Left Ventricular Diastolic Pressure-Segment Length Relations and End-Diastolic Distensibility in Dogs with Coronary Stenoses

An Angina Physiology Model

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SUMMARY. Isovolumic relaxation abnormalities have been noted in the ischemic left ventricle, but altered end-diastolic distensibility, as well as the role of right ventricular distention, is debated. Accordingly, left ventricular end-diastolic pressure and myocardial segment length were studied in the open-chest dogs with critical (90% diameter reduction) stenoses on both left anterior descending and circumflex coronary arteries. Regional segment length was measured with ultrasonic crystals placed subendocardially, and ischemia was induced by pacing tachycardia for 3 minutes. Transient vena caval occlusion was done to unload the right ventricle and to produce a series of left ventricular end-diastolic pressure and left ventricular end-diastolic segment length points before and after pacing tachycardia. After pacing tachycardia, left ventricular end-diastolic pressure (9.3 ± 0.9 to 16.9 ± 1.5 mm Hg, \( P < 0.001 \)) and time constant \( T \) of left ventricular isovolumic pressure decline (46 ± 3 to 60 ± 5 msec, \( P < 0.01 \)) increased, with an increase in left ventricular end-diastolic segment length (9.8 ± 0.3 to 10.5 ± 0.3 mm, \( P < 0.001 \)), and a decrease in fractional shortening (17.6 ± 1.7 to 14.5 ± 1.3%, \( P < 0.01 \)) in the ischemic region, although right ventricular end-diastolic pressure was unchanged. With vena caval occlusion, right ventricular diastolic pressure fell promptly to near zero, followed by decrease in left ventricular pressure and segment length. In each dog, the left ventricular end-diastolic pressure-end-diastolic segment length relation shifted upward after pacing tachycardia. This upward shift in end-diastolic left ventricular pressure-segment length relation did not shift upward after pacing tachycardia. These data indicate that extrinsic compression of left ventricle by right ventricle is unlikely to be responsible for the upward shift in this model, and the upward shift in end-diastolic left ventricular pressure-segment length relations, as well as dynamic left ventricular diastolic pressure-segment length, supports the concept that persistent myosin-actin interaction throughout diastole plays an important role in the diastolic abnormalities in this angina physiology model. (Circ Res 55: 203–214, 1984)

A TRANSIENT increase in left ventricular diastolic pressure relative to volume (upward shift in left ventricular diastolic pressure-volume relation) has been observed repeatedly in patients with angina pectoris (Dwyer, 1970; McLaurin et al., 1973; Barry et al., 1974; Fliesas et al., 1976; Gaasch et al., 1976; Mann et al., 1977, 1979; Rickards and Seabra-Gomes, 1978; Carroll et al., 1983). This decreased distensibility of the diastolic left ventricle probably contributes to the dyspnea and pulmonary congestion which commonly accompany anginal attacks. A number of possible mechanisms have been proposed for this increased pressure relative to volume. Extrinsic compression of the diastolic left ventricle by right ventricle and/or pericardium has been suggested as playing a role in the upward shift observed during angina pectoris (Ross, 1979) as well as the ischemia of coronary occlusion (Hess et al., 1983).

On the other hand, the concept of residual diastolic myosin-actin interaction is supported by a number of experimental observations both for normal myocardium (Lappé and Lakatta, 1980; Matsubara et al., 1982; Stern et al., 1983) and during transient myocardial hypoxia/ischemia (Greene and Weisfeldt, 1977; Nayler and Williams, 1978; Grossman and Barry, 1980; Serizawa et al., 1980, 1981; Paulus et al., 1982). Abnormalities of the isovolumic relaxation period, including decreased peak negative dP/dt and prolongation of the time constant \( T \), have been widely observed in angina pectoris (Rutishauser et al., 1971; McLaurin et al., 1973; Mann et al., 1979; Carroll et al., 1983) and experimental models of ischemia (Mathey et al., 1974; Weisfeldt et al., 1974; Palacios et al., 1976; Waters et al., 1977;
Serizawa et al., 1980). However, the relation of these abnormalities of early relaxation to upward shifting of the diastolic pressure-volume curve is uncertain. Furthermore, even if early and mid-diastolic abnormalities occur during the transient ischemia of angiography, altered end-diastolic distensibility is debated. The goal of this study was to examine possible mechanisms for altered diastolic properties using an angiography physiology model developed previously in our laboratory (Serizawa et al., 1980; Paulus et al., 1982). First, the influence of right ventricular distention on the left ventricular diastolic pressure-segment length relation was examined; and, second, the hypothesis that left ventricular end-diastolic pressure-segment length relations (obtained from a series of end-diastolic pressure-segment length points) show similar changes to dynamic diastolic left ventricular pressure-segment length relations (obtained from multiple points throughout a single diastole) was tested.

**Methods**

An angina physiology model which was developed in our laboratory (Serizawa et al., 1980; Paulus et al., 1982) was used. Sixteen mongrel dogs weighing 18-34 kg were anesthetized with intravenous α-chloralose (100 mg/kg), after premedication with a subcutaneous injection of ketamine (10 mg/kg). To prevent ventricular fibrillation, which frequently accompanies ischemia in this model, intravenous propranolol (0.3–0.5 mg/kg) was administered at the beginning of the experiment (Reynolds et al., 1978). Respiration was maintained by a Harvard pump via an endotracheal tube. A left thoracotomy was performed at the 5th intercostal space, and the pericardium was opened widely. Pacing electrodes were sutured on the left atrial appendage. High fidelity micromanometers (Millar Instruments PC-484, 460) were inserted into the left ventricle and right ventricle via the right carotid artery and the right jugular vein, respectively. These high fidelity pressure signals were matched with pressures measured through the catheter lumen before and after each recording. To assess regional wall motion, a pair of ultrasonic crystals were implanted in the subendocardium approximately 1.0 cm apart in an area perfused by the left circumflex artery, and another pair in an area perfused by left anterior descending artery. Crystals were placed in the inner third of the myocardium, following the technique of Gallagher et al. (1982), who chose this location because of the relatively homogeneous fiber orientation at a distance of 15–20% of the full wall thickness from the endocardial surface. The crystals were oriented in the circumferential plane and their position confirmed at the end of each experiment. Both areas were perfused by coronary arteries distal to the stenoses, which were created next in 10 of the 16 dogs, as follows. Both proximal left circumflex and left anterior descending coronary arteries were dissected from adipose tissue. Metal clips whose gap diameters are adjusted by a commercially available gap gauge were placed on both left circumflex and anterior descending coronary arteries to create critical stenoses (about 90% diameter reduction), as previously described (Serizawa et al., 1980; Paulus et al., 1982). If a stenosis of excessive severity was created, obvious systolic bulge in segmental wall motion occurred and the stenosis was immediately reduced in severity until segmental function was restored, as assessed visually and by the amplitude of segmental shortening measured by ultrasonic crystals.

An umbilical tape secured with a plastic sheath was placed around the inferior vena cava. Using the preparation described above, left ventricular pressure, left ventricular dp/dt, myocardial segment lengths, and right ventricular pressure were recorded with an Electronics for Medicine Research Recorder. Model SGM carrier type

### TABLE 1

**Effect of Pacing Tachycardia on Hemodynamic Parameters in Dogs without Coronary Stenosis**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre-pacing</th>
<th>Immediately post-pacing*</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>129 ± 3</td>
<td>122 ± 2</td>
<td>6</td>
</tr>
<tr>
<td>LVSPSP (mm Hg)</td>
<td>132 ± 6</td>
<td>120 ± 8</td>
<td>6</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9.8 ± 1.3</td>
<td>10.0 ± 1.7</td>
<td>6</td>
</tr>
<tr>
<td>LVMDDP (mm Hg)</td>
<td>6.1 ± 0.8</td>
<td>6.3 ± 1.3</td>
<td>6</td>
</tr>
<tr>
<td>Peak (+)dp/dt (mm Hg/sec)</td>
<td>1800 ± 130</td>
<td>1600 ± 110</td>
<td>6</td>
</tr>
<tr>
<td>Peak (−)dp/dt (mm Hg/sec)</td>
<td>2530 ± 270</td>
<td>2180 ± 280</td>
<td>6</td>
</tr>
<tr>
<td>TL (msec)</td>
<td>33 ± 2</td>
<td>35 ± 3</td>
<td>6</td>
</tr>
<tr>
<td>TP (msec)</td>
<td>46 ± 3</td>
<td>47 ± 2</td>
<td>6</td>
</tr>
<tr>
<td>RVSPSP (mm Hg)</td>
<td>25 ± 2</td>
<td>23 ± 2</td>
<td>5</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>2.9 ± 0.3</td>
<td>2.9 ± 0.3</td>
<td>5</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>11.6 ± 0.8</td>
<td>11.6 ± 0.9</td>
<td>6</td>
</tr>
<tr>
<td>LVESL (mm)</td>
<td>9.9 ± 0.9</td>
<td>10.0 ± 0.9</td>
<td>6</td>
</tr>
<tr>
<td>%AL</td>
<td>15.7 ± 2.3</td>
<td>15.3 ± 2.3</td>
<td>6</td>
</tr>
</tbody>
</table>

Values were expressed as mean ± SE.

* These values were determined at five beats after discontinuation of pacing tachycardia, immediately before inferior vena cava occlusion.

HR, heart rate; LVSPSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVMDDP, left ventricular minimal diastolic pressure; TL, time constant of left ventricular isovolumic relaxation calculated from the logarithm of pressure; TP, time constant calculated from the derivative of pressure; RVSPSP, right ventricular peak systolic pressure; RVEDP, right ventricular end-diastolic pressure; EDSEL, end-diastolic segment length; %AL, fractional shortening of myocardial segment.
Pacing Tachycardia without Coronary Stenosis

In six dogs without coronary stenoses, the inferior vena cava was occluded before and immediately after pacing tachycardia. Two pairs of ultrasonic crystals were implanted in areas perfused by the left anterior and left circumflex coronary arteries, respectively, as described above. After recovery from the control vena cava occlusion, the heart was paced at 1.7 times resting heart rate for 3 minutes. Immediately after pacing tachycardia, the inferior vena cava was occluded again, as in the protocol for dogs with coronary stenoses described above.

Data Analysis

The fifth beat after the onset of the pre-pacing vena cava occlusion was selected to examine left ventricular dynamic pressure-segment length relations. Left ventricular pressure and segment length recordings in this beat were digitized every 5 msec from high-speed paper recordings, using a Tektronix 4956 graphics tablet. A pressure-segment length loop was constructed from left ventricular pressure and averaged segment length data points of both left anterior descending and left circumflex region, by means of a Tektronix 4052 graphic computer system. Post-pacing pressure-segment length loops were constructed in the same way. To determine left ventricular end-diastolic pressure-segment length relations, left ventricular end-diastolic pressures during pre-pacing and post-pacing vena cava occlusions were plotted against left ventricular end-diastolic segment lengths in each dog. End-diastolic pressure was defined as the left ventricular pressure at the peak of the R wave of a simultaneous lead II ECG, and corresponded to the pressure immediately before the rapid rise in the left ventricular pressure associated with systolic contraction. This definition of "end-diastolic" pressure was used because it is a traditional one. It does not signify a belief on our part that all systolic activity has been dissipated, and that only passive compliances are operative.

The left ventricular end-diastolic segment length of the control beat for pre-pacing vena cava occlusion was defined as 100%. The post-pacing end-diastolic pressure-segment length point whose segment length is the same
or closest to this 100% value was selected. Then, pre-pacing and post-pacing end-diastolic pressure-segment length points whose end-diastolic segment lengths were closest to 99%, 98%, 97%, 96%, and 95% of the control end-diastolic segment lengths were selected. Thus, end-diastolic pressure-segment length points over a range from 100% to 95% of control end-diastolic segment length were obtained in each dog. Using end-diastolic pressure-segment length points obtained in this fashion, averaged pre- and post-pacing left ventricular end-diastolic pressures were plotted at matched segment lengths over a common range of percent end-diastolic segment length in all 10 dogs. The time constant T of left ventricular pressure fall was calculated from both the logarithm of pressure (T_L) (Weiss et al., 1976) and the derivative of pressure (T_D) (Carroll et al., 1983), beginning with left ventricular pressure- 

**Figure 2.** Dynamic left ventricular diastolic pressure-segment length relations obtained from simultaneous recordings of left ventricular pressure and segment length in six dogs without coronary stenoses. The left ventricular diastolic pressure-segment length plots were constructed up to end-diastole, using corresponding points of the digitized pressure and segment length data. Pre- and post-pacing diastolic pressure-segment length relations dropped on the same curve. Pre = pre-pacing, Post = immediately post-pacing.

**Table 2**

Effect of Pacing-Induced Ischemia on Hemodynamic Parameters in Dogs with Severe Coronary Stenoses

<table>
<thead>
<tr>
<th></th>
<th>Pre-pacing</th>
<th>P</th>
<th>Immediately post-pacing*</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>131 ± 6</td>
<td>NS</td>
<td>131 ± 6</td>
<td>10</td>
</tr>
<tr>
<td>DI (msec)</td>
<td>212 ± 18</td>
<td>NS</td>
<td>225 ± 18</td>
<td>10</td>
</tr>
<tr>
<td>LVFSFP (mm Hg)</td>
<td>126 ± 5</td>
<td>NS</td>
<td>130 ± 5</td>
<td>10</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>9.3 ± 0.9</td>
<td>&lt;0.01</td>
<td>16.9 ± 1.5</td>
<td>10</td>
</tr>
<tr>
<td>LVMDP (mm Hg)</td>
<td>6.8 ± 0.9</td>
<td>&lt;0.001</td>
<td>11.4 ± 0.4</td>
<td>10</td>
</tr>
<tr>
<td>Peak (+)dP/dt (mm Hg/sec)</td>
<td>1710 ± 60</td>
<td>NS</td>
<td>1670 ± 110</td>
<td>10</td>
</tr>
<tr>
<td>Peak (-)dP/dt (mm Hg/sec)</td>
<td>2460 ± 170</td>
<td>&lt;0.05</td>
<td>2080 ± 190</td>
<td>10</td>
</tr>
<tr>
<td>T_L (msec)</td>
<td>37 ± 1</td>
<td>&lt;0.001</td>
<td>47 ± 2</td>
<td>10</td>
</tr>
<tr>
<td>T_D (msec)</td>
<td>46 ± 3</td>
<td>&lt;0.01</td>
<td>63 ± 5</td>
<td>10</td>
</tr>
<tr>
<td>RVFSFP (mm Hg)</td>
<td>26 ± 1</td>
<td>NS</td>
<td>27 ± 2</td>
<td>9</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
<td>2.6 ± 0.3</td>
<td>NS</td>
<td>2.9 ± 0.3</td>
<td>9</td>
</tr>
<tr>
<td>LVEDSL (mm)</td>
<td>11.9 ± 0.3</td>
<td>&lt;0.05</td>
<td>12.2 ± 0.3</td>
<td>10</td>
</tr>
<tr>
<td>LVESSL (mm)</td>
<td>9.8 ± 0.3</td>
<td>&lt;0.001</td>
<td>10.5 ± 0.3</td>
<td>10</td>
</tr>
<tr>
<td>%AL</td>
<td>17.6 ± 1.7</td>
<td>&lt;0.01</td>
<td>14.5 ± 1.3</td>
<td>10</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SE. DI, diastolic interval. See Table 1 for other abbreviations.

* These values were determined at five beats after discontinuation of pacing tachycardia, immediately before inferior vena caval occlusion.
FIGURE 3. High speed recordings of left ventricular pressure, left ventricular dP/dt, and segment length before, during, and after pacing tachycardia in a dog with critical coronary stenoses (90% diameter reduction) of left anterior descending and left circumflex coronary arteries. LVEDP and LVEDSL increased immediately after pacing tachycardia, returning to pre-pacing level at 1 minute after pacing. Left ventricular systolic pressure fell during pacing, and rose immediately after discontinuation of pacing, gradually decreasing to pre-pacing level by five beats post-pacing. Left ventricular distensibility is elevated post-pacing, and does not return to pre-pacing values until 30–60 seconds post-pacing.

FIGURE 4. Left ventricular dynamic diastolic pressure-segment length loops constructed up to end-diastole from digitized data in the same dog as shown in Figure 3. Curve 1 = pre-pacing; curve 2 = during pacing; curve 3 = 1st post-pacing beat; curve 4 = 2nd post-pacing beat; curve 5 = 3rd post-pacing beat; curve 6 = 5th post-pacing beat; curve 7 = 10th post-pacing beat; curve 8 = 30 seconds post-pacing; curve 9 = 1 minute post-pacing.

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pressure at the time of peak negative dP/dt, and ending when left ventricular pressure was 5 mm Hg higher than end-diastolic pressure.

Statistical Analysis

Hemodynamic parameters before and after pacing tachycardia were compared statistically by paired t-test. Left ventricular end-diastolic pressures at the matched end-diastolic segment lengths were compared using a non-paired two-sample t-test. Hemodynamic data between experiments with and without coronary stenoses were also compared using a two-sample nonpaired t-test. All values were expressed as mean ± SEM.

Results

Hemodynamic data before and after pacing tachycardia in dogs without coronary stenoses are shown in Table 1. Immediately after pacing, heart rate slowed slightly (129 ± 3 to 122 ± 2 beats/min, P < 0.01). Left ventricular systolic and end-diastolic pressures (LVEDP), peak positive dP/dt, left ventricular end-diastolic and end-systolic segment lengths (LVEDSL, LVESSL), fractional shortening of myocardial segments, and right ventricular pressure were unchanged. The time constant T of left ventricular pressure fall was also unchanged (Tl, 33 ± 2 to 35 ± 3 msec, NS; TD, 46 ± 3 to 47 ± 2 msec, NS), although peak negative dP/dt decreased (2530 ± 270 to 2180 ± 280 mm Hg/sec, P < 0.01).

Hemodynamic tracings before, during, and immediately after pacing tachycardia in one of the dogs without coronary stenosis are shown in Figure 1 (upper panel). Immediately after pacing tachycardia, end-diastolic segment length and end-diastolic pressure were unchanged and shortening was preserved. Correspondingly, the diastolic pressure-segment length relation (Fig. 1, lower panel) was not displaced. Dynamic pressure-segment length relations in all six dogs without coronary stenoses are plotted in Figure 2.

Hemodynamic data in dogs with coronary stenoses are shown in Table 2. Immediately after pacing tachycardia (and before inferior vena caval occlusion), LVEDP increased to 16.9 ± 1.5 mm Hg from 9.3 ± 0.9 in the pre-pacing control (P < 0.001). Left ventricular minimal diastolic pressure (LVMDP) also increased to 11.4 ± 0.4 mm Hg from 6.8 ± 0.9 (P < 0.001). However, differences in right ventricular end-diastolic pressure were not significant (from 2.6 ± 0.3 to 2.9 ± 0.3 mm Hg immediately post-pacing). Heart rate (from 131 ± 6 to 131 ± 6 beats/min) and left ventricular systolic pressure (from 126 ± 5 to 130 ± 5 mm Hg) were unchanged after pacing tachycardia. Left ventricular peak negative dP/dt decreased from 2460 ± 170 to 2080 ± 190 mm Hg/sec (P < 0.01), although peak positive dP/dt was unchanged (from 1710 ± 60 to 1670 ± 110 mm Hg/sec). The time constant of left ventricular isovolumic relaxation increased (Tl, 37 ± 1 to 47 ± 2 msec, P <
FIGURE 5. Dynamic left ventricular diastolic pressure-segment length relations in 10 dogs with critical coronary stenoses. After pacing tachycardia, diastolic pressure-segment length relations generally shifted upward, or upward and to the right. PRE = pre-pacing, POST = post-pacing; curves were constructed from the fifth beat after cessation of pacing tachycardia.

In the presence of coronary stenoses (Fig. 3), left ventricular end-diastolic pressure increased and segment shortening decreased, with pacing. The diastolic dynamic pressure-segment length relation (Fig. 4) shifted upward during pacing (curve 2), upward with rightward displacement immediately following pacing tachycardia (curves 3–6), and then gradually (curves 7–9) returned to baseline over the next 60 seconds. In all 10 dogs with coronary stenoses, left ventricular dynamic diastolic pressure-segment length relations shifted upward, or upward and to the right, after pacing tachycardia (Fig. 5). There was no difference in RVEDP between pre- and post-pacing beats examined for drawing pressure-segment length loops (1.9 ± 0.3 mm Hg, pre-pacing vs. 1.8 ± 0.3 mm Hg, post-pacing).

Typical hemodynamic changes during inferior vena caval occlusion are shown in Figure 6. With inferior vena caval occlusion, RV pressures decreased immediately, followed by LVSL and LV

**TABLE 3**

<table>
<thead>
<tr>
<th>Effect of Inferior Vena Caval Occlusion on Left Ventricular Pressure and Segment Length in Dogs with Coronary Stenoses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>LVSP (mm Hg)</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
</tr>
<tr>
<td>RVPSP (mm Hg)</td>
</tr>
<tr>
<td>RVEDP (mm Hg)</td>
</tr>
<tr>
<td>LVEDSL (mm)</td>
</tr>
</tbody>
</table>

Values expressed as mean ± se. IVCO, inferior vena caval occlusion; other abbreviations are the same as in Table 1.
systolic and end-diastolic pressure. Without coronary stenoses, end-diastolic pressure-segment length points before and after pacing tachycardia fell on the same curve (Fig. 7).

Pressure-segment length loops during inferior vena caval occlusion, before and after pacing tachycardia in one of the dogs with coronary stenoses is shown in Figure 8. After pacing tachycardia with coronary stenoses present, the end-diastolic pressure-segment length relation shifted downward and to the right (upper panel), indicating mild systolic dysfunction, and the diastolic pressure-segment length relation shifted upward (lower panel), indicating decreased distensibility. In Figure 9, it can be seen that the end-diastolic pressure-segment length plots, obtained by inferior vena caval occlusion, showed an upward shift of variable magnitude, similar to the upward shifts seen in dynamic diastolic pressure-segment length plots (Fig. 5). Before pacing, the LVEDP decreased by 57% with transient vena caval occlusion, and post-pacing, it fell by 65% over 20 beats of vena caval occlusion. LVEDSL decreases were 8% pre-pacing, and 10% post-pacing, respectively, with vena caval occlusion. Hemodynamic changes in response to vena caval occlusion are shown in Table 3.

Figure 10 shows the method for obtaining...
Matched LVEDP and LVEDSL for a single dog. The solid dots indicate pre-pacing values for LVEDP vs. LVEDSL with the beat before vena caval occlusion having the highest value for LVEDP and LVEDSL, and the beats following caval occlusion showing progressively lower values for LVEDP and LVEDSL. The LVEDSL of the control beat is defined as 100% (large black dot at upper right of pre-pacing dots), and beats during caval occlusion having LVEDSL equal to 99%, 98%, 97%, 96%, and 95% of this control value were identified (other large black dots). Following pacing tachycardia, beats were identified from the vena caval occlusion records for which LVEDSL equalled 100%, 99%, 98%, 97%, 96%, and 95% of the control value (large open dots). LVEDP could thus be averaged for all experiments at matched segment lengths, before and after pacing tachycardia, to assess change in end-diastolic pressure-segment length relations (Fig. 11).

**Discussion**

The experimental model used in this study was developed in our laboratory (Serizawa et al., 1980) in an attempt to duplicate the essential physiology of angina pectoris. In this model, “dynamic” LV diastolic pressure-volume relations determined from individual diastoles were noted to be shifted upward by pacing tachycardia in open-chest dogs with high-grade stenoses (90% diameter reduction) on both anterior descending and circumflex coronary arteries. Hemodynamic changes in this model, especially the upward shift, were quite similar to those observed during angina pectoris in patients with multivessel coronary disease. To assess regional myocardial dynamics, Paulus et al. (1982) applied ultrasonic crystal methodology to this angina physiology model and showed that LV diastolic pressure-segment length relations in the ischemic region were shifted upward, as well, and that this upward shift was potentiated by caffeine infusion. The finding that this effect of caffeine on LV diastolic properties during ischemia was not accompanied by further slowing of the rate of relaxation was interpreted as consistent with differential control of the rate and extent of myocardial relaxation in this model. However, a variety of other interpretations are also possible, and the mechanism of the upward shift in the left ventricular pressure-volume and pressure-segment length relations in angina is still the subject of controversy.

In this study, transient inferior vena caval occlusion allowed us to assess the effect of possible extrinsic compression of the left ventricle by the right ventricle and to test the hypothesis that left ventricular end-diastolic pressure-segment length relations show similar changes to dynamic diastolic pressure-segment length relations in this model of myocardial ischemia. The vena caval occlusion technique employed in this study has been used by other investigators to remove the influence of right ventricular distention on the left ventricle, and to decrease left ventricular preload (Rankin et al., 1977; LeWinter et al., 1979; LeWinter and Pavelec, 1982; Edwards et al., 1981; Hess et al., 1983; Olsen et al., 1983). Only the inferior vena cava was occluded in our study to obtain relatively moderate hemodynamic changes; i.e., left ventricular systolic pressure at the 20th beat from the onset of vena caval occlusion was 23–25% lower than control.

Direct mechanical interaction between the right and left ventricles during diastole have been extensively investigated (Taylor et al., 1967; Elzinga et al., 1974; Tyberg et al., 1978; Janicki and Weber, 1980; Lorell et al., 1981; Refsum et al., 1981). Ross (1979) emphasized the influence of right ventricular filling on the left ventricle as a possible mechanism for the apparent decrease in left ventricular distensibility during angina pectoris. Since the right ventricle is ordinarily more compliant than left ventricle, it was reasoned that a small change in right ventricular filling pressure could reflect a substantial alteration in right ventricular volume, and factors such as septal displacement, increased septal stiffness, or...
stretching of fibers common to right ventricle and left ventricle could play a role in elevating the left ventricular end-diastolic pressure even without a clear role of the pericardium. Most recently, Hess et al. (1983) observed an upward shift in the left ventricular diastolic pressure-volume relationship with decreased rate of relaxation of ischemic myocardium, during complete coronary occlusion, in an open-chest dog preparation with widely opened pericardium. However, since inferior vena cava occlusion prevented this upward shift, they concluded that a change in right ventricular loading conditions with altered ventricular interaction is an important mechanism for this upward shift.

In our study, the upward shift in left ventricular dynamic and end-diastolic pressure-segment length relations occurred without any increase in right ventricular end-diastolic pressure in the post-pacing period. Furthermore, the upward shift was not abolished by vena caval occlusion in our study, although right ventricular pressure fell to zero. Thus, the effect of right ventricular distention does not seem to be an essential mechanism of the upward shift in left ventricular pressure-segment length relations, although it may conceivably play an additive role in some patients in whom angina is associated with right ventricular ischemia, increased right ventricular loading, and an intact pericardium.

The fact that the left ventricular end-diastolic pressure-segment length curve was shifted upward following pacing tachycardia may be relevant to the mechanism of altered diastolic properties in angina and/or our angina physiology model. First, the time constant T of left ventricular relaxation was prolonged by pacing tachycardia, but the diastolic interval was still longer than 3.5 T, when relaxation has been estimated to be complete (Weisfeldt et al., 1978). Therefore a simple decrease in the rate of relaxation is unlikely as an explanation of the upward shift in the pressure-segment length relations. It must be emphasized that reduced extent of relaxation (due, for example, to cytosolic calcium overload, local ATP deficiency with rigor bonding, or increased sensitivity of the contractile proteins to a given concentration of diastolic calcium) and decreased rate of relaxation are not necessarily syn-
FIGURE 10. Pre- and post-pacing end-diastolic pressure-segment length plots. LVEDP was determined at each matched LVEDSL over a range from 100% to 95% of pre-pacing, pre vena caval occlusion LVEDSL. See text for explanation.

FIGURE 11. Left ventricular end-diastolic pressures were plotted against matched left ventricular end-diastolic segment lengths in each dog, with end-diastolic segment length in the control beats (before pacing and vena caval occlusion) defined as 100%. Data was plotted only for the region of overlap from 95% to 100% control segment length. At each level of end-diastolic segment length, post-pacing end-diastolic pressure is significantly higher than pre-pacing end-diastolic pressure. ● = pre-pacing end-diastolic pressure-segment length point; O = post-pacing end-diastolic pressure-segment length point. † P < 0.05, * P < 0.01, ** P < 0.001.

Conscious, although these two types of relaxation abnormality commonly coexist (Serizawa et al., 1981). Dissociation of these relaxation abnormalities was observed by Paulus et al. (1982) in a study where the influence of caffeine on diastolic properties of the ischemic left ventricle were examined. A similar dissociation was observed during hypoxic contracture by Greene and Weisfeldt (1977). A steady state failure of complete myofilament inactivation in cardiac muscle has also been termed myocardial tone or "tonus," and reversible contracture. To differentiate reduced extent of relaxation from decreased rate of relaxation in present model, observation of pressure-segment length relations in beats with long diastoles induced by sinus node crush or atrioventricular node destruction may be useful. If the upward shift in left ventricular diastolic pressure-segment length relations in a post-pacing beat is maintained throughout a long diastole lasting several seconds, decreased extent of relaxation is more likely as the mechanism of this diastolic abnormality. Left ventricular dysynchrony and the different muscle strengths in ischemic and nonischemic myocardium have also been proposed as possibly contributing to the left ventricular diastolic abnormalities in ischemia (Waters et al., 1977; Wiegner et al., 1978; Kumada et al., 1979). Persistent contractile activity and the elastic recoil of passively stretched elements in ischemic muscle may result in late shortening. This late shortening of ischemic myocardium could lead to an apparent decrease in diastolic compliance and interfere with early ventricular filling. However, since the effects of recoil/delayed inactivation should be largely dissipated by end-diastole, the upward shift in left ventricular end-diastolic pressure-segment length relations observed in our study is unlikely to be due to dysynchrony or delayed inactivation.

The upward shift of LV end-diastolic pressure-segment length relations indicates decreased end-diastolic distensibility of the ischemic myocardial segment. The fundamental mechanisms responsible for this decreased distensibility are uncertain. Persistent contractile interaction of actin and myosin filaments throughout diastole could account for this decreased diastolic distensibility, and in turn might represent the consequence of a number of possible derangements of subcellular metabolism, including ATP deficiency (Katz and Tada, 1972; Nayler and Williams, 1978; Nayler et al., 1979; Lewis et al., 1979, 1980), cytosolic calcium overload (Henry et al., 1977; Grossman and Barry, 1980; Lorell and Barry, 1984; Smith and Katz, 1983), or increased sensitivity of the contractile proteins to a given concentration of diastolic calcium. Cytosolic calcium overload, if present, could result from a variety of factors, including altered influx of extracellular calcium via slow-channels or the Na⁺-Ca⁺ exchange mechanism (Vassort et al., 1978), or decreased diastolic extrusion of Ca⁺⁺ via Na⁺-Ca⁺⁺ exchange or a
selective Ca** pump (Martonosi, 1980). Also, cytosolic calcium overload could result from release of intracellular stores (sarcoplasmic reticulum, mitochondria) consequent to decreased high energy phosphate production. Smith and Katz (1983) have recently summarized the growing evidence supporting a role for altered intracellular metabolism in causing clinically important abnormalities in diastolic relaxation. They have introduced the term "lusitropic" (as a counterpart to "inotropic") to describe the diastolic relaxation properties of the heart. To determine the specific lusitropic defects that contribute to the findings in our study, further experiments focused on cellular metabolism will be needed.

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