Effect of Pacing-Induced Ischemia on Left Ventricular Diastolic Pressure-Volume Relations in Dogs with Coronary Stenoses

Takahì Serizawa, Blase A. Carabello, and William Grossman

SUMMARY  Mechanisms involved in altering left ventricular (LV) diastolic properties during angina were studied in 10 chloralose-anesthetized dogs with chest and pericardium open. Proximal coronary artery stenoses of ≥90% were created in both left anterior descending and circumflex coronary arteries to abolish reactive hyperemia, and the heart was paced at nearly twice its resting rate (115 ± 4 to 200 ± 5 beats/min). After pacing, increases occurred in LV end-diastolic pressure (EDP, 10 ± 2 to 21 ± 2 mm Hg, \( P < 0.001 \)), LV minimum diastolic pressure (5 ± 1 to 13 ± 2 mm Hg, \( P < 0.001 \)), LV end-diastolic volume (55 ± 3 to 60 ± 2 ml, \( P < 0.001 \)), LV end-systolic volume (28 ± 2 to 33 ± 2 ml, \( P < 0.001 \)), right ventricular (RV) systolic pressure (RVP, 27 ± 2 to 32 ± 2 mm Hg, \( P < 0.01 \)), RV EDSDP (5 ± 1 to 6 ± 1 mm Hg, \( P < 0.05 \)), and time constant (\( T \)) of LV pressure fall in diastole (35 ± 4 to 53 ± 4 msec, \( P < 0.001 \)). Decreases occurred in LV peak systolic pressure (121 ± 5 to 102 ± 5 mm Hg, \( P < 0.001 \)), LV maximum negative dP/dt (2300 ± 158 to 1319 ± 154 mm Hg/sec, \( P < 0.001 \)), and LV ejection fraction (0.49 ± 0.02 to 0.44 ± 0.03, NS), whereas heart rate was not significantly different. LV diastolic pressure-volume curves were shifted upward for each dog: at any diastolic volume, pressure was higher than control. In four dogs, the pulmonary artery was abruptly constricted, and saline was infused to produce an acute increase in RV loading (RVP, 29 ± 1/6 ± 1 to 67 ± 5/11 ± 1 mm Hg, \( P < 0.001/P < 0.001 \)), and the effect on the LV diastolic pressure-volume relation was examined. Only minor changes in this relation could be detected in contrast to the changes with pacing-induced ischemia. Since the upward shift in the LV diastolic pressure-volume curve in our ischemia model occurred in the absence of the pericardium and was associated with only small changes in RV EDSDP, we conclude that altered myocardial diastolic properties play an important role in this phenomenon. Circ Res 46: 430–439, 1980

DRAMATIC increases in left ventricular (LV) diastolic pressure relative to volume have been observed in patients during angina pectoris induced by pacing or isometric exercise and have been considered a result of both impaired LV systolic performance and altered LV diastolic properties (Dwyer, 1970; McLaurin et al., 1973; Barry et al., 1974; Mann et al., 1977, 1979; Grossman and Mann, 1978; Grossman and McLaurin, 1976; Flessas et al., 1976; Rickards and Seabra-Gomes, 1978). The alteration in diastolic properties observed in these patients has been an upward shift in the diastolic pressure-volume relationship, such that LV diastolic pressure is higher for any given volume compared to control. However, it has been reported that LV diastolic pressure-volume or pressure-length relationships do not shift upward in experimental acute global myocardial ischemia or acute regional myocardial infarction in the dog (Palacios et al., 1976; Wong et al., 1978). Furthermore, recent studies have emphasized the importance of right ventricular (RV) filling pressure, intrapericardial pressure, and ventricular interaction through the shared interventricular septum (Glantz et al., 1978; Shirato et al., 1978; Ross, 1979; Mirsky and Rankin, 1979) as possible causes for acute shifts in LV diastolic pressure-volume curves.

In the studies of Mann and co-workers (1979), peak negative dP/dt fell, whereas LV diastolic pressure and the time constant (\( T \)) of LV pressure decline in diastole both rose during postpacing ischemia in patients with severe coronary stenoses. However, RV diastolic pressure showed only minimal changes in these patients during angina. These data suggested that impaired LV relaxation and/or altered diastolic myocardial tone were important factors contributing to the altered diastolic properties during angina pectoris. To pursue the mechanism of this phenomenon in a more controlled setting, we have developed a dog model resembling human angina in that fixed severe stenoses were induced in both left anterior descending and circumflex coronary arteries, and increased myocardial oxygen demand was induced by rapid pacing. In addition, comparative effects of altered RV loading and pacing-induced ischemia on LV diastolic pressure-volume relations were assessed in the same animal. The results were strikingly similar to observations in patients with angina and support the concept of altered myocardial diastolic properties with ischemia.
Methods
Ten mongrel dogs weighing between 23 and 28 kg (mean 26 ± 1) were anesthetized with intravenous α-chloralose (100 mg/kg) in polyethylene glycol. Dogs were premedicated with a subcutaneous injection of ketamine (10 mg/kg), and if necessary, additional doses of α-chloralose were given to maintain sufficient anesthesia to suppress the corneal reflex. An endotracheal tube was placed, and ventilation was controlled by a Harvard pump delivering room air. A left thoracotomy was performed via the 5th intercostal space and the pericardium was opened widely. The proximal circumflex coronary artery and left anterior descending artery (usually just distal to the bifurcation of first diagonal branch) were freed from adipose tissue, and electromagnetic flow probes (Statham electromagnetic flow meter M-4001, Statham Instrument Inc.) were placed carefully around the arteries. To reduce the antegrade coronary artery blood flow, we used small metal clips which could be placed on the arteries and whose gap diameter could be adjusted by 0.05-mm increments beforehand, using a commercial gap gauge. We chose clips of adequate size and then placed them just distal to the flow probes on both coronary arteries (Fig. 1). By this method, antegrade flow through both circumflex and left anterior descending coronary arteries was reduced to about 50% of resting flow and kept constant during the experiment. It must be emphasized that, although antegrade blood flow was reduced to 50% of control, total myocardial blood flow probably was considerably higher due to inflow through coronary collaterals which are plentiful in the dog. Using the relationship experimentally determined for dogs by Gould (Gould and Lipscomb, 1974) between coronary stenoses and flow meter mean flow, our stenoses caused a reduction in diameter of approximately 90-92%. This corresponds to the typical situation in humans with severe coronary artery disease.

It should be pointed out that the exact degree of stenosis proved critical in our experiments. Stenoses which caused a reduction of 80% or less in diameter and which had no effect on antegrade resting flow produced no effect on resting or postpacing hemodynamics. This may represent the consequence of the unusual richness of coronary collateral pathways which characterize the dog’s coronary vasculature. On the other hand, stenoses causing a 95% or greater reduction in diameter which reduced antegrade resting flow by ≥70% either produced marked changes in resting function and hemodynamics (suggesting myocardial infarction) or predisposed to ventricular fibrillation with pacing tachycardia.

Pacing electrodes were sutured to the left atrial appendage. A high fidelity 7F pressure micromanometer catheter with injection lumen (Millar Instruments Inc.) was inserted via the right carotid artery into the left ventricle. Before and after each pressure record, the high fidelity record of LV pressure was superimposed on the pressure measured through the catheter lumen (which was directly attached to Statham P23Db pressure transducer). Zero level of the fluid-filled transducer was adjusted to 5 cm above the table supporting the dog. In some cases, an 80- to 100-cm 8F Eppendorf catheter (directly attached to Statham P23Db or low displacement P-50 pressure transducers) was used to record LV pressure and a ventriculogram. The natural frequency of this fluid-filled system with large bore catheter attached directly to the pressure transducer and filled with bubble-free saline was 38 Hz. This is in the range shown by Falsetti et al. (1974) to be required for accurate measurement of ventricular pressure. Similar changes in diastolic pressure-volume curves and indexes of relaxation in response to ischemia and RV overload were seen with micromanometer catheters and the fluid-filled system. Central aortic pressure and RV pressure also were recorded using 7F or 8F fluid-filled catheters attached directly to strain gauge transducers. During pressure recording the respirator was turned off with the lungs inflated to avoid effects of ventilation on pressure. The ECG was recorded as a standard limb lead.

Signals were amplified by a Grass model 7 polygraph (Grass Instruments Co.) and recorded on a 1507 Honeywell Visicoder (Honeywell Instruments) at a paper speed of 150 mm/sec.

Recorded pressures were digitized at 10-msec intervals by a Tektronix 4051 computer system.

![Diagrammatic representation of the experimental preparation. Clips were applied to circumflex and left anterior descending (LAD) arteries to produce 90% stenoses in these vessels. Catheters were used to measure RVP, LVP and aortic pressures (AoP) as described in the text.](http://circres.ahajournals.org/lookup/fig/1)
(Tektronix Inc.), and peak positive dP/dt and peak negative dP/dt were calculated (Gunther and Grossman, 1979). The time constant (T) of LV pressure fall was calculated by the method of Weiss et al. (1976) by using this computer system. The period from peak negative dp/dt to LV end-diastolic pressure (EDP) was divided by T and expressed as the diastolic period (DP) (Weisfeldt et al., 1978).

Single plane LV cineangiography was performed using Renografin 76 for contrast, injected at a rate of 5 ml/sec for 2-3 seconds with the dog in the left lateral decubitus position. The ventriculogram was recorded by a Siemens 16-mm cineangiography system at 50 frames/sec and LV volumes were analyzed frame by frame from end-systole to end-diastole using the area-length method (Sandler and Dodge, 1968) as modified and validated in our laboratory for volumes and mass against postmortem measurements (B.A. Carabello, R. Mee, J.J. Collins, Jr., R.A. Kloner, D. Levin, and W. Grossman, unpublished observations). LV diastolic pressure-volume curves were constructed using 20-msec data points for volume and pressure.

Except for dogs 1 and 2, propranolol (0.5 mg/kg) was injected intravenously to prevent ventricular fibrillation during pacing (Reynolds et al., 1978) and to suppress the heightened sympathetic tone associated with the anesthetized state. This was done because, in our initial experience when rapid atrial pacing was attempted in dogs with severe stenoses (~90%) of both left anterior descending and circumflex coronary arteries, ventricular fibrillation commonly occurred, terminating the experiment.

Experimental Protocol

Control Study

Control studies were performed in five dogs with the chest and pericardium open but no coronary artery constriction. Simultaneous LV pressure recording and left ventriculography were performed using a high fidelity pressure manometer with an injection lumen. In experiments using only a fluid-filled catheter, ventriculography was performed just after recording LV pressure. This allowed determination of the LV diastolic pressure-volume relationship prior to coronary stenoses.

In all 10 dogs, before coronary constriction, the left atrium was paced at twice the resting heart rate for 2-3 minutes using a square wave pacing signal 20% above threshold. Care was taken to maintain 1:1 AV conduction. Pacing was abruptly stopped, and records of hemodynamic variables obtained before, during, and after pacing were compared. In five dogs, this procedure was repeated after propranolol administration so that the response to pacing tachycardia before and after β blockade could be compared in dogs without coronary stenoses. After these control studies, coronary stenoses were induced as described above.

Pacing Control Study

After reduction of both left anterior descending and circumflex coronary artery antegrade flow to about 50% of resting flow by coronary constrictor clips, left ventriculography was performed simultaneously with pressure recording or just after measurement of pressure. This provided a control for the pacing studies, but also allowed assessment of the influence of the stenoses themselves in the five dogs that had prestenotic control studies. Isolation of the coronary vessels, placement of the clips, and adjustment of the coronary stenosis took 1.5-2 hours. During this time, some decline in ventricular performance occurred, as characterized by a fall in ejection fraction and a rise in LV end-systolic volume (Table 1).

Postpacing Study

After all pressures and heart rate recovered from the control cineangiogram, the left atrium was paced at twice the resting heart rate for 2-3 minutes as above. Pacing was stopped abruptly, and left ventriculography was done with hemodynamic recording. We analyzed one beat in the immediate postpacing period during the first 5-15 beats, when LVEDP was typically elevated. Extrasystolic and postextrasystolic beats were excluded.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Effect of Circumflex and Left Anterior Descending Coronary Stenoses on Resting Hemodynamics in Dogs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without stenosis (n = 5)</td>
<td>With stenosis (n = 10)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>114 ± 6</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>134 ± 10/11 ± 2</td>
</tr>
<tr>
<td>LVMDP (mm Hg)</td>
<td>6 ± 1</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>47 ± 5</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>17 ± 2</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.65 ± 0.02</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113 ± 8</td>
</tr>
<tr>
<td>RV pressure (mm Hg)</td>
<td>29 ± 1/6 ± 1</td>
</tr>
<tr>
<td>+dp/dt (mm Hg/sec)</td>
<td>1781 ± 166</td>
</tr>
<tr>
<td>−dp/dt (mm Hg/sec)</td>
<td>2709 ± 245</td>
</tr>
<tr>
<td>T (msec)</td>
<td>34 ± 2</td>
</tr>
<tr>
<td>DP (msec)</td>
<td>261 ± 33</td>
</tr>
<tr>
<td>DP, multiples of T</td>
<td>8.2 ± 0.5</td>
</tr>
</tbody>
</table>

Values expressed as mean ± se: HR = heart rate; DP = time from peak dp/dt to LVEDP.

* P < 0.01.
Right Ventricular Overload

In four dogs with opened pericardium and no coronary constriction, the main pulmonary artery was constricted by umbilical tape, and rapid infusion of 0.9% saline (10–20 ml/min) was given via a catheter introduced into the inferior vena cava to elevate RV systolic and end-diastolic pressures. Care was taken not to reduce LV systolic pressure excessively. Left ventriculography was done simultaneously with pressure recording or just after measurement of pressures. This permitted assessment of the effects of acute RV loading on LV diastolic pressure-volume relations in the absence of ischemia or the pericardium.

Statistics

Hemodynamic and angiographic studies before and after pacing were compared using Student’s t-test for paired data, and other comparisons were performed using two-sample Student’s t-test. Values were expressed as mean ± standard error of mean (mean ± SEM).

Results

Effect of Pacing with and without β Blockade

Pacing-induced tachycardia with a doubling of heart rate was followed by abrupt discontinuation of pacing in all 10 dogs prior to coronary constriction. Heart rate, LV systolic and diastolic pressures, RV pressure, aortic pressure, and other hemodynamic variables measured immediately (5–15 beats) postpacing showed no change compared to the pre-pacing control measurements. In five dogs, the pacing-induced tachycardia was repeated after iv propranolol but prior to coronary constriction. Again, immediate pre- and postpacing hemodynamics were not significantly different.

Effect of Coronary Constriction (Table 1)

After coronary constriction and reduction of antegrade coronary flow in the circumflex and anterior descending arteries, there was a significant increase in LV end-systolic volume (LVESV) of 17 ± 2 to 28 ± 2 ml whereas LV ejection fraction (EF) declined from 0.65 ± 0.02 to 0.49 ± 0.02. No significant changes were observed in heart rate, LV systolic pressure (LVP), LVEDP or minimum diastolic pressure (LVMDP), RV systolic pressure (RVP), RVEDP, mean aortic pressure (MAP), LV peak positive, and peak negative dp/dt, and T.

LV diastolic pressure-volume curves shifted rightward as a reflection of the increased LV volume.

Effect of Pacing-Induced Ischemia in Dogs with Coronary Stenoses (Table 2)

After pacing (Fig. 2, Table 2), LVEDP increased from 10 ± 2 to 21 ± 2 mm Hg (P < 0.0001), and LVMDP also increased from 5 ± 1 to 13 ± 2 mm Hg (P < 0.001). RVP and RVEDP increased from 27 ± 2 to 32 ± 2 mm Hg (P < 0.01) and 5 ± 1 to 6 ± 1 mm Hg (P < 0.05). LVEDV and LVESV increased and EF decreased, although the decline was not statistically significant. LVP and MAP decreased significantly, as did LV (+) dp/dt and LV (-) dp/dt. T prolonged from 35 ± 4 to 53 ± 4 msec (P < 0.001), and the DP shortened. Heart rate showed no significant change.

All LV diastolic pressure-volume curves shifted upward remarkably and rightward slightly with pacing-induced ischemia (Figs. 3 and 4). Thus, although part of the increased diastolic pressure was due to increased diastolic volume, pressure was higher at any given volume after pacing. The shifts seen in the two dogs that did not receive propranolol (dogs 1 and 2, Fig. 3) were of similar magnitude to those seen in the eight dogs that had received β blockade (dogs 3–10, Figs. 3 and 4).

Depressed LVP returned to control usually within 1 minute after cessation of pacing, and after the recovery of systolic pressure, LVEDP returned to the control level in all cases. In some cases, the increase in LVEDP was quite brief, and this variable had returned to control by 20–30 seconds post-pacing.

Table 2 Effect of Pacing-Induced Ischemia in Dogs with Severe Stenoses of Left Anterior Descending and Circumflex Coronary Arteries (n = 10)

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Postpacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>115 ± 4</td>
<td>109 ± 6</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>121 ± 5/10 ± 2</td>
<td>102 ± 5/21 ± 2*</td>
</tr>
<tr>
<td>LVMDP (mm Hg)</td>
<td>5 ± 1</td>
<td>13 ± 2*</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>55 ± 3</td>
<td>60 ± 2*</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>28 ± 2</td>
<td>33 ± 2*</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.49 ± 0.02</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>108 ± 4</td>
<td>92 ± 5*</td>
</tr>
<tr>
<td>RV pressure (mm Hg)</td>
<td>27 ± 2/5 ± 1</td>
<td>32 ± 2*/6 ± 1†</td>
</tr>
<tr>
<td>+dp/dt (mm Hg/sec)</td>
<td>1526 ± 156</td>
<td>1209 ± 131*</td>
</tr>
<tr>
<td>−dp/dt (mm Hg/sec)</td>
<td>2300 ± 158</td>
<td>1319 ± 154*</td>
</tr>
<tr>
<td>T (msec)</td>
<td>35 ± 4</td>
<td>53 ± 4*</td>
</tr>
<tr>
<td>DP (msec)</td>
<td>261 ± 15</td>
<td>318 ± 31†</td>
</tr>
<tr>
<td>DP, multiples of T</td>
<td>8.9 ± 1.3</td>
<td>6.8 ± 1.4†</td>
</tr>
</tbody>
</table>

Values expressed as mean ± se.

P < 0.01; †P < 0.05.
FIGURE 2 Pressure record of dog 7. Upper left: control without coronary artery stenoses. Upper right: RV overload without coronary artery stenoses. Lower left: Pacing control with coronary artery stenoses. Lower middle: during pacing. Lower right: postpacing. EKG, AoP, LVP, and RVP are shown. With RV overload (pulmonary constriction and saline infusion), there is little upward shift in LV diastolic pressure in this pericardium-open model. With pacing-induced ischemia, there is substantial shift in LV diastolic pressure, but only minor changes in RV diastolic pressure.

FIGURE 3 LV diastolic pressure-volume relations in dogs 1-5 with coronary stenoses before (unfilled circles) and immediately after (filled circles) pacing-induced ischemia. Although end-diastolic and end-systolic volumes were higher postpacing, diastolic pressure is clearly higher for any given diastolic volume.
Effect of RV Overload (Table 3, Figs. 2 and 4)

After main pulmonary artery constriction and rapid saline infusion, RVP increased to 67 ± 5 mm Hg (Fig. 2) and was higher than control (29 ± 1 mm Hg, $P < 0.001$), pacing control (27 ± 2 mm Hg, $P < 0.001$), and postpacing (32 ± 2 mm Hg, $P < 0.001$). RVEDP also increased (Fig. 2) from 6 ± 1 to 11 ± 1 mm Hg ($P < 0.001$) and was higher than the postpacing value (6 ± 1 mm Hg, $P < 0.001$). Compared to control, there were no significant changes in all other hemodynamic and volume parameters.

LV diastolic pressure-volume curves, which were shifted rightward (unfilled circle compared to unfilled squares), and after pacing, shifted upward remarkably and rightward slightly (filled circles). With RV overload (triangles), LV diastolic pressure-volume curves did not change consistently and were quite different from the postpacing pressure-volume curves (filled circles).

**Table 3** Effect of Right Ventricular Overload on Left Ventricular Hemodynamics and Relaxation Parameters with Pericardium Open

<table>
<thead>
<tr>
<th></th>
<th>Control ($n = 4$)</th>
<th>RV overload ($n = 4$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV pressure (mm Hg)</td>
<td>29 ± 1/6 ± 1</td>
<td>67 ± 5/11 ± 1*</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>114 ± 6</td>
<td>117 ± 9</td>
</tr>
<tr>
<td>LV pressure (mm Hg)</td>
<td>134 ± 10/11 ± 2</td>
<td>128 ± 5/12 ± 1</td>
</tr>
<tr>
<td>LVMDP (mm Hg)</td>
<td>6 ± 1</td>
<td>6 ± 2</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>47 ± 5</td>
<td>43 ± 5</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>17 ± 2</td>
<td>18 ± 2</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.65 ± 0.02</td>
<td>0.58 ± 0.03</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>113 ± 8</td>
<td>115 ± 10</td>
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<td>+dp/dt (mm Hg/sec)</td>
<td>1781 ± 166</td>
<td>1440 ± 111</td>
</tr>
<tr>
<td>−dp/dt (mm Hg/sec)</td>
<td>2709 ± 245</td>
<td>2400 ± 200</td>
</tr>
<tr>
<td>T (msec)</td>
<td>54 ± 2</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>DP (msec)</td>
<td>291 ± 33</td>
<td>283 ± 39</td>
</tr>
<tr>
<td>DP, multiples of T</td>
<td>8.2 ± 0.5</td>
<td>9.8 ± 1.6</td>
</tr>
</tbody>
</table>

Values expressed as means ± se.

*$P < 0.01$. 
obtained from four dogs, overlapped to the control or shifted slightly downward (Fig. 4).

Discussion

It has been widely observed that, in patients with coronary artery disease, angina is evoked by dynamic exercise or rapid atrial pacing (Dwyer, 1970; O'Brien et al., 1969; Grossman and McLaurin, 1976) and that, during angina, LV diastolic pressure rises remarkably with LV diastolic pressure increased at any given volume (Barry et al., 1974; Mann et al., 1977; Rickards and Seabra-Gomes, 1978; Grossman and Mann, 1978; Grossman and McLaurin, 1976; Grossman and Barry, 1980).

In contrast, in experimental global ischemia (Palacios et al., 1976) or regional myocardial infarction (Wong et al., 1978) in the dog, an upward shift of the diastolic pressure-volume curve has not been observed. If elevation of LVEDP occurred, it was due to increased diastolic volume. However, global low coronary flow ischemia and coronary occlusion models differ substantially from angina pectoris in man. In these models, systolic work and MVO₂ of the ischemic segment are reduced and this tends to protect against ATP depletion, whereas, in typical exertion-related angina, these parameters are increased. Also, in low flow global ischemic and coronary ligation models, local acidosis will develop since metabolic products are not washed away. This may be of importance since acidosis has been shown to be protective against Ca²⁺-induced increases in diastolic tension with hypoxia (Greene and Weisfeldt, 1977). Finally, species differences may play a role, with the dog relatively resistant to hypoxia-induced changes in diastolic tension as compared to man. With regard to species differences, Nayler et al. (1978) have recently reported on the hypoxia-induced rise in resting tension in the guinea pig heart, a phenomenon whose time course and responsiveness to interventions (e.g., tachycardia) are similar to observations in human angina.

To create a model more closely resembling the physiology of angina in man, coronary stenoses of both proximal circumflex and left anterior descending arteries were created in dogs, since, from our clinical experience, almost all patients whose LV diastolic pressure-volume curves shifted upward during angina had two- or three-vessel coronary artery disease with severe stenosis of proximal vessels. Gould (Gould and Lipscomb, 1974) found that antegrade coronary flow in a dog model began to decrease with a stenosis causing a reduction of ≥85% in diameter, and the hyperemic response was abolished with a reduction of 88–93% in arterial diameter. According to the regression equation, the average 49% antegrade flow reduction in left anterior descending and 52% reduction in circumflex coronary arteries produced in our model would correspond to stenoses causing a reduction in diameter of 90 and 91% in these vessels. This is comparable to the clinical situation in the average patient with angina pectoris due to severe obstructive coronary disease.

As emphasized by Vatner et al. (1971) and others, the anesthetized dog frequently has heightened sympathetic tone. Not only does this lead to a high resting heart rate, but it predisposes to ventricular fibrillation during pacing. Propranolol suppressed the heightened sympathetic tone induced by anesthesia, slowed heart rate to give enough room for pacing, and protected the heart from ventricular fibrillation during pacing-induced ischemia (Reynolds et al., 1978). We gave propranolol (0.5 mg/kg) to each dog except dogs 1 and 2, and no decrease of LVP was observed. The propranolol administration to eight of the 10 dogs in this study fortuitously made our "study population" similar to that in many of the reported studies of LV diastolic properties during angina, in which the majority of the patients were receiving propranolol at the time of the study. Propranolol administration may have been important also in our results, since studies by Weisfeldt et al. (1978) and others suggest that propranolol impairs myocardial relaxation, as will be discussed below. However, since dogs 1 and 2 showed shifts in the LV diastolic pressure-volume curve without propranolol, it seems that β-adrenergic blockade is not a necessary precursor to this phenomenon.

Compared to our previously reported patient studies (Mann et al., 1977, 1979), this experimental model exhibited differences in the aortic and LVP response to pacing-induced ischemia. MAP and LVP increased significantly in the patients but decreased significantly in the dogs following pacing. These differences may reflect more widespread and intense ischemia in the animals, since we have seen occasional patients who developed particularly severe angina with pacing and in whom arterial pressure fell substantially postpacing. Also, it is known that a fall in arterial pressure during treadmill exercise-induced angina generally signifies extensive myocardial ischemia (e.g., left main coronary stenosis or three-vessel disease). Finally, it should be pointed out that the anesthetized dog may have blunted baroreceptor responsiveness (Vatner et al., 1971) so that the rise in arterial pressure usually seen in patients did not occur.

The mechanism for the upward shift of LV pressure-volume relations associated with pacing-induced angina in patients has been debated. Grossman and Barry (1980) have suggested a role for persistent diastolic interaction of contractile elements within the LV myocardium, possibly related to both incomplete myocardial relaxation and altered diastolic tone during ischemia. On the other hand, Glantz (Glantz et al., 1978; Glantz and Parmley, 1978) and others (Ross, 1979; Shirato et al., 1978; Mirsky and Rankin, 1979) have emphasized the importance of RV filling pressure and intraper-
icardial pressure as determinants of acute shifts of the LV diastolic pressure-volume curve.

In the present study, the upward shift in the LV pressure-volume curve with pacing-induced ischemia that occurred in dogs with open pericardium militates against an important role for the pericardium in this phenomenon. Also, acute RV overload induced by pulmonary artery constriction could not produce an upward shift of the LV pressure-volume curve similar to that seen with ischemia, even though the increase in RV systolic and diastolic pressures (and, therefore, presumably in ventricular interaction) was much greater with the pulmonary artery constriction. This finding, that with the pericardium widely opened acute alteration in RV loading did not affect LV pressure-volume relations, is consistent with the results of Tyberg and co-workers (1978) who found no shift in the LV diastolic pressure-diameter relationship with pulmonary artery constriction if the pericardium was open.

Increased coronary artery pressure and flow were recognized as possible factors in causing alteration of LV diastolic properties during angina (Salisbury et al., 1960; Ahn et al., 1977). In the present study, LVP and mean arterial pressure fell during and after pacing, and the coronary arteries were mechanically constricted to such a degree that any hyperemic reaction was abolished, and no increment of flow in the constricted coronary arteries was observed. Thus, an "erectile effect" for the LV also can be neglected as an important contributing factor in these experiments.

LV peak negative dp/dt and the time constant T, which were considered as indexes of the early LV relaxation period (Weiss et al., 1974; Weisfeldt et al., 1974), were changed after pacing. Since in present study LVP also decreased significantly, it is not possible to interpret the matter of incomplete relaxation based on decreased LV (−) dp/dt (Weisfeldt et al., 1974; Grossman and McLaurin, 1976). On the other hand, T is apparently little affected by changed preload and afterload within the physiological range, although it is affected by alterations in contractility (Frederiksen et al., 1978; Weiss et al., 1976). T is also affected by ischemia; in acute global ischemia, Palacios and co-workers, (1978) demonstrated significant prolongation of T. We have previously reported significant prolongation of T in patients with pacing-induced angina (Mann et al., 1979). Serizawa (1978) found transient prolongation of T and deviation of the LV pressure curve after peak negative dp/dt from an exponential fit after occlusion of the left anterior descending coronary artery in the dog. In parallel with these changes, abnormal wall motion in the ischemic region was observed, and it was concluded that inhomogeneity of contraction and relaxation processes caused by regional ischemia might be responsible for prolongation of T. From these observations, we can speculate that factors which contribute to prolongation of T in the present experimental study include: (1) decreased LV contractility associated with ischemia; (2) altered diastolic cardiac muscle relaxation associated with ischemia; and (3) inhomogeneity or dysynchronism of the contraction-relaxation process.

The relationship between the DP (isovolumic relaxation period + diastolic filling period) and T has been analyzed by Weisfeldt and co-workers (1978). In a right heart bypass preparation without ischemia, they found that LV relaxation was complete by 3.5 T after peak negative dp/dt occurred. In the present study, the DP shortened significantly after pacing but did not coincide with proposed value of 3.5 T. The relevance of Weisfeldt's finding of complete relaxation of the normal dog heart by 3.5 T to the present study is uncertain. Whether ischemic myocardium follows the same time course as normal myocardium with relaxation complete at 3.5 T is not known. More important, T as measured reflects summation of relaxation of all areas of the ventricle. If the ischemic area was relaxing extremely slowly (with a hypothetical "T" of 130 msec) while the rest of the ventricle was relaxing normally (hypothetical "T" of 20-30 msec), the overall ventricular T might be prolonged to 50-70 msec, depending on the relative size of the ischemic area. Thus, 3.5 T for the whole ventricle would be 175-245 msec, but 3.5 T for the ischemic area would be 455 msec. In such an instance, incomplete relaxation could persist in one area to end diastole even though other areas were relaxed.

It is of interest that Weisfeldt and co-workers (1978) found that an upward shift of LV diastolic pressure-dimension curve could be induced in a nonischemic, incompletely relaxed heart by a combination of β-adrenergic blockade (propranolol) and tachycardia. Since propranolol was used in eight of our 10 studies, it may have contributed to the upward shift in diastolic pressure-volume relations with ischemia.

Acute increases in diastolic pressure relative to volume during the transient ischemia of angina pectoris have been observed by many investigators (Grossman and Barry, 1980), and the present study offers an animal model in which this phenomenon can be be reproducibly demonstrated under controlled conditions. The cause of this altered diastolic distensibility is uncertain, although a number of mechanisms need to be considered, including incomplete or impaired myocardial relaxation (Frist et al., 1978; Nayler and Williams, 1978), altered diastolic tone, tension prolongation during recovery from hypoxia (Bing et al., 1971), and even partial and reversible ischemic "contracture" of some myofibrils within the distribution of the stenotic coronary arteries (Apstein et al., 1978; Gaasch et al., 1978; Greene and Weisfeldt, 1977). These four possible mechanisms have been reviewed recently by
Grossman and Barry (1980), who proposed a hypothesis to account for the upward shift in LV diastolic pressure-volume relations in angina pectoris. According to this hypothesis, the ischemic myocardial cell is confronted with both increased net calcium influx (Henry et al., 1977) and decreased rate and extent of calcium sequestration (impaired relaxation). The increased net calcium influx could result from increased inward calcium movement and/or decreased efflux (possibly via the sodium-calcium exchange mechanism) during each contraction-relaxation cycle. The decreased rate and extent of calcium sequestration probably represents decreased ATP availability to sarcoplasmic reticulum (Nayler and Williams, 1978). Thus, in this concept, impaired relaxation due to depressed function of the sarcoplasmic reticulum coincident with excessive net calcium influx results in increased diastolic calcium concentration in the myoplasm surrounding the contractile proteins. The result is an increase in diastolic interaction of contractile elements, manifested as an increase in LV diastolic pressure relative to volume. The experimental data base on which this hypothesis rests is reviewed elsewhere (Grossman and Barry, 1980). Studies to test this hypothesis are now possible, using the experimental model described in this study.

In summary, LV diastolic pressure-volume relations shifted upward remarkably in anesthetized dogs with chest and pericardium open, during pacing-induced ischemia. Measurements of simultaneous RVP, as well as studies of acute pulmonary artery constriction in the same animals, do not support a role for increased RV filling pressure and/or intrapericardial pressure in causing this phenomenon. Although the mechanism is uncertain, persistent diastolic interaction of contractile elements manifest as an increase in diastolic pressure relative to volume remains an intriguing possibility.

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