The Effect of Generalized Alpha-receptor Stimulation on Regional Myocardial Blood Flow Distal to a Severe Coronary Artery Stenosis

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AND DAVID O. WILLIAMS, M.D.

SUMMARY Stimulation of coronary artery α receptors may decrease regional myocardial blood flow in patients with coronary artery disease. We studied 13 closed-chest conscious pigs to compare the role of vasocstriction of coronary conductance vessels and that of arteriolar resistance vessels in this response. An artificial stenosis 7.5 mm long that caused an 82% reduction in vessel diameter was placed within the lumen of the left anterior descending coronary artery. Radioactive microspheres were used to determine regional myocardial blood flow in endocardium and epicardium distal to the stenosis and in endocardium and epicardium supplied by the circumflex coronary artery. In seven pigs, hemodynamics and regional myocardial blood flow were measured (1) during control conditions, (2) at the tenth minute of i.v. norepinephrine infusion (to increase mean arterial pressure 20 mm Hg), (3) during a second control period and (4) at the tenth minute of i.v. adenosine infusion (to lower diastolic arterial pressure to 55 mm Hg).

In response to norepinephrine, regional myocardial blood flow (ml/min · g⁻¹, mean ± SD) increased in the distal zone epicardium (1.07 ± 0.20 to 1.29 ± 0.23 mean ± SD, p < 0.004) and endocardium (1.04 ± 0.24 to 1.21 ± 0.24, p < 0.05). Flow increased to a similar extent during norepinephrine in the circumflex zone epicardium (1.11 ± 0.16 to 1.48 ± 0.48, p < 0.01) and endocardium (1.22 ± 0.19 to 1.62 ± 0.54, p < 0.02). In contrast, during adenosine, regional myocardial blood flow increased in circumflex zone endocardium (1.60 ± 0.51 to 3.07 ± 0.83, p < 0.005) and epicardium (1.44 ± 0.44 to 3.83 ± 1.35, p < 0.005), declined in distal zone endocardium (1.21 ± 0.39 to 0.62 ± 0.22, p < 0.005) and remained unchanged in distal zone epicardium (1.33 ± 0.36 to 1.23 ± 0.29, NS).

Six additional pigs were given i.v. propranolol, 2.0 mg/kg, and studied as described above. Regional myocardial blood flow during infusion of norepinephrine did not change significantly compared with control. Calculated coronary arteriolar resistance increased significantly (p < 0.01) compared with control in both endocardium and epicardium distal to the stenosis. The results suggest that in the presence of a severe fixed coronary artery stenosis, α-mediated arteriolar vasoconstriction may compete with, but is unlikely to overwhelm, metabotically mediated vasodilatation.

ATTENTION has been focused on the role played by coronary artery α receptors in regulating a local myocardial blood flow. Data from animal and human studies indicate that under normal resting circumstances, basal coronary artery α tone exerts a modest inhibiting effect on myocardial blood flow. Stimulation of coronary α receptors may compete with, and even limit, increases in coronary blood flow required to meet increases in myocardial oxygen demand. Studies by Mudge and co-workers indicate that in the presence of a severe coronary stenosis and limited or no hyperemic reserve, systemic vasoconstriction elicited by cold pressor stress can decrease coronary blood flow despite an increase in arterial blood pressure and an associated increase in myocardial oxygen demand. Activation of coronary artery α receptors is thought to be responsible for this paradoxical response. It is not known whether the increase in resistance and decline in blood flow result from vasomotor constriction of conductance vessels or coronary arterioles (resistance vessels), although Raizner et al. showed that vasoconstriction of conductance vessels at the site of preexisting atherosclerotic lesions can occur after cold pressor stimulation. It is also unknown to what extent α-adrenergic blockade contributes to this response.

We undertook the present investigation in closed-chest pigs in which severe proximal, coronary artery stenosis was created to determine if α stimulation of coronary resistance vessels distal to a severe stenosis can cause a decrease in regional myocardial blood flow. One group of pigs was subjected to β blockade; the other group was not.

Materials and Methods

Animal Preparation

Thirteen anesthetized closed-chest pigs (mean weight 40.5 kg, range 37–46 kg) were prepared as follows. A double-lumen #8F catheter was placed in the central aorta through a cutdown of the left femoral artery. The catheter was used to monitor pressure (Hewlett-Packard transducer model 1280) and to withdraw samples of blood for determination of pH, Po2 and Pco2. Another #8F double-lumen catheter was placed in the inferior vena cava through the left femoral vein and used to administer medications and fluids. A #8F NIH angiographic catheter was placed...
under fluoroscopic control retrograde into the left atrium through a cutdown of the right femoral artery and used to monitor pressure and to administer radiolabeled microspheres (diameter 15 ± 1 μ) (New England Nuclear) for determination of regional myocardial blood flow. A different isotope was chosen at random for each flow determination. Approximately 4.0 × 10^6 spheres with 85–105 μCi of activity were given with each injection. The spheres were suspended in 10% dextran with 0.01% Tween-80 and sonically dispersed for 15 minutes before each injection. A reference collection of arterial blood was obtained by catheter in the central aorta for 2 minutes after each administration of microspheres (withdrawal rate 10 ml/min). The pig's heart rate was monitored with ECG lead II.

After the left atrial catheter was placed, the pig was systemically anticoagulated with i.v. heparin (225 U/kg). Under fluoroscopic control, the left anterior descending coronary artery was selectively catheterized through the right carotid artery with a modified #7F Amplatz catheter. The artery was visualized by hand injection of 3–5 ml of Renografin-76. Then, a 0.021-mm Teflon-coated guidewire with a 3-cm floppy end was inserted through the catheter into the distal portion of the left anterior descending artery. The catheter then was removed, leaving the wire guide in the vessel. After this, a specially made plastic stenosis was advanced over the wire and into the proximal third of the left anterior descending artery with the aid of a small, thin, flexible pushing catheter (i.d. 0.76 mm; o.d. 1.10 mm). Then, the wire and pushing catheter were withdrawn quickly to permit blood flow through the central lumen of the stenosis. The artificial stenosis is a truncated cone 7.5 mm long, with outer diameter tapering from 3.5 mm (proximal end) to 3.25 mm (distal end). Its central lumen was 0.625 mm in diameter and caused an 82% reduction in the diameter of the vessel. To prevent clotting within its lumen, the stenosis was coated with benzalkonium-chloride heparin complex (North American Science Associates) before placement. The device and results of validation studies with a 5-mm version have been described in detail.

In six pigs, the stenosis was modified to permit recording of arterial pressure distal to it. This was accomplished by boring a 1.5-mm hole through the stenosis. A thin-walled flexible plastic catheter 50 cm long (o.d. 1.5 mm; i.d. 1.4 mm) was secured inside the second lumen with its distal end flush with the distal end of the stenosis. The device was inserted into the coronary artery as described above. However, once in place, the proximal end of the catheter could be used to monitor pressure at the distal end of the stenosis. In these pigs, a #7F angiographic catheter was advanced from the internal jugular vein to the right atrium and coronary sinus and finally to the proximal end of the anterior interventricular vein (AIV). This catheter was used to obtain samples for determination of oxygen content using a Lex-O2-Con (Lexington Instruments).

After the catheters had been placed, all cutdown sites were closed with 2-0 silk sutures. Halothane (0.5–1.5%) and nitrous oxide (50%) anesthesia was discontinued and the pigs were allowed to awaken. The pigs’ lungs were ventilated frequently with an Ambu-bag to maintain pH, P02 and Pco2 within the physiologic range. To keep the pigs comfortable and quiet during the experiment, small doses of i.v. sodium thiamylol (20–30 mg) were given every 60–90 minutes. Although mildly sedated, the pigs were easily roused and had brisk corneal reflexes. At least 1 hour was allowed to elapse so that any effects the injections of Renografin might have had on myocardial blood flow would have dissipated by the time the study was started. In dogs, the peak hyperemic effect of sodium diatrizoate occurs 6 seconds after intracoronary injection in amounts sufficient to visualize the vessel, and the response lasts no more than 3–4 minutes.

**Intravenous Norepinephrine**

Seven pigs were studied as follows. After control recording of hemodynamics (heart rate, systemic arterial and left atrial pressure) and determination of regional myocardial blood flow, i.v. norepinephrine, 6–14 μg/min, was infused to increase mean arterial pressure approximately 20 mm Hg above control levels so as to mimic the blood pressure increase (15–20 mm Hg) in humans subjected to cold pressor stress. After 10 minutes, hemodynamics were recorded, a second injection of radiolabeled microspheres was performed, and the infusion was then discontinued. After the pig had recovered for 20–30 minutes, hemodynamics were again recorded and microspheres again injected to determine regional myocardial blood flow. Next, to compare the vasodilatory reserve of the coronary bed distal to the stenosis with that of the normal, unobstructed circumflex coronary artery, i.v. adenosine was infused at a rate of 20–40 mg/min to lower diastolic arterial pressure to 55–60 mm Hg. The infusion was maintained for 10 minutes, after which hemodynamics were recorded and regional myocardial blood flow was determined.

The Amplatz catheter was reinserted into the carotid artery and advanced to the left anterior descending artery. A cineangiogram was then recorded to confirm the location and patency of the stenosis and to be sure that blood continued to flow through it. The angiogram was recorded at 60 frames/sec on 35-mm film (Kodak CFX) with a Phillips image-intensifier system. The system has a fine line grid (6:1), a cesium iodide phosphor and minimal resolution of 1.5–2.0 line pairs/mm. Film exposure was at 100 kV and 150 mA with the pig in the 45° left anterior oblique position. Then, potassium chloride was injected directly into the left anterior descending artery and the heart was removed and sectioned for determination of microsphere activity.

**Intravenous Norepinephrine with β Blockade**

Six additional pigs were studied as follows. Propranolol, 2.0 mg/kg, was given intravenously. Thirty
to 60 minutes later control hemodynamics and regional myocardial blood flow were determined as described above. Next, i.v. norepinephrine, 2.8–5.0 μg/min, was infused to raise mean arterial pressure 20 mm Hg. After 10 minutes, hemodynamics and regional blood flow measurements were repeated, and the infusion was discontinued. When the pig had recovered for 20–30 minutes, hemodynamics and blood flow were measured again. Paired samples of arterial and AIV blood were obtained for measurement of oxygen content just before each blood flow determination. Next, approximately 300,000 radio-labeled microspheres (15 μ in diameter; total activity ~ 4.0 μCi) were injected directly into the distal left anterior descending coronary bed through the pressure catheter attached to the stenosis. This was done to label myocardium perfused by the stenosed portion of the left anterior descending coronary artery. The pig was then sacrificed and the heart removed and sectioned for determination of microsphere activity.

Recording of Distal Coronary Artery Pressure

Distal coronary artery and central aortic pressures were recorded simultaneously in the pigs given norepinephrine after β blockade with propranolol. The coronary artery and central aorta pressure transducers were kept at the same level throughout the study. The zeros for each transducer were identical (confirmed by switching the pressure lines at the start of each experiment), as were the calibrations, (confirmed by the fact that identical phasic pressures were recorded from each vessel when the lines were switched to the opposite transducer). Pressures (range 0–200 mm Hg) were recorded on paper with a Hewlett Packard eight-channel recorder (model 7788A).

A “pop” test performed with the fluid-filled perfusion catheter attached to the stenosis demonstrated an acceptable frequency response (3 dB roll off at 5.5 Hz) for the system. Patel et al.13 showed in a canine preparation that roughly 95% of all phasic information in the arterial pressure wave form is found in its first four harmonics. The pigs in our study had heart rates in the range of 1.5 Hz, so it can be shown that the catheter-transducer system can recover 90–95% of all phasic information available in the pressure signal.

Sectioning the Heart and Determining Regional Myocardial Blood Flow

After the heart was removed, it was thoroughly rinsed in tap water and blotted dry. The location of the proximal end of the stenosis was marked with a silk suture, after which the coronary vessel was opened with Metzenbaum scissors and the stenosis removed.

The inside of the stenosis showed no evidence of fibrin deposition or blood clot formation in any of the pigs.

In the seven pigs that did not receive β blockade, the heart was divided into a distal zone, defined visually by tracing the distribution along the free wall of the left ventricle of epicardial vessels distal to the location of the stenosis, and into a circumflex (i.e., normal) zone. The latter consisted of a rectangular block of tissue approximately 5 × 3 cm at the base of the heart in the distribution of the circumflex coronary artery. After fat and epicardial blood vessels were removed, each tissue block was cut into 1–2-g cubes. The cubes were divided into endo- and epicardial halves. The location of each tissue sample was recorded on a diagram of each large tissue block.

Each sample was placed in a preweighed tube and weighed. The samples were then placed in a gamma well-counter (Packard Instruments), and the radioactive activity of each isotope was measured. A computer was used to correct overlapping isotope counts. Regional myocardial blood flow (ml/min • g⁻¹) was also determined by computer for each intervention. Distal zone samples were included in the data analysis only if the absolute value of endocardial flow during adenosine infusion decreased compared with control levels and the distal zone endocardial-to-epicardial blood flow ratio under control conditions was at least 0.60.

A decline in flow during adenosine infusion was specified to ensure that vasodilatory reserve was substantially reduced in endocardial samples selected for analysis. Adherence to this criterion yielded corresponding epicardial samples in which flow reserve also was considerably reduced. To avoid analysis of severely ischemic myocardial samples, all distal zone samples had to have control endocardial-to-epicardial blood flow ratios of at least 0.60.

In the six pigs that received β blockade, the distal and circumflex zones were defined based on the tissue distribution of the radioactive microspheres. Tissue specimens that were in the anatomic distribution of the left anterior descending artery distal to the stenosis and contained high concentrations of microspheres (at least 7500 spheres per g of tissue) were defined as belonging to the distal zone.14 Tissue specimens in the anatomic distribution of the circumflex artery that contained negligible concentrations of marker microspheres (i.e., more than 3 SD below distal zone levels) were classified as belonging to the normal zone. Distal zone samples with control endocardial-to-epicardial flow ratios less than 0.60 were excluded from analysis. This method of defining the distal and circumflex zones provided an objective anatomic basis for defining the two zones which was independent of other criteria except for the criterion concerning the control distal zone endocardial-to-epicardial blood flow ratio.

A value of at least 0.60 for this ratio ensured that the samples studied in this group would be similar to those of the group that received norepinephrine but not β blockade. Inspection of the tissue sample maps for both groups showed that the anatomic locations of distal and circumflex zone samples were similar.

Statistical Analysis

Data are expressed as mean ± SD. The significance of group mean changes in hemodynamic variables, coronary vascular resistance, arterial-AIV oxygen difference and regional myocardial blood flow was assessed by blocked one-way analysis of variance13
and paired t tests. The null hypothesis tested in each case stated that the mean value for the group mean during the intervention (i.e., norepinephrine or adenosine infusion) did not differ significantly ($p < 0.05$) from that of control. Although multiple $t$ tests were performed, the group mean values were independent, and therefore, $p < 0.05$ was considered significant.

**Results**

**Intravenous Norepinephrine**

**Hemodynamics (table 1)**

Systolic arterial pressure and rate-pressure product (heart rate × systolic arterial pressure) increased significantly during norepinephrine infusion compared with control. After norepinephrine was discontinued, the rate-pressure product and systolic arterial pressure declined toward control levels but remained increased ($p < 0.05$). Compared with control 2 values, adenosine resulted in a significant decline in systolic arterial pressure and an increase in heart rate; however, the rate-pressure product during adenosine did not differ significantly from that of control 2. Mean left atrial pressure did not change significantly during the study.

**Regional Myocardial Blood Flow (fig. 1, table 2)**

In response to adenosine infusion both endocardial and epicardial blood flow in the circumflex zone increased markedly compared with control. In contrast, as anticipated based on selection criteria, distal zone endocardial flow during adenosine infusion decreased compared with control 2. Flow in the distal epicardial zone tended to decline ($p = 0.382$) compared with control 2, as did the endocardial-to-epicardial flow ratios in distal and circumflex zones. Thus, in contrast to the circumflex zone, flow reserve in the distal zone was

### Table 1. Hemodynamic Results—Intravenous Norepinephrine Protocol

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Norepinephrine</th>
<th>Control 2</th>
<th>Adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>77 ± 15</td>
<td>80 ± 16</td>
<td>85 ± 16</td>
<td>105 ± 23†</td>
</tr>
<tr>
<td>Systolic arterial pressure (mm Hg)</td>
<td>118 ± 8.11</td>
<td>142 ± 11.1†</td>
<td>129 ± 16.4*</td>
<td>88 ± 6.4‡</td>
</tr>
<tr>
<td>Rate-pressure product (mm Hg/min)</td>
<td>9050 ± 1680</td>
<td>11300 ± 1710*</td>
<td>10950 ± 2380*</td>
<td>9170 ± 1980</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>4.9 ± 3.5</td>
<td>6.4 ± 3.1</td>
<td>4.6 ± 4.2</td>
<td>4.9 ± 4.8</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* $p < 0.05$ vs control 1.

† $p < 0.01$ vs control 1.

‡ $p < 0.05$ vs control 2.

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**Figure 1.** Distal and circumflex zone regional myocardial blood flow for each pig during each phase of the norepinephrine (without β blockade) protocol. Circumflex zone endocardial and epicardial flows increased markedly in six of seven pigs during adenosine (AD) infusion, indicating substantial vasodilatory reserve in this region. One pig did not exhibit the expected increase in circumflex flows with adenosine but was included in the analysis because both calculated resistance and arterial pressure declined during the infusion. Distal zone flow responses to adenosine were opposite to those of the circumflex zone, indicating that vasodilatory reserve was considerably impaired in the vascular bed distal to the stenosis. Despite the presence of very different vascular reserves in the two beds at the time of stimulation with norepinephrine (NE), the endocardial and epicardial flow responses in the two zones were similar. The distal zone epicardial flow response to norepinephrine was similar in all pigs despite the presence of relatively more vasodilatory reserve in two (labeled a and b).
minimal in the endocardium and considerably reduced in the epicardium.

The two zones responded similarly to norepinephrine infusion. Epicardial flow in each zone increased by a comparable amount compared with control 1 (distal zone 21.1 ± 12.5% vs circumflex zone 31.3 ± 22.9%, p = 0.333). The percent increase in endocardial flow did not differ significantly between the two zones (distal zone 18.3 ± 19.2% vs circumflex zone 30.6 ± 25.3%, p = 0.395). Distal zone endocardial blood flow decreased in only one pig. Finally, the endocardial-to-epicardial blood flow ratio for both distal and circumflex zones failed to change significantly during norepinephrine infusion compared with control 1.

**Intravenous Norepinephrine with β Blockade**

### Hemodynamics (table 3)

As required by the study protocol, the mean aortic pressure increased significantly during norepinephrine infusion and then returned to control levels once the infusion was discontinued. The mean distal coronary pressure also increased significantly during norepinephrine and returned to control once the infusion was stopped. The heart rate did not change significantly during the study. In contrast, mean left atrial pressure increased modestly but significantly during norepinephrine infusion and then returned to control levels after the drug was discontinued. Finally, although the rate-pressure product increased compared with control in each pig during norepinephrine administration, the changes were not statistically significant.

### Regional Myocardial Blood Flow (table 4)

During norepinephrine infusion, neither endocardial nor epicardial blood flow distal to the stenosis changed compared with control; thus, the endocardial-to-epicardial blood flow ratio distal to the stenosis did not change significantly during the study. In the circumflex zone, endocardial and epicardial flows and the endocardial-to-epicardial flow ratio did not change. Endocardial flow and epicardial flow distal to the stenosis were significantly (p < 0.05) decreased under control conditions compared with their respective flow in the circumflex zone. Further, the control left anterior descending-to-circumflex endocardial flow ratio was significantly reduced compared with that of 63 normal pigs (0.75 ± 0.18 vs 0.99 ± 0.09, p < 0.001) studied in our laboratory under similar conditions. The same was true of the left anterior descending-to-circumflex epicardial flow ratio, which was 1.02 ± 0.09 in 63 normal pigs, compared with 0.84 ± 0.09 in the six pigs in this study (p < 0.001).

### Coronary Vascular Resistance (table 5)

Arteriolar resistance in endocardial and epicardial layers distal to the stenosis was calculated in the traditional fashion as the quotient of mean distal coronary pressure and flow. This approach was adopted to conform with other reports in the literature, but even though the effective backpressure in the system may be substantially greater than zero, calculation of resistance using a waterfall model provided results comparable to those obtained using the conventional method, which ignores backpressure.

Both endocardial and epicardial resistances distal to the stenosis increased significantly (p < 0.01) during norepinephrine infusion in the setting of β blockade, and returned to control levels after the infusion was terminated. In contrast, neither endocardial nor epicardial resistance in the circumflex zone changed significantly during norepinephrine infusion compared

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**TABLE 2. Distal and Circumflex Zone Endocardial and Epicardial Blood Flow — Intravenous Norepinephrine Without β Blockade**

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Norepinephrine</th>
<th>Control 2</th>
<th>Adenosine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal zone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>1.04 ± 0.24</td>
<td>1.21 ± 0.24*</td>
<td>1.21 ± 0.39</td>
<td>0.62 ± 0.22**</td>
</tr>
<tr>
<td>Epicardium</td>
<td>1.07 ± 0.20</td>
<td>1.29 ± 0.23†</td>
<td>1.33 ± 0.36</td>
<td>1.22 ± 0.29</td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>0.97 ± 0.09</td>
<td>0.94 ± 0.07</td>
<td>0.91 ± 0.11</td>
<td>0.53 ± 0.20**</td>
</tr>
<tr>
<td><strong>Circumflex zone</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>1.22 ± 0.19</td>
<td>1.62 ± 0.54‡</td>
<td>1.60 ± 0.51</td>
<td>3.07 ± 0.83**</td>
</tr>
<tr>
<td>Epicardium</td>
<td>1.11 ± 0.16</td>
<td>1.48 ± 0.48§</td>
<td>1.44 ± 0.44</td>
<td>3.83 ± 1.35**</td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>1.10 ± 0.07</td>
<td>1.09 ± 0.05</td>
<td>1.11 ± 0.04</td>
<td>0.85 ± 0.20—</td>
</tr>
<tr>
<td><strong>Distal/Cx flow ratio</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocardium</td>
<td>0.84 ± 0.11</td>
<td>0.78 ± 0.15</td>
<td>0.78 ± 0.16</td>
<td>0.23 ± 0.15**</td>
</tr>
<tr>
<td>Epicardium</td>
<td>0.96 ± 0.07</td>
<td>0.90 ± 0.12</td>
<td>0.91 ± 0.11</td>
<td>0.37 ± 0.21**</td>
</tr>
</tbody>
</table>

Values are mean ± sd; blood flow is given in ml/min/g.

* p < 0.05 vs control 1.
† p < 0.004 vs control 1.
‡ p < 0.02 vs control 1.
§ p < 0.01 vs control 1.
— p < 0.02 vs control 2.
** p < 0.005 vs control 2.

Abbreviations: Endo = endocardium; epi = epicardium; Cx = circumflex.

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TABLE 3. Hemodynamic Results — Intravenous Norepinephrine with β Blockade

<table>
<thead>
<tr>
<th></th>
<th>Control 1</th>
<th>Norepinephrine</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>73.5 ± 9.2</td>
<td>72.8 ± 15.4</td>
<td>77.8 ± 9.8</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
<td>145.0 ± 15.6</td>
<td>182.0 ± 15.7*</td>
<td>150.0 ± 10.5</td>
</tr>
<tr>
<td>Rate pressure product (mm Hg/min)</td>
<td>10700 ± 2000</td>
<td>13100 ± 2100</td>
<td>11700 ± 1780</td>
</tr>
<tr>
<td>Mean left atrial pressure (mm Hg)</td>
<td>8.3 ± 2.4</td>
<td>10.9 ± 1.7*</td>
<td>7.8 ± 1.1</td>
</tr>
</tbody>
</table>

*p < 0.01 vs control 1.

with control. However, the resistance values in both layers of the circumflex zone did increase during norepinephrine infusion in five of six pigs. One pig had a decrease in resistance with norepinephrine, which resulted in failure of the change in the group mean to attain statistical significance.

Regional Myocardial Oxygen Consumption (Table 6)

The arterial-AIV oxygen difference and regional myocardial oxygen consumption (arterial-AV oxygen difference multiplied by mean transmural myocardial blood flow in the distal zone) during norepinephrine did not change compared with control values. Myocardial oxygen extraction decreased significantly (p < 0.01) during norepinephrine infusion and then returned to the control level after the infusion was discontinued. Both arterial and AIV oxygen content increased during norepinephrine infusion, but the AIV content increased relatively more and percent extraction therefore decreased.

Discussion

The purpose of this study was to test the hypothesis that a decline in regional myocardial blood flow distal to a severe coronary artery stenosis could be induced by a generalized increase in α-adrenergic tone. Theoretically, α-mediated vasoconstriction of epicardial conductance or arteriolar resistance vessels could cause flow to decline distal to a severe coronary artery stenosis. To isolate and study arteriolar resistance vessels, we studied pigs in which conductance vessel resistance was held constant by a fixed, rigid artificial stenosis. We then administered norepinephrine, a physiologic α-agonist, and measured the response of regional myocardial blood flow distal to the stenosis. Because stenosis resistance was fixed we could relate the distal zone blood flow response to norepinephrine to changes in arteriolar resistance. To determine to what extent the β-agonist properties of norepinephrine influenced the distal zone blood flow response to the drug, one group of pigs was subjected to β-adrenergic blockade and the other group was not.

Intravenous norepinephrine given in a dose sufficient to produce a 20-mm Hg increase in systemic arterial pressure does not cause a decrease in myocardial blood flow distal to a severe coronary artery stenosis. Indeed, when the β-agonist properties of the drug were unopposed, blood flow distal to the stenosis actually increased. Although distal coronary pressure was not measured in pigs given norepinephrine without β blockade, calculated coronary vascular resistance (based on proximal mean coronary artery pressure) did not change significantly compared with control in response to norepinephrine in either distal zone endocardium (103.0 ± 27.2 to 105.7 ± 32.5 mm Hg/ml • min⁻¹ • g⁻¹) or epicardium (97.9 ± 19.0 to

TABLE 4. Distal and Circumflex Zone Endocardial and Epicardial Blood Flow — Intravenous Norepinephrine with β Blockade

<table>
<thead>
<tr>
<th>Distal zone</th>
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<tbody>
<tr>
<td>Endocardium</td>
<td>1.07 ± 0.20</td>
<td>1.07 ± 0.18</td>
<td>1.09 ± 0.22</td>
</tr>
<tr>
<td>Epicardium</td>
<td>1.17 ± 0.25</td>
<td>1.16 ± 0.24</td>
<td>1.27 ± 0.20</td>
</tr>
<tr>
<td>Endo/epi ratio</td>
<td>0.93 ± 0.16</td>
<td>0.93 ± 0.11</td>
<td>0.89 ± 0.12</td>
</tr>
</tbody>
</table>

Circumflex zone

| Endocardium | 1.49 ± 0.40| 1.58 ± 0.38   | 1.72 ± 0.37|
| Epicardium  | 1.42 ± 0.39| 1.47 ± 0.34   | 1.57 ± 0.31|
| Endo/epi ratio | 1.05 ± 0.05| 1.07 ± 0.08   | 1.10 ± 0.06|
| Distal/Cx ratio | 0.75 ± 0.18| 0.69 ± 0.11   | 0.67 ± 0.24|
| Epicardium  | 0.84 ± 0.09| 0.80 ± 0.07   | 0.91 ± 0.06|

Values are mean ± sd (ml/min • g⁻¹).

Abbreviations: See table 2.
97.8 ± 24.2 mm Hg/ml min⁻¹ g⁻¹. Accordingly, it is unlikely that resistance increased in these pigs, although we cannot be certain of this in the absence of distal coronary pressure measurements. Pretreatment with propranolol resulted in no change in blood flow distal to the stenosis, even though perfusion pressure increased significantly. Because distal zone vasodilatory reserve was extremely limited in our model, increased regional myocardial blood flow would be expected in response to increased perfusion pressure. Instead, blood flow did not change and arteriolar resistance increased. Thus, in the setting of β-adrenergic blockade, the α effects of norepinephrine may compete with metabolic vasodilation. In this respect, our data are consistent with those of other investigators who have shown that α-mediated vasoconstriction may compete with the demands of metabolic vasodilation.

Although such competition can occur, α-mediated vasoconstriction of coronary resistance vessels alone does not appear sufficient to decrease myocardial flow distal to a severe coronary artery stenosis. Infusion of a larger dose of norepinephrine might have caused a more intense degree of arteriolar vasoconstriction and with it an actual decline in distal zone blood flow, but this seems unlikely because the dose administered caused an increase in mean arterial pressure comparable to that in humans in whom regional myocardial blood flow declined in response to cold pressor stress. Further, the fact that heart rate did not increase in the pigs not subjected to β blockade, is probably the result of baroreceptor stimulation caused by an increase in arterial pressure and does not necessarily mean that the dose of norepinephrine administered was too small to stimulate cardiac adrenergic receptors effectively. Even though norepinephrine infusion caused an elevation of systolic pressure, heart rate failed to decline. This indicates that cardiac β₁ stimulation almost certainly occurred and was intense enough to cancel a reflexly mediated slowing of the heart rate. In humans, heart rate usually increases very little if at all in response to cold pressor stress (3.4 ± 5.1 beats/min, NS). In the group not subjected to β blockade, heart rate increased in response to norepinephrine in five pigs, did not change in one pig and declined in the other (mean change 3.4 beats/min, range −10 to 11 beats/min). Thus, both the heart rate and blood pressure responses to norepinephrine were comparable to those in humans subjected to cold pressor stress. Accordingly, the dose of norepinephrine was probably adequate to mimic the effects of cold pressor stress. Thus, α-mediated coronary arteriolar vasoconstriction does not appear to overwhelm metabolic arteriolar vasodilation.

The results of this study imply that vasoconstriction of epicardial conductance vessels is the most likely mechanism for a decline in myocardial blood flow in some humans with coronary artery disease who have been studied during cold pressor stress. Cold pressor stress has been shown to cause vasoconstriction at the site of preexisting coronary artery lesions in man. Only slight additional narrowing at the site of an epicardial lesion would be required to produce a large change in resistance to flow because resistance is proportional to the reciprocal of vessel radius raised to the fourth power. Thus, our data do not conflict with those of Mudge et al., but add information that improves our understanding of their studies. By holding stenosis resistance constant, which could not be done in human studies, we showed that coronary arteriolar vasoconstriction after systemic administration of norepinephrine does not reduce myocardial blood flow distal to a severe coronary stenosis. Regional blood flow does not decline, probably because metabolic vasodilation is too strong a stimulus to be fully overcome by α-mediated arteriolar vasoconstriction.

Support for this hypothesis may be found in a recent study from our laboratory in which sustained intracoronary administration of phenylephrine failed to decrease regional myocardial blood flow in pigs with normal coronary vessels. When phenylephrine was given as a bolus injection into the coronary circulation, a modest but statistically significant vasoconstrictor response was observed. These observations support the concept that in a steady state, metabolically mediated vasoregulation tends to predominate over α-mediated arteriolar vasoconstriction. Accordingly, it appears unlikely that a decline in blood flow after sympathetic stimulation in humans with ischemic heart disease is the result of arteriolar vasoconstriction. It is more likely that vasoconstriction at the site of established atherosclerotic lesions is responsible.

We also examined the effects of increased arteriolar resistance on regional myocardial oxygen metabolism distal to a severe coronary artery stenosis. Although norepinephrine administration in the setting of β-adrenergic blockade resulted in a modest increase in arterial oxygen content, AIV oxygen content increased relatively more, and thus, regional myocardial oxygen extraction (％)
cardiac oxygen extraction declined. However, the changes in arterial and AIV oxygen content during norepinephrine were such that the arterial-AIV oxygen difference remained constant. Thus, although arteriolar resistance distal to a severe coronary stenosis was increased by norepinephrine in the setting of $\beta$-adrenergic blockade, AIV oxygen content actually increased and myocardial oxygen extraction declined. Impairment of regional myocardial function distal to the stenosis could account for these findings, but it is difficult to reconcile this hypothesis with the fact that regional myocardial oxygen consumption remained constant. When contractility and heart rate are constant, myocardial oxygen consumption is closely related to extent of myocardial tension development and, to a lesser extent, fiber shortening. In the pigs subjected to $\beta$ blockade, heart rate (and presumably contractility) did not change during norepinephrine administration. Accordingly, it is reasonable to interpret constant myocardial oxygen consumption in this setting as evidence against a decline in systolic function distal to the stenosis. By increasing arteriolar resistance distal to a severe coronary stenosis, norepinephrine in the setting of $\beta$-adrenergic blockade may prevent an increase in regional myocardial blood flow that might otherwise occur as a result of increased coronary perfusion pressure. However, the increase in resistance is not sufficient to adversely affect steady-state levels of indexes of regional myocardial oxygen delivery, such as arterial-AIV oxygen difference or AIV oxygen content.

In conclusion, the results of this study show that blood flow distal to a severe fixed coronary artery stenosis does not decline and indeed may increase after systemic administration of an $\alpha$-receptor agonist. This finding is consistent with the results of previous investigators who have shown that $\alpha$ agonists may reduce signs of myocardial ischemia and increase regional myocardial blood flow in canine models of acute myocardial infarction. Finally, metabolic autoregulation of coronary resistance vessels can be modified only to a modest extent by $\alpha$-mediated arteriolar vasconstriction.

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