and endocardial circumferences of the left ventricle.

Results are expressed as mean ± 1 SEM. One way analysis of variance was performed to determine the presence of significant differences between the various groups and to estimate the pooled error mean square. The significance of the difference between the mean of the control group and each of the three infarct groups was tested with Bonferroni’s modified t statistic for three planned comparisons (Gill, 1978). Linear correlation and least squares linear regression were performed according to standard methods.

Results

Autopsy Data

The 23 rats with left coronary artery ligation demonstrated well-healed areas of infarction, ranging from 12 to 46% of the left ventricular circumference. For analysis, rats with infarcts were divided into those with small infarcts (<30%, $n = 8$), moderate infarcts (30 to 39%, $n = 8$), and large infarcts (>40% $n = 7$). In these three groups, infarct sizes were 22 ± 2%, 34 ± 1%, and 43 ± 1% of the left ventricular circumference, respectively. Body weight and kidney weights of rats with and without infarctions were identical. Rats with large infarcts showed a slight (12%) but significant reduction in total left ventricular mass and a marked (63%) increase in right ventricular mass (Table 1).

Pressure-Volume Data

Ventricular volumes measured in the potassium-arrested heart were significantly increased in the three groups of rats with infarcts at transmural pressures from 2.5 to 30 mm Hg (Fig. 3A). The increase was substantial in that rats with large infarcts had 99 ± 10% greater volumes at 5 mm Hg than did rats without infarctions. However, most of this increase was already present at low (less than 2.5 mm Hg) transmural pressures (Fig. 3A). Thus, at 2.5 mm Hg, the difference in absolute volume between control and large infarct groups (0.236 ± 0.025 ml) was similar to that at 30 mm Hg (0.252 ± 0.038 ml). Figure 3B displays the same data on a logarithmic scale and demonstrates that the pressure-volume curves are parallel above 2.5 mm Hg and that an exponential function fits the data moderately well. However, there was a systematic deviation of the data from a single linear model with a change in the slope of the pressure-volume relation occurring at 10 mm Hg (Fig. 3B) and an analysis using separate exponential functions for inter-
mediate and high pressure ranges provided the best fit (Fig. 1). The stiffness constants were significantly greater in the high pressure range ($k_2$, 15–30 mm Hg) than in the intermediate pressure range ($k_1$, 2.5–10 mm Hg) in each group (Table 2), but there were no significant differences between rats with and without infarctions in either $k_2$ or $k_1$ (Table 2).

In the low pressure range (i.e., from 0 to 2.5 mm Hg) the stiffness constant, $k_i$, decreased significantly in proportion to infarct size (Table 2). Thus, healed infarction resulted in major increases in ventricular volume and compliance at transmural pressures less than 2.5 mm Hg. Above this pressure, the left ventricular pressure-volume curves were

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**TABLE 1 Left and Right Ventricular-to-Body Weight Ratios, Prethoracotomy Left Ventricular and Systemic Arterial Pressures of Control Rats and Rats with Myocardial Infarcts of Different Sizes**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>&lt;30%</th>
<th>30–39%</th>
<th>≥40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>13</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Left ventricular-to-body weight ratio (mg/g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.20 ± 0.06</td>
<td>2.22 ± 0.05</td>
<td>2.00 ± 0.10</td>
<td>1.95 ± 0.06*</td>
</tr>
<tr>
<td>Right ventricular-to-body weight ratio (mg/g)</td>
<td>0.57 ± 0.03</td>
<td>0.66 ± 0.03</td>
<td>0.65 ± 0.03</td>
<td>0.93 ± 0.08†</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>4 ± 1</td>
<td>6 ± 1</td>
<td>13 ± 2†</td>
<td>28 ± 2†</td>
</tr>
<tr>
<td>Arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>142 ± 4</td>
<td>136 ± 5</td>
<td>124 ± 5†</td>
<td>111 ± 4†</td>
</tr>
<tr>
<td>Diastolic</td>
<td>102 ± 3</td>
<td>104 ± 3</td>
<td>92 ± 4</td>
<td>86 ± 3†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

* $P < 0.05$; †$P < 0.01$, control vs. infarct group.
Hemodynamic Data

Prior to thoracotomy, rats with small infarcts had normal values for all variables (Table 1). In rats with large infarcts, the presence of right ventricular hypertrophy was associated with severe left ventricular dysfunction at rest, as evidenced by marked elevations in left ventricular end-diastolic pressure and a substantial reduction in systemic arterial pressure (Table 1). Rats with moderate infarcts and no right ventricular hypertrophy showed smaller reductions in arterial pressure and increases in left ventricular end-diastolic pressure. Following thoracotomy and placement of the flow probe, maximal preload stress with infusion of Tyrode’s solution revealed an increasing impairment of flow-generating capacity as infarct size increased (Table 3). Among the 23 rats with infarcts, there was a significant negative correlation between infarct size (IS) and peak cardiac index [pCI = 480 ml/min per kg - 4.9(IS); r = - 0.76, P < 0.01], peak stroke volume index [pSVI = 1.24 ml/kg - 0.01(IS); r = - 0.64, P < 0.01] and peak stroke work index [pSWI = 1.99 gm·m/kg - 0.027(IS); r = - 0.85, P < 0.01].

With maximal afterload stress during the first second of aortic occlusion, there was a highly significant reduction in left ventricular developed pressure (Dev P) (Table 3) which was also closely correlated with infarct size in the 23 rats with infarcts [Dev P = 243 mm Hg - 2.2(IS); r = -0.89, P < 0.01; Fig. 4].

The combining of data from the passive diastolic pressure-volume relation with that obtained in vivo during the hemodynamic study allowed a more accurate estimate of left ventricular systolic function. The ejection fraction index, at the time when peak cardiac output was reached during the infusion of Tyrode’s solution, varied inversely with infarct size (Fig. 5). Similarly, when the first isovolumic beat during aortic occlusion was analyzed, there was a close inverse relationship between the ventricular diastolic volume index (VI) and the subsequent developed pressure [Dev P = 288 mm Hg - 53 (VI); r = -0.93, P < 0.01; Fig. 6].

Discussion

The present study demonstrates that in rats with healed myocardial infarction there is an increase in

![Figure 3](image)

**Figure 3** Average left ventricular pressure and volume in control rats (n = 13) and in rats with small (n = 8), moderate (n = 8), and large (n = 7) myocardial infarctions. In A, pressure is displayed on a linear scale. In B, pressure is displayed on a logarithmic scale from 2.5 to 30 mm Hg to emphasize the similar slopes of the diastolic pressure-volume relationship at similar pressure levels.

<table>
<thead>
<tr>
<th>Infarct groups</th>
<th>Control 30-39%</th>
<th>30-39%</th>
<th>40-49%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiffness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k1 (0-2.5 mm Hg)</td>
<td>21.7 ± 1.4</td>
<td>124 ± 1.0*</td>
<td>82 ± 0.7*</td>
</tr>
<tr>
<td>k5 (2.5-10 mm Hg)</td>
<td>7.5 ± 0.3</td>
<td>7.4 ± 0.5</td>
<td>6.4 ± 0.5</td>
</tr>
<tr>
<td>k3 (15-30 mm Hg)</td>
<td>11.5 ± 0.8</td>
<td>11.9 ± 0.8</td>
<td>11.4 ± 0.5</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

* P < 0.01, control vs. infarct group.
left ventricular diastolic volume at low transmural filling pressure, that this increase is a function of infarct size, and that the diastolic pressure-volume curve is shifted in parallel fashion, on the volume axis, at normal and high filling pressures. Furthermore, the degree of left ventricular dilation correlates closely with the impairment of cardiac performance which previously had been observed to be related to infarct size.

In dogs with experimental myocardial infarction, only small increases in left ventricular volume have been reported early (1 hour) after infarction (Forrester et al., 1972), followed by a leftward shift of the pressure-volume curves in the convalescent phase due to an increased stiffness of the infarcted segment (Hood et al., 1970; Weisse et al., 1970). The latter is widely regarded as an important cause of elevated left ventricular filling pressures in patients following myocardial infarction (Swan et al., 1972). The presence of relatively normal ventricular volumes after coronary occlusion may be related to the relatively small size and range of infarct sizes which are associated with only minor degrees of functional impairment in the recovery phase (Kumar et al., 1970; Weisse et al., 1970). In contrast, the rat model displays a wide range of infarct sizes and the whole range of functional impairment observed clinically, from barely detectable changes to overt congestive heart failure (Pfeffer et al., 1979). Another major difference between this study and that carried out by Hood et al. (1970) on dogs was that the latter's observations were made 3-5 days after ligation when extensive myocardial necrosis is still present. In the rat studied more than 3 weeks after coronary occlusion, all necrotic and inflammatory tissue has been replaced by fibrous scar (Fishbein et al., 1978a), a change which occurs in humans only after several weeks to months following infarction (Fishbein et al., 1978b).

In patients studied within 3 weeks of acute infarction, shifts of the diastolic pressure-volume relationship in both directions have been reported

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**TABLE 3** Peak Cardiac Output, Peak Stroke Volume, Mean Arterial Pressure, Peak Stroke Work and Peak Left Ventricular End-Diastolic Pressure during Infusion of Tyrode's Solution, and Maximum Left Ventricular Developed Pressure during the First Second of Aortic Occlusion in Control Rats and Rats with Myocardial Infarction

<table>
<thead>
<tr>
<th>Metric</th>
<th>Control</th>
<th>&lt;30%</th>
<th>30-39%</th>
<th>≥40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak cardiac output (ml/min)</td>
<td>120 ± 6</td>
<td>101 ± 7*</td>
<td>86 ± 5†</td>
<td>80 ± 4†</td>
</tr>
<tr>
<td>Peak stroke volume (ml/beat)</td>
<td>0.34 ± 0.01</td>
<td>0.27 ± 0.011</td>
<td>0.26 ± 0.02†</td>
<td>0.23 ± 0.01†</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>104 ± 4</td>
<td>112 ± 5</td>
<td>95 ± 4</td>
<td>92 ± 3</td>
</tr>
<tr>
<td>Peak stroke work (g-m/beat)</td>
<td>0.43 ± 0.02</td>
<td>0.38 ± 0.03</td>
<td>0.30 ± 0.02†</td>
<td>0.25 ± 0.02†</td>
</tr>
<tr>
<td>Peak left ventricular end-diastolic pressure (mm Hg)</td>
<td>18 ± 1</td>
<td>23 ± 1†</td>
<td>24 ± 1†</td>
<td>35 ± 2†</td>
</tr>
<tr>
<td>Maximum left ventricular developed pressure (mm Hg)</td>
<td>226 ± 3</td>
<td>196 ± 5†</td>
<td>169 ± 4†</td>
<td>148 ± 4†</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM

* P < 0.05, †P < 0.01, control vs. infarct group.

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**Figure 4** Relationship of maximum developed pressure (max dev P) to infarct size (IS,%) in 23 rats with myocardial infarcts ranging from 12 to 46% of the left ventricular circumference. The solid line and hatched area are the mean ± 2 SD for the 13 rats without infarcts.

**Figure 5** Relationship of ejection fraction index (EFI,%) calculated as described in the text, to infarct size (IS,%) in 23 rats with myocardial infarcts ranging from 12 to 46% of the left ventricular circumference. The solid line and hatched area are the mean ± 2 SD for the 13 rats without infarcts.
(Bertrand et al., 1978, 1979). Betrand et al. (1978) documented shifts to the right (larger volumes at any given pressure) in four patients with anterior infarction studied sequentially. Studies in the healed phase of myocardial infarction (2-12 months after the event) demonstrated an increased end-diastolic volume in approximately 50% of all patients (Feild et al., 1974), and in patients with clinical evidence of heart failure, end-diastolic volumes were increased in almost 90% of cases (Baxley et al., 1971). Kitamura et al. (1973) found that, in patients with a healed anterior infarction, end-diastolic volumes were uniformly increased when the antero-apical scar occupied more than 20% of the left ventricular circumference. In many patients with myocardial infarction it is difficult to define the diastolic pressure-volume relation of the left ventricle, since both end-diastolic pressure and volume are increased. Under these circumstances one cannot determine whether the dilation represents only upward movement along a normal diastolic pressure-volume curve and/or a rightward shift (increased volume at any pressure) of the pressure-volume curve and/or a rightward shift (increased volume at any pressure). One cannot determine whether the dilation represents only upward movement along a normal diastolic pressure-volume curve and/or a rightward shift (increased volume at any pressure) of the pressure-volume curve.

The present study indicates that both of these mechanisms contribute to the increased end-diastolic volume in healed anterior myocardial infarction in the rat. [Most of the rats in this investigation had infarcts constituting more than 20% of the left ventricle (Fig. 4) and are comparable to moderately to-large infarcts in patients (Kitamura et al., 1973).] Moreover, the complex shape of the curves (Fig. 1) indicate the hazard of assessing ventricular diastolic properties from a limited number of pressure-volume coordinates. Many investigators have used linear (Smith et al., 1974a, 1974b), exponential (Gaasch et al., 1976; Bertrand et al., 1978; 1979), or even more complicated derived indices (Diamond and Forrester, 1972; Bleifeld et al., 1974; Laird, 1975) with variable findings. In the present study it was observed that the diastolic pressure-volume relationship is not a single exponential, even if one excludes the linear segment below 2.5 mm Hg (Diamond et al., 1971). We have used two separate exponential functions purely to define different regions of the curve and permit mathematical comparisons between rats with and without infarctions, but even this is an oversimplification.

Our findings are not consistent with the assumption that the intercept of the curve on the volume axis is constant and that its slope is variable (Gaasch et al., 1976; Bertrand et al., 1979). Rather, we observed that it is the intercept which varies as a function of infarct size while the slope remains constant (Fig. 3B). The effect of this type of alteration of the left ventricular pressure-volume relation depends largely on the level of end-diastolic pressure. Thus, at transmural pressures below 2.5 mm Hg, compliance is increased in direct proportion to infarct size, i.e., the change in volume relative to a change in pressure is increased as infarct size increases. Above 2.5 mm Hg, the curves are shifted in parallel and are independent of infarct size. Thus, compliance is reduced in infarcted ventricles with higher end-diastolic pressures, largely because they operate on a progressively steeper part of the diastolic pressure-volume relationship.

When ventricular pressure was below 2.5 mm Hg, the infarcted area of the left ventricle appeared to be collapsed, and the initial filling from 0 to 2.5 mm Hg was associated with distension of the scar. The close relationship between infarct size and the increase in ventricular volume existing at low filling pressures implies that the physical distension of infarcted tissue is the major factor operating to shift the pressure-volume curve to the right. On histological examination, the infarcted areas were composed largely of fibrous tissue and were free of muscle, suggesting that their diastolic length-tension relations should be similar to that of the fibrous aneurysms which Parmley et al. (1973) reported were very much stiffer than normal cardiac muscle. When the relatively low transmural pressure of 2.5 mm Hg was reached, the infarct was fully distended and, at higher pressures, it operated on the very steep part of its length-tension curve as a relatively rigid, inextensible fibrous scar, and the increase in ventricular volume over the remainder of the pressure-volume curve was determined largely by the diastolic properties of the residual myocardium. The shift to the right of the pressure-volume relationship of the infarcted ventricles occurs at low pressures and therefore does not necessarily imply that muscle compliance is shifted in a similar direction (Spotnitz and Sonnenblick, 1973, Mirsky, 1979).
Whatever the mechanisms underlying the change in the diastolic properties of the infarcted left ventricle, left ventricular dilation may account for the relationship between infarct size and impairment of peak cardiac performance, which we reported previously (Pfeffer et al., 1979) and which was confirmed in the present study. Although coronary artery occlusion in rats provides an experimental model of ventricular function following recovery from a myocardial infarction, care must be taken in direct comparisons with studies in humans. Ventricular performance post-myocardial infarction in humans may be complicated by the status of the residual myocardium, extent of coronary artery disease, presence or absence of valvular heart disease, arrhythmias, and variables not present in the rat model. Nevertheless, the inverse relationship between the index of ejection fraction and infarct size observed in the rat (Fig. 4) is very similar to that reported for patients by Kitamura et al. (1973), Horii et al. (1977), and Bertrand et al. (1979). The closeness of the observed relationship is remarkable, considering that it was derived from three independent experiments (peak stroke volume, ventricular diastolic pressure, and ventricular diastolic volume) and emphasizes the central role of changes in cardiac morphology in the functional significance of the diastolic pressure-volume relationship in vivo. Although both left ventricular developed pressure and volume at any given distending pressure are related primarily to infarct size, the relationship between them is not likely to be fortuitous. Moreover, the overall linearity of the relationship between left ventricular developed pressure and volume (Fig. 3B) suggests that peak systolic wall tension is close to normal, even in large infarcts, implying that systolic performance is normal in non-infarcted muscle, as suggested by findings on the function of non-infarcted papillary muscle in rats with large infarcts (Radvany et al., 1978).

The dilation resulting from the rightward shift of the ventricular pressure-volume curve preserves the pumping ability of the ventricle. Animals with normal left ventricles operate on the relatively compliant portion of their pressure-volume curve near 5 mm Hg (Fig. 1) and volume loading produces large increases in both diastolic volume and stroke volume until the stiff, noncompliant portion of the pressure-volume curve is reached, at left ventricular diastolic pressures in the range of 15-20 mm Hg. Rats with healed infarcts have pressure-volume curves of similar shape, but operate at end-diastolic pressures which are higher and therefore on steeper portions of their pressure-volume curves. Volume loading produces smaller increases in both diastolic and stroke volumes, reflecting a reduced preload reserve. Rats with large infarcts operate at almost maximum preload, i.e., on the stiff, noncompliant portion of the pressure-volume curve to maintain resting flow, and volume loading results in a minimal additional increase in diastolic volume and stroke volume.

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