Influence of the Pericardium on Left Ventricular End-Diastolic Pressure-Segment Relations during Early and Later Stages of Experimental Chronic Volume Overload in Dogs

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SUMMARY. Although the pericardium can exert a restraining effect on filling of the normal left ventricle, it is uncertain to what extent the pericardium influences left ventricular filling during chronic volume overload. We measured left and right ventricular pressure and left ventricular segment dimension before and after pericardiectomy over a range of left ventricular end-diastolic pressure from \( \geq 5 \) to \( \geq 20 \) mm Hg in open-chest dogs with volume overload due to a prior systemic arteriovenous fistula. In six dogs studied “early” (7-9 days) during volume overload, left ventricular end-diastolic dimension was significantly larger and right ventricular end-diastolic pressure lower following pericardiectomy at matched levels of left ventricular end-diastolic pressure greater than 10-12 mm Hg. In six dogs studied “late” (34-50 days) during chronic volume overload, there were no significant changes in left ventricular end-diastolic dimension after pericardiectomy at comparable levels of end-diastolic pressure. To account for the influence of changes in right ventricular end-diastolic pressure after pericardiectomy, we also compared left ventricular end-diastolic dimensions before and after pericardiectomy at matched “corrected” left ventricular end-diastolic pressure \[ \text{(left ventricular end-diastolic pressure)} - \text{(right ventricular end-diastolic pressure \times interventricular septal surface area/total left ventricular surface area)} \]. This “correction” of the left ventricular end-diastolic pressure did not significantly alter the results in either the “early” or “late” group. These results indicate that restraint to filling by the pericardium in this model of volume overload is present early but becomes markedly diminished during later phases. (Circ Res 50: 501-509, 1982)

A NUMBER of prior studies have demonstrated that the pericardium may normally restrain left ventricular filling (Hefner et al., 1961; Bartle et al., 1968; Spotnitz and Kaiser, 1971; Glantz et al., 1978; Shirato et al., 1978; Mirkky and Rankin, 1979; Stokland et al., 1980). Although the absolute magnitude of this effect and the level of diastolic pressure and volume at which it begins are uncertain, it appears to be present consistently at left ventricular diastolic pressures above the normal operating range. Therefore, early during the course of volume overload lesions, before there has been a chance for either major left ventricular dilatation and hypertrophy, it is possible that the pericardium might have a physiologically significant restraining effect, providing the left ventricular diastolic pressure is abnormally elevated. Indeed, there is inferential evidence in patients (Bartle and Hermann, 1967) that this occurs. However, there is no information available as to whether the effect persists during later phases of chronic volume overload or whether, instead, the pericardium enlarges in parallel with an increase in cardiac mass, thus diminishing any restraining effect. In the present study, we sought to determine directly whether the pericardium limits left ventricular filling early during the course of experimental chronic volume overload by comparing left ventricular diastolic pressure and dimension before and immediately after pericardiectomy. Second, in order to determine whether such an effect changes with time, we performed an identical protocol later during chronic volume overload, at a time when significant cardiac hypertrophy had occurred.

Methods

We first produced a chronic volume overload state in 12 mongrel dogs weighing 17-33 kg by surgical construction of an approximately 1 cm long, side-to-side infra-renal anastomosis of the inferior vena cava and abdominal aorta. This anastomosis was produced through a midline abdominal incision after anesthesia with pentobarbital (25 mg/kg). After recovery, the following experimental protocol was carried out in each animal, in one group of six after 7-9 days of volume overload (termed “early” volume overload) and in the remaining six after an average of 41 (range 34-50) days of volume overload (termed “late” volume overload).

The experimental protocol consisted of first anesthetizing the animals with morphine sulfate (3 mg/kg) and chloralose (90 mg/kg). The chest then was opened through a midline sternotomy while ventilation was maintained with a positive pressure respirator attached to auffed endotracheal tube. After the chest had been opened, a 7F pigtail catheter was passed from the left carotid artery into the left ventricle.
Left ventricular pressures then were recorded through this catheter with a Statham P23Db transducer with zero reference level at the mid-right atrium, while respiration was suspended at end-expiration. Recording of a suitable limb lead electrocardiogram was also begun at this time. The left ventricular end-diastolic pressure present at this point of the procedure was noted and is subsequently referred to as the "operating" left ventricular end-diastolic pressure. Propranolol, 1 mg/kg, was then administered intravenously in an attempt to obtain as low a heart rate as possible during the rest of the procedure. A catheter identical to that inserted into the left ventricle was advanced into the right ventricle from the internal jugular vein and also connected to a Statham P23Db pressure transducer, and a Konigsberg P-20 micromanometer transducer was advanced from a left pulmonary vein across the mitral valve and into the left ventricle. For purposes of timing left ventricular end-diastolic as precisely as possible, all subsequent left ventricular end-diastolic pressures were determined from the micromanometer as described below. An ultrasonic dimension gauge (Horwitz et al., 1968) was then implanted in the subendocardial layer of the anterior free wall of the left ventricle through a pericardial incision no larger than 2 cm in length. The piezoelectric crystals comprising the gauge were positioned about 1 cm apart and oriented approximately perpendicular to the ventricular wall halfway between apex and base. The crystals then were connected to a sonomicrometer (Schuessler and Associates) which was coupled to a DC amplifier. The distance between the two crystals is proportional to the transit time of sound between them. The transit time is converted to a voltage by the sonomicrometer-amplifier system which, in turn, was calibrated with a signal of known delay. By means of a similar sonomicrometer system, the length of a minor axis segment of this magnitude has previously been shown to correlate well with overall ventricular volume during acute studies (Buge-Asperheim et al., 1969). Once a satisfactory dimension signal was obtained, the pericardial incision was loosely reapproximated. Finally, an inflatable occlusion cuff was positioned about the inferior vena cava and a femoral vein was cannulated for administration of fluids.

The caval occlusion cuff then was inflated until the left ventricular end-diastolic pressure was 5 mm Hg or less, and recordings of left and right ventricular pressure and left ventricular dimension were made with respiration again suspended at end-expiration. The caval occlusion cuff then was deflated step-wise to increase left ventricular end-diastolic pressure by increments of 2-4 mm Hg until the cuff was completely deflated. Recordings were repeated after each cuff deflation. After complete deflation of the occlusion cuff, a solution of 6% dextran in 0.9% NaCl was administered intravenously in 50-ml increments, and recordings once again were made as left ventricular end-diastolic pressure was raised to at least 20 mm Hg. Once this level of end-diastolic pressure was obtained, the caval occlusion cuff was reinflated to reduce left ventricular end-diastolic pressure to a level as close to the "operating" level as possible. End-diastolic pressure was maintained at this level by further small inflations or deflations of the occlusion cuff, a solution of 6% dextran in 0.9% NaCl was administered intravenously in 50-ml increments, and recordings once again were made as left ventricular end-diastolic pressure was raised to at least 20 mm Hg. Once this level of end-diastolic pressure was obtained, the caval occlusion cuff was reinflated to reduce left ventricular end-diastolic pressure to a level as close to the "operating" level as possible. End-diastolic pressure was maintained at this level by further small inflations or deflations of the occlusion cuff as necessary for 15-20 minutes. The pericardium then was incised widely and the sequence of vena caval cuff inflation and deflation, followed by dextran infusion, was repeated. Heart rate remained quite constant during the course of caval cuff deflation and dextran infusion in both the "early" and "late" volume overload group, averaging 93 ± 10.4 (s) beats/min at time of maximal cuff inflation and 91 ± 11.3 beats/min at time of maximal dextran infusion. All data points were obtained by averaging at least 10 cardiac cycles and an equilibrium period of at least 20-30 seconds was allowed after each step-wise cuff deflation and increment of dextran infusion. Left ventricular pressure was obtained from the micromanometer catheter after it had been matched to the simultaneous fluid-filled pressure recording at peak systolic pressure and either end-diastole or during slow filling. The micromanometer was balanced and checked for linearity before each procedure, and the tracing was checked frequently for drift throughout each study. Left ventricular end-diastolic pressure was identified as the pressure trough following the a wave. If no clear a wave or trough was identifiable, end-diastolic pressure was taken at the peak of the electrocardiographic R wave. Right ventricular end-diastolic pressure was obtained from the fluid-filled catheter in a similar fashion as left ventricular end-diastolic pressure. Left ventricular end-diastolic dimension was taken as the dimension at time of end-diastolic pressure. All data were recorded on a Brush-Clevite Model 2000 polygraph at paper speeds of 100 or 200 mm/sec.

For statistical purposes, we compared left ventricular end-diastolic pressure-dimension relations before and after pericardiectomy in both the "early" and "late" volume overload groups with two techniques. Using the first technique, we selected paired data points before and after pericardiectomy by matching heart rate by no more than 1 mm Hg of left ventricular end-diastolic pressure and which were as close as possible to 5, 11, 18 mm Hg and the highest level of end-diastolic pressure recorded. Left ventricular end-diastolic dimension then was compared at these matched levels of end-diastolic pressure, using the paired t-test. In addition, since there were alterations in right ventricular end-diastolic pressure before and after pericardiectomy when compared at matched left ventricular end-diastolic pressure (see Results), we also attempted to account for the influence of these changes in right ventricular diastolic pressure on the left ventricular end-diastolic pressure-dimension relation by "correcting" the left ventricular end-diastolic pressure for the "effective" right ventricular end-diastolic pressure, as suggested by Mirsky and Rankin (1979). Specifically, the "corrected" left ventricular end-diastolic pressure = (measured left ventricular end-diastolic pressure) - (right ventricular end-diastolic pressure × interventricular septal surface area/total left ventricular surface area). Septal and total left ventricular surface areas were determined directly postmortem (see Results, below). As previously, statistical comparisons were made by comparing left ventricular end-diastolic dimension before and after pericardiectomy, in this case at matched "corrected" left ventricular end-diastolic pressures. Data points selected before pericardiectomy were identical to those used for comparisons of end-diastolic dimensions at "uncorrected" left ventricular end-diastolic pressures. Data points after pericardiectomy were then selected which differed by no more than 1 mm Hg of "corrected" left ventricular end-diastolic pressure.

The second technique, which was used to further test statistically whether a shift of the end-diastolic pressure-dimension relation was present after pericardiectomy in both groups and to quantify the magnitude of any significant shifts, involved modification of an approach recently suggested by Glantz (1980). As originally described, this method was designed to test for parallel shifts of the diastolic pressure-volume relation by fitting pressure-volume data to a fourth order polynomial of the form

\[
p(V) = a_4 V^4 + a_3 V^3 + a_2 V^2 + a_1 V + a_0 + S(b)
\]
where \( p \) = pressure, \( V \) = volume, and \( S \) is a dummy variable which = 0 for the control pressure volume curve and 1 for the curve to be tested for a possible shift. The term \( b \), therefore, represents the average parallel shift (in mm Hg) of the second curve. Standard errors of the estimate of the shift may then be calculated, along with confidence intervals for its magnitude and a \( t \) statistic to test for significance of the shift. We modified this technique by substituting end-diastolic dimension (\( d \)) for volume in the polynomial equation and empirically adding an additional constant (\( c \)) multiplied by the fractional change in \( d \) (\( \Delta d \)) to the coefficient of the dummy variable so that the final equation was

\[
p(d) = a_d + a^2_d + a^3_d + b_d + c \cdot \Delta d.
\]

Using this modification, if \( b \) was significant after pericardectomy, a parallel shift of the pressure-dimension relation was deemed to be present, whereas if \( c \) was significant, a non-parallel shift proportional to \( \Delta d \) was present. We restricted our analysis to data points with end-diastolic pressures of 5 mm Hg or greater, since values less than 5 mm Hg were not available in all animals. To simplify comparison between animals, we assigned a value of 1 to the end-diastolic dimension present before pericardectomy at an end-diastolic pressure of 5 mm Hg or, if a data point was not available at this level of end-diastolic pressure, we assigned this value to whichever data point was closest to 5 mm Hg. Other values for \( d \) were then calculated in reference to the dimension assigned a value of 1.

At the end of each study, the animal was killed by an overdose of pentobarbital. The heart was then excised and the aorta, pulmonary artery, venae cava, and pulmonary veins were sectioned at their junctions with the cardiac chambers. The entire heart was weighed. Following this, the atria and right ventricle were trimmed and the intact left ventricle was weighed. To obtain a ratio of septal-to-left ventricular surface area, the interventricular septum was trimmed from the remainder of the left ventricle and its surface area and that of the remainder of the left ventricle measured directly by planimetry of tracings of the tissues. Total heart weight and left ventricular weight were normalized to the weight of each animal before arteriovenous fistula surgery and compared in the "early" and "late" groups by employing the unpaired \( t \)-test.

### Results

#### "Early" Volume Overload Group

The "operating" left ventricular end-diastolic pressure in this group averaged 17.8 \( \pm \) 2.9 mm Hg. From visual inspection of the pressure-dimension data points, the relation between left ventricular end-diastolic pressure and dimension appeared to be shifted downward and to the right after pericardectomy in all of these dogs. The level of end-diastolic pressure at which this shift was apparent and the magnitude of the shift were variable. Thus, in three animals, a shift was apparent at end-diastolic pressures as low as the 5 mm Hg range. At end-diastolic pressures above 10-12 mm Hg, a shift was apparent in each animal. Examples of the end-diastolic pressure-dimension relation obtained before and after pericardectomy in two of this group are presented in Figure 1, and tracings obtained at closely matched end-diastolic pressure before and after pericardectomy are shown in Figure 2. The magnitude of the pericardial effect is illustrated by the examples shown in Figure 1, with the top example representing one of the larger shifts and the bottom the smallest shift. Statistical comparisons of this group at matched levels of left ventricular end-diastolic pressure before and after pericardectomy are shown in Figure 3. The increase in end-diastolic dimension following pericardectomy was statistically significant at the two highest levels of end-diastolic pressure. At the 11 mm Hg range, it did not quite reach statistical significance at the \( p < 0.05 \) level (\( P = 0.059 \)). Also shown in Figure 3 is the right ventricular end-diastolic pressure obtained before and after pericardectomy at matched left ventricular end-diastolic pressure. After pericardectomy there was a modest, but consistent, decrease in right ventricular end-diastolic pressure, which would favor a shift of the interventricular septum to the right. This decrease in right ventricular end-diastolic pressure was significant at all four levels of left ventricular end-diastolic pressure. Comparison of left ventricular end-diastolic dimension at matched levels of "corrected" end-diastolic pressure before and after pericardectomy resulted in very little alteration in the
rightward shift of this relation which was observed using the "uncorrected" end-diastolic pressure because the decline in right ventricular end-diastolic pressure following pericardiectomy was relatively small (Fig. 3) and the ratio of septal-to-total left ventricular surface area was invariably close to 0.3 (see "Postmortem Results"). An example is provided in Figure 4, in which group data are shown for end-diastolic dimension at an "uncorrected" left ventricular end-diastolic pressure in the 18 mm Hg range before and after pericardiectomy and plotted together with the "corrected" end-diastolic pressure-dimension data obtained at this same level of "uncorrected" end-diastolic pressure.

By the polynomial fitting technique, a significant shift of the end-diastolic pressure-dimension relation was judged to be present in each animal in this group. Values for the constants b and c, along with their statistical significance and correlation coefficients for the polynomial fit, are presented in Table 1, while an example of the fitting technique in one of these animals is shown in Figure 5, top. The constant b was significant alone in four animals, indicating a parallel shift, while c was significant alone in one animal, indicating a non-parallel shift proportional to Ad. In one animal, both b and c were significant. Except for one animal with an r value of 0.74—which had the largest shift following pericardiectomy—correlation coefficients for the polynomial fit were all greater than 0.83.

"Late" Volume Overload Group

The "operating" left ventricular end-diastolic pressure averaged 16.8 ± 3.1 mm Hg in this group. In contrast to the "early" volume overload group, no consistent change in the left ventricular end-diastolic pressure-dimension relation was observed following...
TABLE 1

Values* for Constants b and c and r Values for Fourth Order Polynomial Fit

<table>
<thead>
<tr>
<th>Dog no.</th>
<th>b</th>
<th>P</th>
<th>c</th>
<th>P</th>
<th>r</th>
</tr>
</thead>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-31.7</td>
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<td>&lt;0.001</td>
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</tr>
<tr>
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<td>&lt;0.001</td>
<td>0.88</td>
</tr>
<tr>
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<td>-24.6</td>
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<td>0.86</td>
</tr>
<tr>
<td>5</td>
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<td>-</td>
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</tr>
<tr>
<td>6</td>
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<td>&lt;0.04</td>
<td>-</td>
<td>-</td>
<td>0.92</td>
</tr>
<tr>
<td>Late group</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.89</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.91</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.97</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.92</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-18.1</td>
<td>&lt;0.03</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* Dashes indicate that b or c were not significant at P < 0.05 level.

Pericardiectomy. On visual inspection of the pressure-dimension data points, minimal rightward shifts in this relation appeared to be present in three animals at relatively high levels of left ventricular end-diastolic pressure following pericardiectomy, an example of which is shown in Figure 6.

Grouped data comparing end-diastolic pressure and dimension at matched end-diastolic pressure before and after pericardiectomy are shown in Figure 7. There was no significant change in end-diastolic dimension at any level of end-diastolic pressure. As also shown in Figure 7, right ventricular end-diastolic pressure tended to be lower after pericardiectomy at matched left ventricular end-diastolic pressure, but this was statistically significant only at the 18 mm Hg level. “Correction” of the left ventricular end-diastolic pressure in this group, once again, did not significantly influence the results.

Results of the polynomial fitting technique in this group are presented in Table 1 and an example of the application of this technique to one of the animals is shown in Figure 5, bottom. Based on this technique, there was a significant shift in the pressure-dimension relation in one of this group (see Fig. 5), with only the c term being significant, indicating a nonparallel shift. All r values for the polynomial fit were 0.89 or greater.

Postmortem Results

In the “early” volume overload group, total heart weight to body weight ratio was 6.9 ± 0.52 g/kg, while in the “late” volume overload group, this ratio was 8.6 ± 0.61 g/kg (P < 0.001). In the “early” volume overload group, left ventricular weight to body weight ratio was 4.2 ± 0.34 g/kg, whereas in the “late” volume overload group, this ratio was 5.3 ± 0.41 g/kg (P < 0.001). The ratio of septal surface area to total left ventricular end-diastolic pressure-dimension relation before and after pericardiectomy in a “late” volume overload dog. In this case, there is a very small rightward shift of this relation at higher levels of end-diastolic pressure. LVEDP = left ventricular end-diastolic pressure; LVEDD = left ventricular end-diastolic dimension.
left ventricular surface area was very similar in both groups, averaging 0.32 ± 0.03 in the “early” volume overload group and 0.31 ± 0.02 in the “late” volume overload group.

Discussion

Based on studies which indicate that, in the normal dog, the pericardium can restrain left ventricular filling (Hefner et al., 1961; Bartle et al., 1968; Spotnitz and Kaiser, 1971; Glantz et al., 1978; Shirato et al., 1978; Mirkny and Rankin, 1979; Stokland et al., 1980), and consistently does so at levels of diastolic pressure higher than the normal operating range, it is possible that in acute volume overload lesions, such as mitral or aortic regurgitation, elevation of left ventricular diastolic pressure at a given diastolic volume is in part due to the influence of the pericardium. It has also been noted, in patients, that there are similarities between the hemodynamics of acute, severe volume overload and that of constrictive pericardial disease, particularly the occurrence of equalization of diastolic pressures in the cardiac chambers (Bartle and Herrmann, 1967). To prove that pericardial restraint occurs, however, and to quantify its magnitude, it is most desirable to compare diastolic pressure and volume (or dimension) immediately before and after removal of the pericardium. In the present study, we sought to document the occurrence of pericardial restraint to filling early during the course of chronic volume overload both by comparing diastolic left ventricular dimensions at selected, closely matched levels of diastolic pressure before and after pericardiectomy and by fitting all the observed pressure-dimension data points to a fourth-order polynomial which allowed statistical testing of the significance of any change in the diastolic pressure-dimension relation. Whereas the level of diastolic pressure at which pericardial restraint was apparent and the magnitude of the pericardial effect were variable in this group of animals, such an effect was invariably present at diastolic pressures above the normal operating range and, in particular, at what we have defined as the “operating level” of left ventricular end-diastolic pressure. It must be recognized that this “operating” level is somewhat arbitrary, because the animals were anesthetized and may not have had hemodynamic conditions comparable to those present in the conscious state. Although, under these conditions, the operating level of end-diastolic pressure was uniformly increased and was quantitatively similar to that present in other studies employing the arteriovenous fistula model in conscious dogs (Taylor et al., 1968; McCullough et al., 1972; LeWinter et al., 1980), it is important to note that in prior studies using this model the pericardium was disrupted prior to measurement of the left ventricular pressure. Hence, it is unknown to what extent left ventricular diastolic pressure would actually have been elevated had measurements been made in the conscious, unsedated state with an intact pericardium. Nonetheless, the levels of “operating” diastolic pressure which we recorded are similar to, and, if anything, lower than, those recorded in most patients with acute, severe volume overload lesions.

As indicated previously, the level of diastolic pressures at which pericardial restraint was apparent was variable, as was the magnitude of this effect. This latter point is underscored by the variability noted in the constants b and c obtained from the polynomial fits of the data. There are at least three factors which could have contributed to this variability. First, Stokland et al. (1980) have shown that large (6–7 cm), reapproximated pericardial incisions artifically magnify pericardial restraining effects. Although we attempted to keep the pericardial incision small and uniform in size and to loosely reapproximate its edges, the possibility that some variability was due to the pericardial incision itself cannot be excluded. Second, it is likely that, even after 1 week of volume overload, small and possibly variable amounts of hypertrophy had already occurred (Wikman-Coffelt et al., 1979) which could have influenced the relationship between the pericardium and the level of left ventricular filling. Third, pericardial strips exhibit creep when appropriately loaded (Rabkin et al., 1974). To the extent that early pericardial creep may have occurred, it is possible that the pericardium may have been variably prestretched as a result and, hence, variably stiffer in this group of animals.

We also found that the right ventricular end-diastolic pressure tended to be reduced in relation to the left ventricular end-diastolic pressure following pericardiectomy, particularly in the “early” volume overload dogs. This is consistent with data from studies performed before and after pericardiectomy in normal dogs (Glantz et al., 1978; Rabson and Permutt, 1978; Robatham and Mitzner, 1979; Spaduro et al., 1979;
alteration in ventricular interaction mediated by re-volume overload, at a time when a significant increase in diastolic pressure was relatively small and the ratio of right ventricular end-diastolic pressure to left ventricular end-diastolic pressure multiplied by the area of the interventricular septum/the total left ventricular surface area. The resulting difference between the "corrected" left ventricular pressure at matched diastolic dimensions before and after pericardiectomy should reflect the "effective" pericardial pressure (Mirsky and Rankin, 1979) and represent the extent to which the pericardium is directly responsible for diastolic pressure elevation in the left ventricle at a given diastolic dimension. Since the absolute decrease in right ventricular end-diastolic pressure following pericardiectomy when measured at matched left ventricular end-diastolic pressure was relatively small and the ratio of septal to total left ventricular surface area was invariably close to 0.3, this "correction" of left ventricular end-diastolic pressure resulted in little alteration in the magnitude of change in end-diastolic dimension which occurred after pericardiectomy. These findings suggest that most of the shift following pericardiectomy is due directly to restraint by the pericardium rather than to secondary alterations in ventricular interaction resulting from pericardiectomy.

In animals studied later during the course of chronic volume overload, at a time when a significant increase in total cardiac and left ventricular mass had occurred, pericardial restraining effects were essentially absent or minimal over a range of left ventricular diastolic pressure comparable to that examined in the early volume overload group. Once again, these results were unaltered when the left ventricular end-diastolic pressure was "corrected" for any changes in right ventricular end-diastolic pressure which occurred following pericardiectomy. It is, of course, entirely possible that, if diastolic left ventricular pressure had been raised even higher than that which we attained with dextran infusion, restraint of filling by the pericardium would have been detected in the "late" group of animals. This possibility is suggested by the small shifts in diastolic dimension which were observed after pericardiectomy at high levels of diastolic pressure in three of the animals in this group, including the one animal with a statistically significant shift as judged from the polynomial curve fit.

The implication of our results in the "late" group is that, during the approximately 6-week period of volume overload, the pericardium itself increased in volume. This implication is based on the demonstration of a significant increase in left ventricular and overall cardiac mass when the "late" group was compared to the "early" group, a change which is especially important because we did not directly measure left ventricular volumes during the course of our studies. Prior studies employing the arteriovenous fistula model performed after pericardiectomy (McCullough et al., 1972; LeWinter et al., 1980) have shown a major serial rightward shift of the left ventricular diastolic pressure-volume (or dimension) relation during the development of volume overload hypertrophy at times comparable to when our "late" animals were studied, a finding which also appears to be present in patients with chronic aortic insufficiency (Gault et al., 1970). As a result, at the same level of volume, diastolic pressure is actually reduced compared to normal. These data would also support the concept that the pericardium must increase its volume in order to account for our results in the "late" group of animals. Further, these same studies also suggest that the slope of the diastolic pressure-volume relation is increased in dogs with chronic volume overload, i.e., left ventricular chamber compliance may be reduced. Although we did not attempt to measure compliance directly in our studies, if a similar reduction occurred in our "late" group of animals in comparison to the "early" group, it could have independently influenced the magnitude of change in volume or dimension which occurred after pericardiectomy at a given intracavitary diastolic pressure. This can be appreciated by considering the fact that, using the techniques employed in this study, a chronic intervention may result in diminution of the apparent restraining effects of the pericardium on left ventricular filling not only as a result of an increase in the volume of the pericardium available, but alternatively, as a result of a reduction in the volume of the left ventricle at a given transmural pressure. The latter could occur by virtue of an isolated decrease in chamber compliance in the absence of any change in left ventricular mass or pericardial volume. An analysis of the potential effects of a decrease in chamber compliance in relation to our results is complicated, however, by the fact that—if such a change does occur—it must be interpreted in light of the aforementioned increase in left ventricular mass and rightward shift of the diastolic pressure-volume relation. This situation is depicted schematically in Figure 8. Here, the diastolic pressure-volume relations obtained in the absence of the pericardium are represented by the solid lines for the normal and chronic volume overload state. (It is further assumed that our "early" dogs are not substantially different than normal in this regard.) In the chronic volume overload state, this relation is shown as being shifted to the right and markedly increased in steepness, i.e., chamber compliance is markedly reduced. Nos. 1-4 refer to specific levels of unstressed pericardial volume which could be available to the left ventricle in the chronic volume overload state. It should be recognized that this may well be somewhat of an oversimplification, since it is
assumed that the pericardial volume available to the left ventricle remains constant as left ventricular volume is altered—i.e., if left ventricular volume is altered by infusing volume intravenously, the other chambers will also dilate and likely compete for the available pericardial space, so that the space available to the left ventricle might itself change. No. 1 represents a volume which is unchanged from normal, and No. 2, a volume which is increased but remains on the relatively flat portion of the pressure-volume relation. In the presence of an intact pericardium, filling of the left ventricle would be restrained when its volume began to approach the pericardial volume available to it, resulting in the intracavitary diastolic pressure-volume relations depicted by the dashed lines. In either case, removal of the pericardium would result in a significant increase in left ventricular volume when measured at the same level of intracavitary pressure before and after pericardiectomy, a result which is incompatible with those obtained in our "late" group. No. 3 represents an increased pericardial volume corresponding to the steep portion of the left ventricular pressure-volume relation, while No. 4 represents an increase such that the volume of the left ventricle never reaches the available pericardial volume over the range of pressures studied. In either case, pericardiectomy would result in either very small or nonexistent increases in left ventricular volume at a common intracavitary pressure, a result which is consistent with those in the "late" group. Thus, in the particular case in which the diastolic pressure-volume relation is shifted to the right, even if there is a marked reduction in left ventricular chamber compliance, a significant increase in pericardial volume must be postulated to explain our results. Conversely, a decrease in chamber compliance is of trivial importance in interpreting our results with respect to changes in pericardial volume, providing the aforementioned rightward shift occurs.

Since compliance changes could, in theory, have exerted some influence on our results, it is also worth considering the possibility that the sequence of caval occlusion and dextran infusion employed in our experiments could have elicited neurohumoral responses which, in turn, might influence diastolic compliance. Any adrenergically mediated effects should have been abolished by the use of high-dose \( \beta \)-blockade. Whereas cholinergic stimulation is not known to exert any direct effect on myocardial diastolic properties, cholinergically mediated heart rate and secondary diastolic timing changes could conceivably have influenced our results. In this regard, the constancy of heart rate during the experimental protocol would exclude this possibility. Finally, although highly unlikely, we cannot exclude the possibility that the experimental protocol elicited some form of nonadrenergic, noncholinergic humoral response which could have influenced our results.

This apparent increase in pericardial volume in the "late" group could have resulted from creep, as indicated previously. However, pericardial creep, at least when examined over a short period of time, appears to be a relatively modest effect (Rabin et al., 1974). Whether the pericardium could undergo creep for a prolonged period of time and thereby enlarge to an extent sufficient to account for our observations in the "late" volume overload group is uncertain. It is also unknown whether the pericardium can itself hypertrophy in response to chronic cardiac dilation and increase its volume by this means.

In contrast to acute volume overload (Bartle and Herman, 1967), patients with chronic cardiac dilation due to volume overload lesions do not generally manifest diastolic pressure equilibration suggestive of constrictive pericardial disease. This could indicate that a similar increase in pericardial volume occurs clinically. However, several factors suggest that extrapolation of our results to the clinical situation must be made very cautiously. First, species differences between dogs and man, especially those relating to posture, could play a major role in pericardial adaptations to cardiac dilation. Thus, the changes in body posture from supine to upright which occur routinely in humans could result in a greater opportunity, at least in theory, for stretching of the pericardium by virtue of changes in cardiac volumes (Rankin et al., 1975) and/or as the result of the attachments of the pericardium to the diaphragm. While potentially important, however, the actual contribution of such postural differences must remain entirely speculative. Second, most adult patients with major volume overload lesions have left-sided valvular heart disease resulting in predominantly left heart dilation, whereas the systemic arteriovenous fistula model is a high-output state resulting in four chamber enlargement and, hence, the potential for greater stretch of the pericardium. Pertinent to the latter question is the study of Brodie et al. (1977) in which nitroprusside infusion produced a downward shift of the left ventricular diastolic pressure-volume relation in patients with chronic left-sided volume overload. These results are similar to those observed by Shirato et al. (1978) in normal dogs, in which the effects of nitroprusside were shown to be abolished by pericardiectomy.
Thus, while it has not been shown that pericardectomy would have similar effects in the setting of left-sided volume overload, the effects of nitroprusside observed by Brodie et al. (1977) suggest that, in patients with only left heart dilation, the pericardium does not undergo enlargement comparable to that observed in our animals with four chamber dilation. However, a more appropriate clinical study in relation to our results would be comparison of the diastolic pressure-volume relation before and after nitroprusside administration in patients with idiopathic, congestive cardiomyopathy and major right and left heart dilation, or patients with appropriately located left-to-right shunts. Such studies would constitute an interesting avenue for further investigation.

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