Effect of Coronary Artery Pressure on Transmural Distribution of Adrenergic Coronary Vasoconstriction in the Dog

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SUMMARY. The transmural distribution of α-receptor coronary vasoconstriction was studied in 14 closed-chest, morphine- and chloralose-anesthetized dogs. The α-receptor-blocking agent, phenoxybenzamine (0.25 mg/kg), was infused into either the anterior or circumflex coronary artery while collection of coronary sinus blood mimimized recirculation. The left main coronary artery was cannulated and perfused at constant pressure. Myocardial lactate extraction and blood flow (9 μm radioactive microspheres) were measured during adrenergic activation with intracoronary norepinephrine (2 μg/min) at coronary artery pressures of 100, 70, 50, and 38 mm Hg. Flow was 15–25% less in the control region (α-receptors intact) than in the α-receptor-blocked region, in all layers of the left ventricular wall, at coronary pressures of 100 and 70 mm Hg. When coronary pressure was 50 mm Hg, lactate production resulted (~4% extraction) and significant α-receptor vasoconstriction was observed in the outer layer, but was marginal (P = 0.043) in the inner layer, of the left ventricle. Flows were not different in control and α-receptor-blocked regions at a coronary pressure of 38 mm Hg (lactate extraction ~49%). These data indicate a uniform transmural α-receptor vasoconstriction at normal coronary artery pressures that diminished as the heart was progressively underperfused. (Circ Res 53: 613-621, 1983)

SYMPATHETIC coronary vasoconstriction has been observed in a number of laboratories (Szentiványi and Juhasz-Nagy, 1959; Berne et al., 1965; Granata et al., 1965; Feigl, 1967; Ross, 1976), is of the α-receptor type (Feigl, 1967; Pitt et al., 1967; McRaven et al., 1971; Gewirtz et al., 1982; Gwirtz and Stone, 1982; Macho et al., 1982), and is capable of competing with metabolic vasodilation (Mohrman and Feigl, 1978; Murray and Vatner, 1979; Gwirtz and Stone, 1982; Heyndrickx et al., 1982). A recent study from this laboratory demonstrated α-receptor-mediated coronary vasoconstriction in the presence of coronary stenosis (Buffington and Feigl, 1981). This observation of α-vasoconstriction, even at a low coronary artery pressure, suggested the present investigation of the transmural distribution of adrenergic vasoconstriction in the left ventricular wall during normal and reduced coronary artery pressures.

Transmural blood flow, determined with radioactive microspheres, was compared in α-receptor-blocked and α-receptor-intact regions of the same hearts during norepinephrine infusion. α-Vasoconstriction was uniform across the left ventricular wall at normal coronary artery pressures, diminished at intermediate pressures, and lost in all layers at a coronary pressure of 38 mm Hg.

Methods

General Preparation

Sixteen closed-chest dogs weighing 25–31 kg were studied. Approximately 1 hour after sedation with morphine sulfate (2.5 mg/kg, sc), each dog was anesthetized with an initial injection of α-chloralose (100 mg/kg, iv). Anesthesia was maintained with a continuous infusion of α-chloralose (10 mg/kg per hour, iv) during the experiment. The animals were ventilated with a positive-pressure pump (Harvard 601) operating with a 5-cm H2O end-expiratory back pressure. Oxygen enrichment of room air was adjusted by means of a variable demand valve so that arterial blood oxygen tension was kept between 125 and 150 mm Hg throughout the experiment. End-expiratory carbon dioxide was monitored continuously with an infrared absorption meter (Beckman LB-2) and was held between 4.5% and 5% by adjustment of rate of ventilation and tidal volume. Metabolic acidosis due to chloralose anesthesia was prevented by infusion of 150 mL sodium bicarbonate, 5 ml/kg per hour, iv (Arfors et al., 1971). Rectal temperature was held at 37°C with a heating pad and temperature controller (Yellow Springs 73A). Blood coagulation in the extracorporeal circuits was prevented by infusion of sodium heparin (750 U/kg bolus plus 250 U/kg per hour, iv).

Arterial blood pressure was measured with a catheter-tip transducer (Millar) introduced into the thoracic aorta via the left femoral artery. Pulmonary artery wedge pressure was measured through a balloon-tip catheter inserted into the pulmonary artery via the left external jugular vein. A schematic diagram of the experimental preparation appears in Figure 1.

Regional α-Receptor Blockade

The experimental strategy was to compare myocardial blood flow in a region of the left ventricle that had received an α-receptor-blocking agent (phenoxybenzamine) with flow to an area that had not. To achieve this, regional α-receptor block, either the anterior descending...
FIGURE 1. Schematic diagram of the experimental preparation. Arterial blood was withdrawn from a femoral artery and delivered to a cannula wedged into the ostium of the left main coronary artery. A balloon at the cannula tip provided a tight seal. An internal auxiliary tube allowed measurement of coronary pressure at the cannula tip, which was held constant by a servo-controlled roller pump. Total coronary blood flow was measured with an electromagnetic flowmeter, and regional coronary flow by the injection of radioactive microspheres into the perfusion tubing upstream from a magnetic stirring bar mixing chamber and a reference sample withdrawal pump. Blood from the coronary sinus was withdrawn continuously and passed a sampling site and oxygen electrode before being returned to the dog. A cannulating electromagnetic flow transducer was used to measure femoral artery flow during graded norepinephrine infusions before and after infusion of phenoxybenzamine selectively to the left anterior descending coronary artery (stippled area, seven dogs) or the circumflex coronary artery (seven dogs) was selectively cannulated via the right carotid artery with a modified Smith cannula (Smith et al., 1974) and perfused at constant pressure (100 mm Hg) with blood from a femoral artery. The coronary sinus was drained in order to collect as much phenoxybenzamine as possible and thus prevent recirculation and α-receptor blockade of the uncanulated region of the left ventricle. A 14Fr Foley catheter was maneuvered into the coronary sinus via the right external jugular vein with the aid of a fluoroscope. Inflation of the Foley balloon occluded the coronary sinus ostium. The catheter was attached to 5-mm i.d. tubing that led to a collection vial positioned 30-35 cm below the level of the heart. This gravity drain was used to collect coronary sinus blood during and for 1 minute after a 45-second period in which phenoxybenzamine (0.25 mg/kg body weight) was infused into the cannulated coronary artery. The collected blood (150-250 ml) was discarded and replaced by an equal volume of low molecular weight dextran (10%) in normal saline (iv). Following phenoxybenzamine administration, the Foley catheter was replaced with a Sones catheter for sampling coronary sinus blood (see below).

125I-containing microspheres mixed with the phenoxybenzamine solution were used to identify the blocked region. Tissue samples with uniformly high 125I counts were considered alpha blocked, and those with no 125I counts were considered unblocked. Samples with intermediate counts were excluded from analysis.

Recirculation Check

Phenoxybenzamine that escaped capture by the coronary sinus drain entered the systemic circulation and produced α-receptor blockade. This blockade would likely be of similar magnitude in all arterial beds, including the control coronary bed. To assess the magnitude of this unwanted effect, the response of femoral artery flow to intra-arterial norepinephrine was measured before and
after infusion of phenoxybenzamine. A cannulating electromagnetic flow transducer was inserted in the femoral artery. The hindpaw was temporarily excluded from the circulation by a tight band above the ankle. Norepinephrine was infused in the artery in graded doses ranging from 0.013 to 8 \( \mu \)g/min. One to 2 minutes were allowed for flow to stabilize at each infusion rate. The infusions were repeated following intracoronary phenoxybenzamine.

Femoral artery flow was plotted against the log of norepinephrine dose to construct a dose-response curve. Since phenoxybenzamine is not a competitive antagonist, shifts in the ED50 were not useful. Data from an experimental animal were excluded if femoral flow after administration of phenoxybenzamine was more than twice that observed before phenoxybenzamine at the three norepinephrine doses that fell on the steepest part of the curve. Two animals were excluded on this basis.

Coronary Blood Flow Measurements

After segmental coronary \( \alpha \)-receptor blockade with phenoxybenzamine, the selective coronary cannula was removed and a larger cannula (Mohrman and Feigl, 1978) was advanced into the aorta via the right internal carotid artery. A circumferential balloon at the tip was inflated and the cannula was wedged into the ostium of the left coronary artery. Arterial blood from the left femoral artery was supplied to the cannula by a Sarns roller pump at constant coronary pressure (Fig. 1). Coronary pressure was measured at the cannula tip via a small internal stainless steel tube. The seal was tested by a 10-second period of stopped flow; coronary pressure fell below 20 mm Hg if the seal was complete.

The seal was also tested by raising coronary perfusion pressure 20-30 mm Hg above mean arterial pressure; a sharp increase in cannula flow would indicate a leak. The seal was further checked at the end of the experiment with a crystal violet dye injection into the coronary cannula. Contrast medium (Hypaque 50%) was injected into the coronary cannula, and a fluoroscope was used to ensure that all branches of the left coronary artery filled evenly and rapidly. Total flow into the left coronary artery was measured with an electromagnetic flowmeter (Zepeda SWF-3RD) located in the extracorporeal circuit. The flowmeter was calibrated with the dog’s blood, after each experiment, by means of a Harvard syringe pump.

Regional myocardial blood flow was measured with the radioactive microspheres (Freymann et al., 1977). Microspheres (9 \( \pm \) 1 \( \mu \)m) labeled with \( ^{125} \text{I}, ^{99m} \text{Tc}, ^{85} \text{Sr}, \) or \( ^{51} \text{Cr} \) were injected into the tubing that supplied blood to the left coronary artery. Approximately 2 \( \times \) \( 10^4 \) microspheres were injected over a 30- to 45-second period. The injection site was upstream of a mixing chamber and a port for reference sample withdrawal (Fig. 1). The mixing chamber was cylindrical in shape and 1-2 mm larger in all dimensions than the 8-mm fluted magnetic stir bar that was rapidly rotated inside it. The reference sample withdrawal rate was 6.87 ml/min. Withdrawal was started 30 seconds prior to microsphere injection and continued for 2 minutes after the injection. Following the experiment, the heart was removed and placed in a 4% solution of formaldehyde. Contrast medium (Hypaque 50%) was injected into the coronary sinus via the right jugular vein and right atrium with the aid of a fluoroscope. The location of the catheter tip, measured postmortem, ranged from 30 to 45 mm into the coronary sinus in the 14 dogs studied. Blood was withdrawn continuously from the coronary sinus catheter at a rate of 12 ml/min with a roller pump (Cole-Parmer 4420). This combination of withdrawal rate and catheter tip placement was chosen to prevent contamination of the coronary sinus sample with blood from the right atrium (Koberstein et al., 1969). Coronary sinus blood was passed a sample site and oxygen tension electrode (Feigl and D’Aley, 1971) before being returned to the dog. The oxygen tension measurement was corrected for the transit delay from the sampling point to the electrode. The oxygen electrode was calibrated with nitrogen and oxygen mixtures. Provision was made for intermittent sampling of arterial blood (Fig. 1), and inspired oxygen concentration was adjusted to maintain arterial oxygen tension between 125 and 150 mm Hg. Arterial hemoglobin concentration was determined by the cyanmethemoglobin method (Bauer et al., 1974). Plasma lactate extraction or production across the coronary circulation was determined by measurements of simultaneously drawn arterial and coronary venous samples. Samples were promptly chilled, precipitated with 8% perchloric acid, and centrifuged at 3°C. Lactate concentration was determined photometrically by the enzymatic method (Drewes, 1974). The myocardial lactate extraction was calculated as the ratio of arterial-coronary venous concentration difference divided by the arterial concentration, \( (C_a - C_v)/C_a \), and expressed as a percent.

Experimental Protocol

The experiment involved measuring regional myocardial flows, hemodynamic, and metabolic variables during intracoronary norepinephrine infusion at four sequential coronary pressures: 100, 70, 50, and 35-40 mm Hg. The order of perfusion pressures was not randomized because of the danger of long-lasting effects following low pressure perfusion. Measurements at the four coronary pressures were completed within an hour. A middle norepinephrine dose of 2 \( \mu \)g/min was chosen from a previously determined dose response (Buffington and Feigl, 1981). This norepinephrine dose gives cardiac and coronary effects of...
a magnitude similar to that observed during carotid baroreceptor reflex sympathetic activation (Mohrman and Feigl, 1978). The objective was to measure transmural blood flow over a range of perfusion pressures. Pilot experiments in which coronary pressure was lowered below 30 mm Hg resulted in rapid development of left ventricular failure and death. The lowest coronary pressure used in these experiments was 35–40 mm Hg, and was adjusted to be slightly above the pressure that produced a dramatic rise in pulmonary wedge pressure. After 7–10 minutes at each perfusion pressure, arterial and coronary sinus blood samples were drawn for lactate and hemoglobin determinations, and radioactive microspheres were injected into the tubing supplying blood to the coronary cannula. After measurements at the lowest perfusion pressure were complete, 1 ml of a crystal violet solution was injected into the coronary cannula and cardiac arrest produced by KCl (iv). The heart was excised, trimmed of great vessels and fat, and the weight of the dyed myocardium was determined. The heart then was fixed in a 4% formaldehyde solution for 48 hours, and regional myocardial flows were determined, as described above.

**Propranolol Group**

A second group of experiments was performed in seven additional dogs. These dogs were given propranolol (2 mg/kg, iv) after the regional phenoxybenzamine infusion to determine the contribution of prejunctional α2-blockade to the regional flow differences observed following phenoxybenzamine. Blockade of prejunctional α1-receptors leads to an increase in norepinephrine release from sympathetic nerve terminals. If such a neuronal release occurred during norepinephrine infusion, it would stimulate myocardial β1-receptors and augment coronary blood flow by a local metabolic mechanism, rather than by postsynaptic α-receptor blockade. In these seven dogs, the same protocol was employed as in the main group of experiments, except that all measurements were made at a coronary pressure of 100 mm Hg. Two regional blood flow measurements were made during norepinephrine infusion (2 μg/kg, ic): one that followed regional phenoxybenzamine infusion, and a second after intravenous propranolol.

**Data Analysis**

The data were grouped into four periods corresponding to coronary pressures of 100, 70, 50, and 35–40 mm Hg. Data from seven dogs in which the anterior descending coronary artery received phenoxybenzamine were pooled with data from seven dogs in which phenoxybenzamine was infused into the circumflex branch, inasmuch as analysis of variance failed to demonstrate a geographic difference in the effect of phenoxybenzamine. Hemodynamic and metabolic data were analyzed by two-way analysis of variance (ANOVA, SPSS for DEC system-10, version H, Release 8.1, August 15, 1980). Period served as one independent variable, and the experimental animal, the second. When two-way analysis of variance demonstrated a significant period effect, one-way analysis of variance using linear contrasts was used to compare the values with those observed at a coronary pressure of 100 mm Hg. Because of unequal variance, the lactate extraction data were also subjected to a sign test.

The flow difference produced by phenoxybenzamine was computed for each myocardial layer (outer, middle, inner) by subtracting the flow in the unblocked regions from the flow in the blocked regions for each dog. Paired t-tests were used to assess the significance of blood flow differences due to α-receptor blockade with phenoxybenzamine.

In the seven dogs given propranolol, regional flow increases caused by phenoxybenzamine were calculated on a layer-by-layer basis in each dog and expressed as a percent to take into account the change in absolute flow caused by decreased metabolic demand following propranolol.

**Results**

During a continuous norepinephrine infusion of 2 μg/min, coronary blood flow decreased as coronary artery pressure was lowered (Table 1; Fig. 2). The inner:outer (i:o) flow ratios in the left ventricular wall of both control and phenoxybenzamine-treated regions fell as coronary pressure was decreased (Table 1). Coronary hypotension also resulted in metabolic and hemodynamic evidence of myocardial ischemia. Coronary sinus oxygen tension fell to 9 mm Hg anti-normal myocardial lactate uptake reversed to net production at coronary pressures of 50 and 38 mm Hg (Table 1). Systolic arterial pressure was reduced and pulmonary wedge pressure increased slightly at coronary pressures of 50 and 38 mm Hg, suggesting ventricular dysfunction (Table 1).

Blood flow into regions of myocardium that were α-receptor blocked with phenoxybenzamine was significantly greater than flow to control regions at coronary artery pressures of 100 and 70 mm Hg during norepinephrine infusion (Fig. 3). During a coronary artery perfusion pressure of 50 mm Hg, coronary blood flow was significantly greater in the α-receptor-blocked regions than in the α-receptor-intact regions for the subepicardial layer (P = 0.002), but this difference was marginal (P = 0.043) in the subendocardium (Fig. 3). This indicates that α-receptor coronary vasoconstriction probably was lost in the subendocardium before it was lost in the subepicardium with progressive coronary artery hypotension. No significant differences in flows were observed in any layer of the left ventricle during severe underperfusion at a coronary artery pressure of 38 mm Hg (Fig. 3).

**Propranolol Group**

Transmural blood flow was higher in the phenoxybenzamine-treated region than in the α-receptor-intact region during norepinephrine infusion at a coronary pressure of 100 mm Hg (Table 2). The flow differences in these seven dogs were similar to those observed in the main experimental group. After β-receptor blockade with propranolol (2 mg/kg, iv), absolute flow was decreased in both regions, presumably due to diminished myocardial metabolism, but the relative (percent) flow increase caused by α-receptor blockade remained in the inner and middle layers of the left ventricle and was insignificantly diminished in the outer layer (Table 2).
TABLE 1

<table>
<thead>
<tr>
<th>Hemodynamic and Metabolic Changes during Norepinephrine Infusion</th>
</tr>
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<tbody>
<tr>
<td>Coronary pressure (mm Hg)</td>
</tr>
<tr>
<td>99.8 ± 0.8</td>
</tr>
<tr>
<td>Systolic aortic pressure (mm Hg)</td>
</tr>
<tr>
<td>132.8 ± 16.5</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
<tr>
<td>117.0 ± 25.5</td>
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<tr>
<td>Arterial hemoglobin (g/dl)</td>
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<tr>
<td>12.2 ± 2.4</td>
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<tr>
<td>Pulmonary artery wedge pressure (mm Hg)</td>
</tr>
<tr>
<td>4.5 ± 1.7</td>
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<tr>
<td>Coronary sinus oxygen tension (mm Hg)</td>
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<tr>
<td>20.3 ± 4.0</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
</tr>
<tr>
<td>40.8 ± 12.7</td>
</tr>
<tr>
<td>Total coronary flow (ml/min per g, emf)</td>
</tr>
<tr>
<td>1.13 ± 0.26</td>
</tr>
<tr>
<td>I:O flow ratio, α-intact region</td>
</tr>
<tr>
<td>0.96 ± 0.17</td>
</tr>
<tr>
<td>I:O flow ratio, α-blocked region</td>
</tr>
<tr>
<td>0.91 ± 0.19</td>
</tr>
</tbody>
</table>

Average values from 14 animals ± 1 sd. P values were calculated by one-way analysis of variance using linear contrasts.
* The sign test for lactate extraction data yielded P < 0.01 for both comparisons.

2). These results indicate that prejunctional α2-receptor blockade is not responsible for the augmented flow in phenoxybenzamine-treated regions.

Discussion

These data indicate homogeneous α-receptor coronary vasoconstriction in all layers of the left ventricular wall during norepinephrine infusion at normal coronary artery pressures of 100 and 70 mm Hg. α-Receptor vasoconstriction was diminished at a coronary pressure of 50 mm Hg, when net lactate production occurred. At a coronary pressure of 38 mm Hg, no evidence of α-receptor vasoconstriction was observed, probably because of the intense metabolic vasodilation resulting from an imbalance between oxygen delivery and demand.

The present study employed paired comparisons between regions with intact and blocked α-receptors, in the same heart, where heart rate, preload, afterload, arterial oxygen content, and blood viscosity were the same in both regions. Phenoxybenzamine was injected into either the anterior descending (seven dogs) or circumflex (seven dogs) branch of the left coronary artery.

Since the coronary sinus drains only about 70% of left ventricular blood flow (Brunsting et al., 1975), it is unlikely that all of the phenoxybenzamine that passed through the coronary circulation was trapped by coronary sinus drainage. The untrapped phenoxybenzamine recirculated and produced an unknown amount of α-receptor blockade in the "unblocked" control region of the heart. The partial blockade due to recirculation would tend to make the differences between "unblocked" and blocked regions of the heart smaller than they would be with no recirculation. Two experiments were discarded because of excessive phenoxybenzamine recirculation, using the independent criterion of a large shift in the norepinephrine vasoconstrictor dose-response curve in the femoral artery bed. Phenoxybenzamine was chosen because it binds irreversibly to α-receptors and produces long-acting α-receptor blockade (Harvey and Nickerson, 1954). It is unlikely that regional blockade could be accomplished with a competitive antagonist that binds reversibly to α-receptors. The 45-second exposure to phenoxybenzamine may have been too short for optimal α-receptor blockade, but the significant differences observed between control and blocked regions (Fig. 3) indicate there was at least partial blockade. A partial α-receptor blockade would tend to diminish...
NOREPINEPHRINE INFUSION

OUTER MYOCARDIUM

\( n = 14 \)
\( x \pm 1 \text{ SEM} \)

MID MYOCARDIUM

INNER MYOCARDIUM

\( \alpha \)-BLOCKED

\( \alpha \)-INTACT

MEAN CORONARY PRESSURE (mm Hg)

FIGURE 2. Pressure-flow relationship for control and phenoxybenzamine-treated regions of the left ventricle. Adrenergic vasoconstriction was observed in all layers at coronary artery pressures of 100 and 70 mm Hg, was diminished when coronary pressure was decreased to 50 mm Hg, and was lost at a coronary pressure of 38 mm Hg. Each point is the average of 14 microsphere flow determinations, and the bars indicate \( \pm 1 \) SEM. The differences between \( \alpha \)-intact and \( \alpha \)-blocked regions are given in Figure 3.

the differences observed, rather than artifically increase them.

The present results could conceivably result from phenoxybenzamine blocking inhibitory prejunctional \( \alpha_2 \)-receptors. This blockade would increase norepinephrine release from sympathetic nerve terminals and augment coronary blood flow in the blocked region by an increase in local myocardial metabolism mediated by \( \beta \)-receptors. The data from the group of animals given propranolol (2 mg/kg, iv) argue against this possibility, since the observed flow increases remained after \( \beta \)-blockade (Table 2). It seems unlikely that a prejunctional effect was observed in the present study because adrenergic activation was produced by norepinephrine infusion rather than sympathetic nerve activation (Johannsen et al., 1982b). Furthermore, the postjunctional \( \alpha \)-receptor-blocking action of phenoxybenzamine is 30 times greater than its prejunctional blocking action (Dubocovich and Langer, 1974; Doxey et al., 1977).

If one combines the observations of Constantine and Lebel (1980), that phenoxybenzamine is a more powerful postjunctional \( \alpha_1 \) than postjunctional \( \alpha_2 \)-receptor-blocking agent, with the recent observations of Holtz et al. (1982), that coronary vasoconstriction is mediated by both \( \alpha_1 \) and \( \alpha_2 \) postjunc-

NOREPINEPHRINE INFUSION

OUTER MYOCARDIUM

\( n = 14 \)
\( x \pm 1 \text{ SEM} \)

MID MYOCARDIUM

INNER MYOCARDIUM

\( \alpha \)-BLOCKED

\( \alpha \)-INTACT

MEAN CORONARY PRESSURE (mm Hg)

FIGURE 3. The paired difference (\( \alpha \)-blocked minus \( \alpha \)-intact regions) in coronary blood flow due to phenoxybenzamine in the subendocardium, midmyocardium, and subepicardium at four coronary artery pressures, during norepinephrine infusion are shown. \( \alpha \)-Receptor vasoconstriction was observed in the subepicardium and midmyocardium at coronary artery pressures of 100, 70, and 50 mm Hg. Significant \( \alpha \)-vasoconstriction was observed in the subendocardium at coronary artery pressures of 100 and 70 mm Hg but became marginal (\( P = 0.043 \)) at 50 mm Hg. No significant \( \alpha \)-receptor vasoconstriction was observed in any layer at a coronary artery pressure of 38 mm Hg. The brackets indicate \( \pm 1 \) SEM of the difference. \( P \) values indicate the probability that the difference between \( \alpha \)-blocked and \( \alpha \)-intact regions differs from zero by paired t-test.
subendocardium, but not present in the subepicardium. Thus it is possible that sympathetic activation via neural pathways might produce a result different from that observed in the present study with norepinephrine infusion. Baroreceptor reflex inhibition of sympathetic discharge to the heart may have resulted from the norepinephrine infusion in the present experiments, but it seems unlikely that this would modify the coronary vascular response to intracoronary norepinephrine infusion.

In addition to sympathetic activation, the effects of sympathetic ablation on transmural myocardial blood flow have also been studied. Chronic regional sympathectomy with 6-hydroxydopamine (Holtz et al., 1977) or topical phenol application (Chilian et al., 1981) produced no difference in the inner:outer flow ratio in innervated compared to denervated myocardium during resting conditions. However, unilateral left stelllectomy increased the inner:outer flow ratio slightly from 1.17 to 1.23 in resting dogs with constant heart rate and mean arterial pressure (Schwartz and Stone, 1977).

An important finding in the present study is that α-receptor vasoconstriction was still present when oxygen delivery was sufficiently reduced to cause myocardial ischemia and lactate production. Transmural gradients of flow and metabolites measured during similar experiments suggest a gradient of ischemia which is maximal in inner layers and declines toward the outer layers (Griggs et al., 1968, 1971; Hoffman and Buckberg, 1976; Rouleau et al., 1979). The present results suggest an opposite gradient of adrenergic vasoconstriction during partial ischemia. If such opposing gradients of metabolic vasodilator influence and adrenergic vasoconstrictor effect were the case, then α-receptor vasoconstriction in subepicardial vessels could provide an "anti-transmural-steal" function. This effect would retard redistribution of blood from inner to outer layers of the myocardium distal to a coronary stenosis during coronary hypotension. A steal phenomenon was impossible in the present experiments with controlled constant-pressure perfusion, since steal results from the lowering of perfusion pressure for one vascular bed by vasodilation in a parallel vas-
cular bed, with both beds being distal to a stenosis. The results of the present study demonstrated no difference in flow between control and phenoxybenzamine-treated regions at a coronary perfusion pressure of 38 mm Hg. The lactate production (–48% extraction), low inner/outer flow ratio (0.68), low coronary sinus blood oxygen tension (9.3 mm Hg), and mildly elevated pulmonary artery wedge pressure (7.0 mm Hg) all indicate myocardial ischemia during a coronary artery pressure of 38 mm Hg. The strong metabolic vasodilator influence under such conditions probably overwhelmed α-vasoconstriction, leading to equal flows in control and α-receptor-blocked regions. Hypoxia has been shown to inhibit the coronary constrictor response to norepinephrine (Heistad et al., 1975). In addition, myocardial metabolism may have been augmented at these low flow rates because the intracoronary norepinephrine infusion rate (2 μg/min) was constant, so that the blood concentration of norepinephrine increased as flow was progressively diminished. Thus it is possible that a part of the diminution of α-receptor vasoconstriction observed at low perfusion pressure could have been due to more intense cardiac β-receptor activation. In contrast, Uchida and Murao (1975) found a sustained decrease in myocardial heat clearance during stimulation of ef- ferent cardiac sympathetic nerves in dogs with coronary constriction sufficient to lower distal coronary pressure to 30–35 mm Hg. In another study suggesting retained α tone during coronary hypotension, Birinyi et al. (1977) found phenoxybenzamine increased coronary flow in dogs bled to a mean arterial pressure of 44 mm Hg. Differences in myocardial metabolic demand probably explain the discrepancies between these studies and the present results.

In conclusion, the present results indicate α-receptor-mediated coronary vasoconstriction caused by norepinephrine infusion was attenuated as coronary perfusion pressure was progressively decreased. A uniform transmural α-receptor vasoconstriction was observed at a coronary pressure of 100 mm Hg. α-Mediated vasoconstriction was diminished, but still present, at a coronary pressure of 50 mm Hg, when the heart was producing lactate. α-Receptor vasoconstriction was lost in all layers during severe ischemia when the coronary perfusion pressure was 38 mm Hg.

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