Effects of Systemic Hypertension on Ischemic and Nonischemic Regional Left Ventricular Function in Awake, Unsedated Dogs After Experimental Coronary Occlusion

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SUMMARY Hypertension and atherosclerotic coronary arterial obstruction frequently coexist in patients. However, the effect of increased aortic pressure on ischemic segmental dysfunction is not well understood. We studied the effects of aortic pressure increases on segmental left ventricular function during myocardial ischemia. Eighty-two dogs instrumented with three to six pairs of pulse-transit piezoelectric crystals were studied in an awake, unsedated state to measure segmental wall thickness. A pneumatic balloon occluder was positioned around the proximal left anterior descending artery (LAD). Thirty-three dogs underwent LAD occlusion and served as normotensive controls (group A). Group B dogs (n = 23) received a 6-hour infusion of phenylephrine (PE) beginning 5 minutes after LAD occlusion to increase aortic diastolic arterial pressure to 120–130 mm Hg; aortic pressure was then allowed to return to normal for the subsequent 18 hours. The eight dogs in group C received a 6-hour infusion of PE, but no coronary arterial occlusion was produced. In group D (n = 12), distal constriction of the thoracic aorta was maintained for 24 hours after LAD occlusion. Regional myocardial blood flow (RMBF) was measured with radioactive microspheres in six conscious dogs and both RMBF and intramyocardial PCO2 were measured in seven open-chest dogs to assess alterations in regional myocardial oxygen supply and demand. Segments of myocardium were arbitrarily grouped according to the amount of net systolic thickening (NET) present 5 minutes after LAD occlusion and before increasing aortic pressure: group 1 retained 67–100% of control NET; group 2 0–67%, and group 3 less than 0% (paradoxical motion). In dogs receiving PE plus LAD occlusion and in dogs with aortic constriction and LAD occlusion, NET was transiently depressed in groups 1 and 2 compared with the normotensive cohort; 24 hours after occlusion, NET in groups 1, 2 and 3 did not differ significantly from that in the normotensive dogs. Systemic hypertension resulted in a significant increase in endocardial and midwall RMBF and, in seven open-chest dogs, decreased the intramyocardial accumulation of carbon dioxide after LAD occlusion. Increased aortic pressure in dogs without coronary occlusion produced reversible decreases in end-diastolic wall thickness, NET and LV dP/dt. Thus, the production of systemic hypertension with diastolic pressures of 110–120 mm Hg acutely or for 6 hours during evolving canine myocardial infarction does not appear to exert an important deleterious effect on myocardial oxygen supply and demand. However, 24 hours of mildly increased aortic pressure accentuates end-diastolic wall thinning in segments with paradoxical systolic motion and results in a failure of their return to control values at this period.

PHYSICIANS frequently encounter patients with ischemic heart disease in whom the myocardial oxygen supply/demand ratio is altered by systemic arterial hypertension. For example, uncontrolled hypertension may provoke episodes of angina in patients with coronary atherosclerosis. Further, approximately one-third of normotensive patients may become hypertensive after a myocardial infarction because of stimulation of aortic chemoreceptors supplied by the coronary arteries, release of norepinephrine from damaged myocardium or pain, fear and excitement. Because both myocardial oxygen supply and demand are increased as systemic pressure increases, the treatment of hypertension in patients with ischemic heart disease is often difficult.

Shell and Sobel suggested that a reduction of blood pressure in hypertensive patients with acute myocardial infarcts may reduce infarct size and mortality, but Shell et al. failed to substantiate these conclusions. Left ventricular (LV) function may improve in patients with acute myocardial infarcts as blood pressure is lowered. In contrast, studies performed in open-chest, anesthetized experimental animals have shown that an increase in aortic pressure may reduce the extent of ischemic injury in nonfailing hearts as assessed with epicardial ST-segment mapping, regional segmental function and myocardial metabolic alterations. Therefore, we evaluated further the early and delayed effects of acute increases in aortic pressure on segmental LV function in ischemic and nonischemic myocardium. Specifically, we investigated during experimental myocardial ischemia how an increase in aortic blood pressure alters myocardial oxygen supply/demand relationships and how LV segmental function varies with elevations in aortic pressure.

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Methods and Materials

Surgical Preparation (fig. 1)

Eighty-two mongrel dogs of both sexes were anesthetized with i.v. pentobarbital, 30 mg/kg, intubated and placed on a Harvard respirator. A thoracotomy was performed in the fifth left intercostal space under sterile conditions and the heart was suspended in a pericardial cradle. A Konigsberg (P-22) catheter-tipped manometer was placed in the LV cavity through an apical stab wound. A polyethylene catheter was placed in the left atrium. In all dogs except dog 8, the proximal portion of the left anterior descending coronary artery (LAD) was then dissected free and an inflatable balloon occluder was placed around its proximal portion. The balloon was then temporarily inflated, occluding the LAD and producing an area of cyanosis over the anterior portion of the left ventricle. Five-megahertz titanate-zirconate piezoelectric crystals, each 2 mm in diameter, were positioned near the endocardium of the left ventricle. Each endocardial crystal was then paired with a second crystal, 5 mm in diameter, sutured to the epicardium after its position was adjusted to obtain an optimal signal by the method of Franklin et al. Three to six pairs of crystals were inserted in or adjacent to the anterior zone of cyanosis produced by temporary LAD occlusion; one pair was sometimes inserted in the high lateral portion of the left ventricle far removed from the area of cyanosis (fig. 1). In 12 dogs, an externally adjustable constrictor was placed around the descending thoracic aorta. This device was fashioned of Teflon and could be inserted around the aorta with its tip exteriorized between the ribs. The degree of constriction could then be adjusted externally to a fine degree while aortic pressure was monitored.

The various catheters and wires were exteriorized between the scapulae and the thoracotomy was closed in layers. One to 2 weeks later, when they appeared to have recovered fully, the dogs were evaluated awake and unsedated. A polyethylene catheter was placed in the carotid artery under light anesthesia 24 hours before the study and, in dogs that subsequently received a phenylephrine infusion, a second catheter was placed in the internal jugular vein.

Experimental Protocol

All dogs were assigned to one of four groups.

Group A consisted of 33 normotensive control dogs. Before LAD occlusion, aortic systolic, diastolic and mean pressures, left atrial mean pressure, peak LV dP/dt, heart rate and segmental LV wall thickness from all crystal pairs were recorded. The LAD was then occluded by inflating the previously implanted pneumatic occluding device. The above measurements were recorded 5 minutes after LAD occlusion and then every 30 minutes for 8 hours and again 24 hours after occlusion. The dogs were then sacrificed and infarct size was determined.

Group B consisted of 23 dogs. Preocclusion control values were obtained in the same manner as in group A. LAD occlusion was then produced. After hemodynamic and segmental wall thickness measurements were recorded 5 minutes after occlusion, phenylephrine was infused at a rate of 0.01 mg/kg/min for 6 hours, with adjustments to maintain diastolic blood pressure at 120-130 mm Hg. The rate of phenylephrine administration was increased progressively to maintain diastolic arterial pressures within the desired range, but not if left atrial mean pressure exceeded 30 mm Hg. In most dogs, the aortic pressure gradually decreased slightly over the 6-hour period despite the augmented infusion of phenylephrine. Data were collected as in group A.

In the eight dogs in group C, no occluding balloon was placed around the LAD. The dogs in this group received phenylephrine in a manner identical to that in group B. Data were collected in the same manner as in group A.

In the 12 dogs in group D, an externally adjustable aortic constrictor was placed around the descending thoracic aorta. Aortic constriction was produced slowly beginning 5 minutes after LAD occlusion until diastolic pressure was 120-130 mm Hg. Aortic constriction was maintained for 24 hours. The constriction was adjusted at 8 hours, then remained in place overnight. Data were collected as in groups A and B.

In six dogs, the LAD was occluded and phenylephrine was infused in a manner identical to that in group B. In addition, 2-4 × 10^6 radioactive microspheres, 8-10 μm in diameter, were suspended in a 0.05% solution of Tween-80 and vigorously agitated in a Genie Vortex mixer (Scientific Industries) before injection. Ten seconds before and 60 second after injec-
tion of microspheres, blood was withdrawn at 7.75 ml/min with an infusion device (Harvard Apparatus). Microspheres were given before and 5 minutes, 30 minutes, 6 hours and 24 hours after LAD occlusion.

In seven dogs, the heart was exposed as described above. The partial pressure of intramyocardial carbon dioxide (Pmco2) was measured in the open-chest anesthetized dog with a Perkin-Elmer mass spectrometer (Model 1100B, Perkin-Elmer Corp.) In each dog, a mass spectrometer probe (EXTC Teflon catheters, Chemetron Corp. or Spectra Caths, Sorenson Research Co.) was inserted through a small nick in the epicardium and advanced gently until the sensing surfaces were entirely within the myocardium; the probes were then affixed to the epicardium by a single suture. Three 10-minute occlusions of the LAD were produced, with a 45-minute reflow period between each occlusion. Regional myocardial blood flow was measured with radioactive microspheres 5 minutes after each occlusion. Pmco2 was measured continuously. Phenylenephrine was infused immediately after the third coronary occlusion, and the infusion rate was adjusted to provide an aortic diastolic blood pressure of approximately 120 mm Hg. Pmco2 is a reliable indicator of myocardial oxygen supply and demand, and the magnitude of rise of Pmco2 after the second and third coronary occlusions is consistent in individual animals. Thus, interventions can be administered after the third coronary occlusion, and their effect on myocardial oxygen supply/demand can be assessed by the alteration in Pmco2 compared with that obtained after the second occlusion.

Measurements

Left atrial and systemic arterial pressures were measured with Statham P23Db transducers. The maximal rate of rise of LV pressure was recorded from the Konigsberg catheter-tipped manometer with an Electronics for Medicine RC differentiator. Continuous analog recordings of segmental wall thickness were recorded simultaneously from all crystal implantation sites on a Hewlett-Packard eight-channel recorder (7758A) interfaced with a Tektronix 465 oscilloscope.

Segmental LV wall thickness (mm) was measured assuming the speed of sound through myocardium to be approximately 1.5 mm/μsec. To correct for the distance, individual crystal pairs were separated, and to correct for the variance in regional performance of the nonischemic ventricle, measurements of wall thickness were expressed as a percent of control values. The analog tracings of wall thickness were digitized by hand with a Graf/Pen (Science Accessories Corp.) and stored and processed by computer (Digital DEC 10).

Three measurements of the wall thickness were made, from which four variables of wall motion were derived (fig. 2). LV end-diastolic wall thickness (EDWTH) was measured just before the rapid upstroke of the LV pressure tracing, at the nadir of the transient wall thinning produced by atrial systole (fig. 2, point A). The maximal extent of systolic wall thickening was measured between peak positive LV dP/dt and peak negative LV dP/dt, which approximate aortic valve opening and closing, respectively (fig. 2, point B). The maximal extent of systolic wall thinning also was measured (fig. 2, point C). Net systolic wall thickening (NET) was defined as the extent of maximal systolic thickening minus the amount of paradoxic systolic thinning, if any. Early diastolic thickening sometimes occurred after the peak negative LV dP/dt (fig. 2, segments A, B and C), but was not included in the measurement of NET.

Regional myocardial blood flow was calculated in endocardial, midwall and epicardial layers using standard techniques. Scintillation vials were counted in a Packard multichannel gamma scintillation counter for 5 minutes per vial with an appropriate window setting for each isotope. Isotope standards for each of the different radioactive labels that were used were also checked periodically in the same gamma scintillation counter to check the accuracy of the window settings and to prevent interference of radioisotopes with one another, which would influence the flow results erroneously.

Data Analysis

To analyze segmental function, crystal pairs were assigned arbitrarily to one of three groups defined according to the amount of NET present 5 minutes after LAD occlusion. Group 1 consisted of segments with a NET value of greater than 67% of control. Group 2 included segments retaining 0–67% of control NET. Group 3 had NET values less than 0% of control. A negative value of NET signifies overall systolic wall thinning or paradoxical bulging.

Because of the extensive system of large coronary collaterals in some dogs, transient decreases in segmental function with full recovery within 30 minutes were sometimes observed. Two dogs were excluded from subsequent analysis because histologic analysis showed no evidence of myocardial necrosis.

Postmortem Infarct Sizing

Twenty-four hours after occlusion, the dogs were sacrificed and the occluding balloon was examined to ensure that it was inflated tightly around the proximal LAD. Further, in 11 dogs, the hearts were suspended and perfused with saline at a pressure of 100 mm Hg. In no case was distal flow demonstrable past the occluding balloon. The hearts from the last 13 dogs from group A and 16 unselected hearts from group B were sectioned into four or five 1-cm thick slices, incubated in a solution of 2,3,5-triphenyl tetrazolium chloride (TTC) for 15 minutes and fixed in 10% buffered formalin. After removal of the right ventricle, infarct size was determined by weighing the unstained areas and was expressed as a percentage of total LV weight.

Statistical Analysis

Statistical comparisons between a control value (before LAD occlusion) and values after LAD occlusion were made using a one-sample $t$ test for segmental function data (where control was always 100%) and a paired $t$ test for hemodynamic data. Compari-
sons between two groups of dogs within a single time period were performed with an unpaired t test. Bonferroni's inequality was used to correct for multiple comparisons; thus, \( p < 0.005 \) was considered statistically significant. All \( t \) tests were two-tailed. All hemodynamic and segmental function data were expressed as the mean ± SEM.

**Results**

**Group A**

Segmental function of dogs with LAD occlusion that were not hypertensive is shown in figure 3. Group 1 segments were depressed below control 2 and 6 hours after LAD occlusion. Segments in groups 2 and 3 were significantly less than control values at each measurement after occlusion. After LAD occlusion, segmental function changed little from that at 5 minutes.

Alterations in EDWTH are displayed in figure 4. Five minutes after occlusion, EDWTH was least for segments with the greatest amount of ischemic functional impairment (group 3) and greatest for segments with the least impairment (group 1). EDWTH in group 3 segments increased markedly 8-24 hours after LAD occlusion; smaller increases in EDWTH also occurred in groups 1 and 2.

**Group B**

NET values for group B are shown along with those of group A dogs in figure 3. NET of group 1 segments decreased markedly as arterial blood pressure was elevated (fig. 3A) and was significantly less than preocclusion control 1-6 hours after LAD occlusion. Two segments showed paradoxic motion, a finding not present in any of the dogs in group A. However, 24 hours after occlusion, there was no significant difference between group A and group B dogs (\( p = 0.16 \)). Segmental NET in group 2 segments was significantly less than control between 5 minutes and 24 hours after occlusion. Systemic arterial hypertension produced by phenylephrine resulted in a further reduction in NET compared with normotensive controls 2-4 hours after occlusion. Twenty-four hours after occlusion, group 2 NET values were similar for both the normotensive (group A) (40 ± 5%) and the hypertensive (group B) dogs (37 ± 13%) (\( p = 0.85 \)). At
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24 hours after occlusion, five of 23 segments showed paradoxical thinning in the hypertensive dogs (group B), compared with three of 25 in the normotensive dogs (group A).*

NET values for group 3 segments are shown in figure 3C. Systemic arterial hypertension had no effect on the extent of paradoxical systolic wall thinning. Twenty-four hours after occlusion, NET in normotensive dogs was $-25 \pm 9\%$ (n = 39) and was $-40 \pm 6\%$ (n = 28) for the dogs receiving phenylephrine. Thus, NET was significantly depressed during the period of increased afterload in group 1 and 2 segments, but not group 3 segments. Twenty-four hours after occlusion, NET in group B dogs did not differ significantly from that in group A.

Alterations in EDWTH for groups 1, 2 and 3 from normotensive (group A) and hypertensive (group B) dogs are shown in figure 4. As in the normotensive dogs, EDWTH was reduced 5 minutes after LAD occlusion in direct proportion to the degree of systolic functional impairment. A pronounced rebound occurred 8–24 hours after LAD occlusion in group 2 and 3 segments (figs. 4B and 4C). Compared with that in the normotensive dogs, EDWTH was significantly less at 4 hours in group 1, at 3–5 hours in group 2 and at 3–4 hours in group 3.

The hemodynamic alterations in dogs in groups A and B are shown in table 1. Compared with the normotensive group, groups A and B had elevated aortic systolic, diastolic and mean pressures 30 minutes to 4 hours after occlusion, elevated left atrial mean pressure 30 minutes to 6 hours after occlusion and depressed heart rate (123 ± 4.8 beats/min) 1 hour after LAD occlusion ($p = 0.001$). Left atrial mean pressure decreased rapidly to the level of the normotensive group after the phenylephrine infusion was discontinued, whereas aortic pressure decreased to levels below those of the group A dogs. Peak LV dP/dt decreased in both groups after LAD occlusion, and the two groups were not significantly different. Heart rate increased in both groups 5 minutes after occlusion and generally remained elevated in the normotensive dogs, but decreased as phenylephrine was infused.

Group C

In group C dogs, all segments were placed in group 1. NET was significantly depressed below control values with the development of hypertension, reached

*Some dogs died 8–24 hours after coronary occlusion; in other dogs, technically adequate signals were lost from several crystal pairs between 8 and 24 hours. Thus, numbers in the text dealing with 24-hour values are less than those at the initiation of the experiment.
TABLE 1. Hemodynamic Alterations in Dogs with Proximal Occlusion of the Left Anterior Descending Coronary Artery and Increased Afterload

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Control</th>
<th>n</th>
<th>5 min</th>
<th>30 min</th>
<th>2 hr</th>
<th>4 hr</th>
<th>6 hr</th>
<th>8 hr</th>
<th>24 hr</th>
</tr>
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<tbody>
<tr>
<td>Dp/dt (mm Hg/sec)</td>
<td>A</td>
<td>2393±111</td>
<td>32</td>
<td>2203±126</td>
<td>2091±111*</td>
<td>2009±108*</td>
<td>1988±121*</td>
<td>2031±121*</td>
<td>1974±119*</td>
<td>1938±129*</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>2667±160</td>
<td>21</td>
<td>2355±121</td>
<td>2431±122</td>
<td>2200±101*</td>
<td>2056±106*</td>
<td>1902±80*</td>
<td>1870±103*</td>
<td>2114±90*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>3043±154</td>
<td>8</td>
<td>2955±194</td>
<td>2555±94*</td>
<td>2486±106*</td>
<td>2481±143</td>
<td>2702±236</td>
<td>2680±204</td>
<td>2921±233</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>2757±219</td>
<td>11</td>
<td>2480±265</td>
<td>2724±153</td>
<td>2544±172</td>
<td>2600±210</td>
<td>2445±184</td>
<td>2615±233</td>
<td>2680±260</td>
</tr>
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<td>HR (beats/min)</td>
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<td>124±4</td>
<td>33</td>
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<tr>
<td></td>
<td>B</td>
<td>117±5</td>
<td>23</td>
<td>130±5*</td>
<td>127±5</td>
<td>127±5</td>
<td>135±6</td>
<td>138±4*</td>
<td>152±6*</td>
<td>145±7*</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>121±6</td>
<td>8</td>
<td>120±5</td>
<td>109±6</td>
<td>105±7</td>
<td>107±11</td>
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<td>110±9</td>
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<td>128±6</td>
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</table>

All interventions were begun after 5-minute time period. All values are expressed as mean ± SEM. Time periods refer to time after proximal LAD occlusion (except group C dogs in which LAD occlusion was not produced).

*P < 0.005 (paired t test) vs preocclusion control values.

†P < 0.005 (unpaired t test) vs group A.

Abbreviations: AOS = aortic systemic pressure; AOD = aortic diastolic pressure; AOM = aortic mean pressure; LAM = left atrial mean pressure; Dp/dt = peak LV dP/dt; HR = heart rate.

A nadir at 5 hours after the phenylephrine infusion was started and remained depressed through 8 hours (fig. 5). Segmental function returned to control levels by 24 hours (NET = 104 ± 8%). NET remained depressed for 1.5 hours after phenylephrine was discontinued (fig. 5A).

Alterations in LV EDWTH mirrored the decreases in NET (fig. 5B). EDWTH was depressed below control between 0.5 and 8 hours, but returned to control levels by 24 hours.

Aortic systolic pressure was significantly elevated (170-180 mm Hg) from 0.5 to 5.5 hours; aortic diastolic pressure was 124-135 mm Hg and left atrial mean pressure increased to 21 ± 3 mm Hg at 0.5 hours and remained above 20 mm Hg for 6 hours after the start of phenylephrine. Peak LV dP/dt decreased from a control value of 3043 ± 154 mm Hg/sec to 2555 ± 94 mm Hg/sec at 0.5 hour (p = 0.005). LV dP/dt remained depressed at 2 hours, but gradually returned to control levels and was 2921 ± 234 mm Hg/sec at 24 hours. Heart rate decreased from a control value of 121 ± 6 to 109 ± 6 beats/min at 0.5 hours, but did not differ significantly from control throughout the 24-hour study period.

Group D

Aortic constriction was produced in the 12 dogs in group D to provide a nonpharmacologic method of elevating aortic pressure. Elevated levels of aortic pressure were maintained continuously for 24 hours to allow an assessment of the effects of more prolonged systemic arterial hypertension.

NET in group 1 was significantly less than in control dogs 3–5 hours after LAD occlusion (fig. 6A). However, 8–24 hours after occlusion, segmental function improved from 49 ± 10% to 83 ± 11% (associated with an increase in left atrial mean pressure from 16 ± 2% to 22 ± 3% despite continued hypertension). Twenty-four hours after LAD occlusion there was no significant difference in group 1 NET between normotensive (87 ± 9%, n = 8) and group D dogs (83 ± 11%, n = 11). In neither group 2 (fig. 6B) nor group 3 (fig. 6C) was NET significantly different from that in the normotensive dogs 24 hours after occlusion.

The alterations in segmental EDWTH in group D dogs are shown in comparison with those in group A dogs in figure 7. Segments in groups 1 and 2 in dogs in group D showed changes in EDWTH similar to those in dogs receiving an LAD occlusion and phenylephrine. EDWTH of group 3 segments (fig. 7C) remained significantly depressed compared with the normotensive group between 0.5 and 24 hours after LAD occlusion. LV segmental EDWTH did not increase between 8 and 24 hours after occlusion; this finding is in contrast to the large increases observed in both the normotensive dogs (group A) and those receiving phenylephrine (group B, fig. 4C). Therefore, although the extent of paradoxical systolic thinning is not affected by prolonged aortic constriction, the segmental EDWTH of such areas is markedly thinned.
not differ significantly from that in group B dogs (21 ± 2%).

Regional Myocardial Blood Flow and Pco2

Alterations in regional myocardial blood flow and regional function are summarized in table 2 for the three segmental function groups. Regional myocardial blood flow did not change significantly in group 1 segments. However, in group 2, endocardial blood flow decreased significantly, from 1.02 ± 0.15 to 0.73 ± 0.12 ml/g/min, 5 minutes after LAD occlusion. In these conscious dogs, phenylephrine increased aortic systolic and diastolic blood pressures (table 3). Blood flow also increased significantly in group 2 endocardial and midwall layers, while segmental function in group 2 decreased from 38 ± 6% to 24 ± 7% (p < 0.05). Twenty-four hours after occlusion, segmental function returned to prehypertensive levels (41 ± 7%). Regional myocardial blood flow increased significantly in all layers in group 2 crystals between 8 and 24 hours.

The decreases in regional function in groups 1 and 2 despite concurrent increases in regional myocardial blood flow suggested that segmental wall stress and segmental stroke work may have increased disproportionately as the blood pressure was elevated. To assess how myocardial oxygen supply/demand ratios were altered by changes in aortic pressure, we measured regional PmCO2 in the left ventricle. Intramyocardial PCO2 is an indicator of overall myocardial oxygen

compared with that in normotensive dogs, over a 24-hour period.

In dogs with aortic constrictors, aortic systolic, diastolic and mean pressures were significantly greater than in normotensive dogs 0.5–24 hours after LAD occlusion (table 1). Peak LV dp/dt did not differ from that in the normotensive dogs, nor did it change significantly from the preocclusion control value of 2757 ± 219 mm Hg/sec through 24 hours after LAD occlusion. The heart rate was 114 ± 7 beats/min in the preocclusion control period and did not change significantly over the subsequent 24 hours; heart rate was significantly less than in the normotensive group only at 8 hours after LAD occlusion (table 1).

Infarct Sizing

Gross infarct size was determined in 13 normotensive dogs (group A) and in 16 dogs that received phenylephrine and LAD occlusion (group B). In the normotensive group, the average infarct size expressed as percentage of LV weight was 19 ± 2%, which did

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**Figure 5.** Alterations in net systolic wall thickening (NET) (panel A) and end-diastolic wall thickness (panel B) are displayed for group C dogs, which received a phenylephrine infusion (striped bar) but did not undergo occlusion of the left anterior descending coronary artery (LAD). *p < 0.005 (one-sample t test) vs preocclusion control.

**Figure 6.** Net systolic thickening (NET) in group D dogs, which underwent occlusion of the left anterior descending coronary artery (LAD), followed by aortic constriction. The duration of aortic constriction is indicated by the striped bar. Compared with normotensive group A dogs, there was no significant difference in NET 24 hours after LAD occlusion in any group. *p < 0.005 (one-sample t test) vs preocclusion control.
Discussion

LV wall tension and coronary arterial flow increase as the systemic arterial pressure increases. It is therefore difficult to predict the resultant effect of increased aortic pressure on myocardial oxygen supply/demand. Regional myocardial function is sensitive to alterations in myocardial oxygen supply and demand.22

The extent of systolic LV wall thickening is a useful and accurate measure of regional function in experimental animals and in man.23-25 Although segmental length can be measured using the same technique, segmental shortening may vary according to the depth from the endocardium at which the crystals are placed.27 In addition, muscle fiber orientation through the myocardial wall changes gradually from endocardium to epicardium;28 thus, segment-length crystals placed parallel to epicardial fibers may be at a considerable angle to the fibers at the midwall. Because it is difficult to reliably and reproducibly place segment-length crystals in the same relative position in the LV wall, we measured segmental wall thickening, which can be quantitated more reliably.

Presented with a sustained increase in aortic pressure, the normal left ventricle responds with an increase in LV end-diastolic pressure and volume as Frank-Starling reserve is used to maintain stroke volume. Wall stress thus increases even more, reducing the extent and velocity of fiber shortening. However, a reduced extent of fiber shortening is necessary at higher end-diastolic ventricular volumes to maintain stroke volume. Thus, if an adequate preload is maintained, stroke volume is normally preserved with a decreased extent of fiber shortening, but at the expense of higher wall tension and stroke work.29

As our results demonstrated, in the dog with a normal left ventricle, an increase in aortic pressure induced a marked decrease in EDWTH and NET with a concomitant increase in left atrial mean pressure (fig. 5). These results are consistent with those described by others.30-33 However, we did note a decrease in peak LV dP/dt at 0.5 and 2 hours after the initiation of phenylephrine (table 1), a result that is at variance

![Figure 7. Alterations in end-diastolic wall thickness (EDWTH) in group D. EDWTH was decreased in group 3 segments 24 hours after occlusion of the left anterior descending coronary artery (LAD) compared with that in normotensive group A dogs. *p < 0.005 (one-sample t test) vs preocclusion control.](http://circ.ahajournals.org/content/circulation/65/1/122/F1.large.jpg)

### Table 2. Regional Myocardial Blood Flow (ml/g/min) and Left Ventricular Segmental Function in Awake Dogs That Underwent Occlusion of the Left Anterior Descending Coronary Artery and Received Phenylephrine

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Control</th>
<th>5 min</th>
<th>30 min</th>
<th>6 hrs</th>
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<tbody>
<tr>
<td>Group 1 END</td>
<td>5</td>
<td>0.89 ± 0.23</td>
<td>0.82 ± 0.15</td>
<td>0.85 ± 0.26</td>
<td>0.69 ± 0.21</td>
<td>0.47 ± 0.18</td>
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<tr>
<td>MID</td>
<td>5</td>
<td>0.91 ± 0.14</td>
<td>0.98 ± 0.32</td>
<td>0.96 ± 0.28</td>
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<tr>
<td>EPI</td>
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<td>0.63 ± 0.18</td>
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<tr>
<td>NET</td>
<td>5</td>
<td>100</td>
<td>105 ± 15</td>
<td>59 ± 13</td>
<td>63 ± 8</td>
<td>69 ± 7</td>
<td>86 ± 7</td>
</tr>
<tr>
<td>Group 2 END</td>
<td>12</td>
<td>1.02 ± 0.15</td>
<td>0.73 ± 0.12*</td>
<td>0.91 ± 0.14†</td>
<td>0.72 ± 0.11*</td>
<td>0.55 ± 0.11</td>
<td>0.75 ± 0.11</td>
</tr>
<tr>
<td>MID</td>
<td>12</td>
<td>1.04 ± 0.16</td>
<td>0.72 ± 0.11</td>
<td>0.99 ± 0.14†</td>
<td>0.73 ± 0.13</td>
<td>0.61 ± 0.10*</td>
<td>0.81 ± 0.09</td>
</tr>
<tr>
<td>EPI</td>
<td>12</td>
<td>0.87 ± 0.10</td>
<td>0.55 ± 0.09</td>
<td>0.60 ± 0.08</td>
<td>0.47 ± 0.07*</td>
<td>0.47 ± 0.06*</td>
<td>0.59 ± 0.05</td>
</tr>
<tr>
<td>NET</td>
<td>12</td>
<td>100</td>
<td>38 ± 6*</td>
<td>24 ± 7**</td>
<td>23 ± 10*</td>
<td>21 ± 10*</td>
<td>41 ± 7**</td>
</tr>
<tr>
<td>Group 3 END</td>
<td>4</td>
<td>1.06 ± 0.40</td>
<td>0.62 ± 0.29</td>
<td>0.79 ± 0.44</td>
<td>0.49 ± 0.25</td>
<td>0.49 ± 0.26</td>
<td>0.63 ± 0.25</td>
</tr>
<tr>
<td>MID</td>
<td>4</td>
<td>1.06 ± 0.28</td>
<td>0.60 ± 0.27</td>
<td>0.76 ± 0.34</td>
<td>0.47 ± 0.20</td>
<td>0.48 ± 0.22*</td>
<td>0.62 ± 0.20</td>
</tr>
<tr>
<td>EPI</td>
<td>4</td>
<td>0.68 ± 0.25</td>
<td>0.46 ± 0.18</td>
<td>0.60 ± 0.29</td>
<td>0.35 ± 0.11</td>
<td>0.39 ± 0.16</td>
<td>0.53 ± 0.09</td>
</tr>
<tr>
<td>NET</td>
<td>4</td>
<td>100</td>
<td>-49 ± 13*</td>
<td>-16 ± 27*</td>
<td>-16 ± 23*</td>
<td>-20 ± 22*</td>
<td>-18 ± 28*</td>
</tr>
</tbody>
</table>

*p < 0.05 vs control.

†p < 0.05 vs 5-minute value.

Abbreviations: END, MID, EPI = endocardial, midwall and epicardial layers; NET = net systolic thickening (% of control); n = number of segments in each group.
with the experience of others. However, in these latter studies the augmentation in afterload was comparatively brief and was produced in open-chest dogs by aortic constriction, in awake dogs by phenylephrine with heart rate held constant, and in isolated cat hearts. Our results indicate that a prolonged augmentation of aortic pressure produced by a 6-hour phenylephrine infusion results in a diminished peak LV dp/dt.

EDWTH and NET remain depressed for 1.5 hours after discontinuation of phenylephrine, despite the earlier return of left atrial pressure to control levels (figs. 5A and 5B, table 1). This persistent ventricular dilatation may represent a form of "creep" or retarded deformation while a muscle is subjected to a constant stress. Alternatively, a depression of myocardial contractility may have occurred as a result of increased wall tension and α-receptor-mediated coronary vasoconstriction. However, relative subendocardial ischemia does not occur with brief periods of increased LVEDP or aortic pressure. Other possible explanations for the apparent depression of myocardial contractile state with increasing afterload include a reflex withdrawal of sympathetic tone resulting from baroreceptor stimulation or a direct depressant effect of phenylephrine. In the awake dog, however, the carotid sinus reflex has only a minor effect on ventricular contractility. Phenylephrine is not a direct myocardial depressant, but rather, produces a mild positive inotropic effect, presumably a result of α-receptor stimulation in the left ventricle. However, increased aortic pressure produced by a 6-hour infusion of phenylephrine results in a transient depression of LV dp/dt in dogs without coronary occlusion and a sustained depression in NET.

One objective of this study was to determine the effects of a transient period of systemic arterial hypertension on myocardial ischemia. A major reduction in the myocardial oxygen supply/demand ratio with augmented LV afterload would be expected to result in an extension of the ischemic process, manifested by a deterioration of segmental function. Aortic pressure was increased by means of a 6-hour phenylephrine infusion (group D). At 24 hours after LAD occlusion, segmental function in dogs made hypertensive by either of the two methods was not different from that in the normotensive dogs. Thus, elevation of systemic arterial pressure to levels achieved after coronary occlusion in nonhypertrophied hearts, whether brief (6 hours) or prolonged (24 hours), does not appear to result in infarct extension as evaluated by measurement of segmental LV function.

Direct measurements of intramyocardial PCO2 with a mass spectrometer in seven open-chest dogs showed that systemic hypertension with diastolic pressures of about 120 mm Hg has a beneficial effect on the myocardial oxygen supply/demand ratio after LAD occlusion (table 4). These results should be considered preliminary because a range of blood pressure elevations should be examined. Further, the measurement of regional myocardial blood flow showed a significant increase in flow in moderately ischemic group 2 segments 30 minutes after LAD occlusion, from 0.73 ± 0.12 to 0.91 ± 0.14 ml/g/min in the endocardial layer. At the same time, however, NET LV segmental function decreased in these dogs from 38 ± 6% to 24 ± 7% (table 3). These data suggest that no major deterioration occurs in ischemic regional myocardial oxygen supply and demand as systemic blood pressure is elevated to 115-120 mm Hg; the decreases in NET are most likely a result of increased wall stress rather than of diminished segmental contractility. These conclusions are also supported by the similarity in gross infarct size in groups A and B.

Other work has shown elevation of mean arterial blood pressure to 140 mm Hg with methoxamine infusion with a consequent increase in myocardial oxygen consumption by 77 ± 12% produced electrocardiographic signs of ischemia in only three of 20 patients with coronary artery disease. In contrast, an augmen-

Table 3. Hemodynamic Variables in Dogs in Which Regional Myocardial Blood Flow Was Measured

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>5 min</th>
<th>30 min</th>
<th>6 hrs</th>
<th>8 hrs</th>
<th>24 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>AOS</td>
<td>6</td>
<td>130 ± 8</td>
<td>130 ± 8</td>
<td>173 ± 7*</td>
<td>151 ± 9*</td>
<td>105 ± 3*</td>
</tr>
<tr>
<td>AOD</td>
<td>6</td>
<td>92 ± 5</td>
<td>95 ± 6</td>
<td>140 ± 6*</td>
<td>122 ± 7*</td>
<td>89 ± 6</td>
</tr>
<tr>
<td>HR</td>
<td>6</td>
<td>107 ± 11</td>
<td>112 ± 6</td>
<td>101 ± 10</td>
<td>128 ± 7</td>
<td>149 ± 6*</td>
</tr>
<tr>
<td>HR × BP</td>
<td>6</td>
<td>14.5 ± 2.3</td>
<td>14.8 ± 1.6</td>
<td>17.8 ± 2.2</td>
<td>19.3 ± 1.4</td>
<td>15.8 ± 1.0</td>
</tr>
</tbody>
</table>

*p < 0.05. Abbreviations: AOS, AOD = aortic systolic and diastolic pressures (mm Hg); HR = heart rate (beats/min). HR × BP = product of heart rate and aortic systolic blood pressure (mm Hg beats/min; ×1000).

Table 4. Intramyocardial Carbon Dioxide Tension and Regional Myocardial Blood Flow in Open-Chest Dogs Before and After Administration of Phenylephrine

<table>
<thead>
<tr>
<th></th>
<th>ΔPmCO2 (mm Hg)</th>
<th>RMBF (ml/g/min)</th>
<th>AOD (mm Hg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occl 2</td>
<td>7</td>
<td>33.5 ± 3.4</td>
<td>0.22 ± 0.06</td>
<td>80 ± 0.3</td>
</tr>
<tr>
<td>Occl 3</td>
<td>7</td>
<td>23.5 ± 2.6*</td>
<td>0.35 ± 0.10</td>
<td>121 ± 2*</td>
</tr>
</tbody>
</table>

*p < 0.05 (paired t test) vs occlusion 2 value. Abbreviations: ΔPmCO2 = increase in intramyocardial P CO2 after LAD occlusion; Occl 2, OCCL 3 = second and third LAD occlusion; RMBF = regional myocardial blood flow to the left ventricular ischemic region; AOD = mean systemic arterial diastolic pressure; HR = heart rate.
tation of myocardial oxygen consumption to similar levels with rapid atrial pacing resulted in ischemic ST-segment changes in 14 of 20 patients. These data, as well as those of the present study, support the concept that elevations of systemic pressure, with diastolic elevations to 120 mm Hg, do not reduce myocardial oxygen supply relative to demand in ischemic myocardium.

EDWTH decreases in ischemic (fig. 4) and in non-ischemic (fig. 5B) myocardium as aortic pressure increases. In the absence of hypertrophy, mass remains constant and therefore, wall thickness decreases as LV volume increases. However, segmental end-diastolic thickness also decreases in direct proportion to the degree of systolic ischemic dysfunction (fig. 4). Thus, group 3 segments (with paradoxic motion) demonstrate the greatest degree of end-diastolic thinning after LAD occlusion (fig. 4). Both ischemic and non-ischemic segments of the same heart are subjected initially to the same levels of wall stress. The rapid and proportionate loss of wall thickness in ischemic areas may result, in part, from the loss of intravascular mural blood volume. Alternatively, the diastolic wall thinning of segments with paradoxic motion has been ascribed to stress-relaxation, or creep, secondary to repeated passive stretching of paradoxic areas, with anatomic disruption of myofibrillar architecture resulting in increased segmental compliance. We cannot differentiate the relative roles these pathophysiological forces may play in this study, but it is evident that both ischemia and increased LVEDP can act in an additive manner to cause diastolic wall thinning, thereby increasing wall stress.

Eight to 24 hours after LAD occlusion, relatively large increases in LV and EDWTH occurred primarily in the most ischemic group 3 segments (fig. 4). In the normotensive group (group A) such increases occurred in the absence of significant changes in left atrial mean pressure. Such changes are presumably due to local tissue edema, inflammatory cellular infiltration and local rigor mortis, and have been reported by others. A new finding of this study is that although the extent of paradoxic systolic thinning of group 3 segments was unaffected by an increased aortic pressure produced by aortic constriction, EDWTH was markedly reduced 24 hours after occlusion (fig. 7C). Further, the rebound in wall thickening in normotensive dogs and dogs that received phenylephrine (group B) did not occur. This finding suggests that prolonged hypertension produced by aortic constriction accentuates wall thinning in severely ischemic areas of myocardium. Such wall thinning has an adverse effect on survival after myocardial infarction in patients. Further, this finding may provide an explanation for the increased incidence of myocardial rupture in patients with hypertension after myocardial infarction, especially in patients without LV hypertrophy.

The application of our findings to patients with hypertension and ischemic heart disease should be undertaken with caution. Many patients have multivessel coronary artery disease or LV hypertrophy or lack the extensive system of relatively large collateral vessels that exist in the canine heart. Further studies in patients are required to assess the clinical applicability of the experimental data we have obtained.

Acknowledgment

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