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Competition between Sympathetic Vasoconstriction and Metabolic Vasodilation in the Canine Coronary Circulation

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SUMMARY The role of a-receptor constriction of coronary vessels in response to cardiac sympathetic activation was evaluated in closed-chest, chloralose-anesthetized dogs. Cardiac sympathetic activation was produced (1) directly by intracoronary norepinephrine infusion at several different rates and (2) reflexly by carotid sinus hypotension. The resulting changes in coronary blood flow and myocardial oxygen consumption were recorded before and after a-receptor blockade with dibozane (3.0 mg/kg, iv) or phenoxybenzamine (0.5 mg/kg, intracoronary). The changes in coronary blood flow were normalized to changes in myocardial oxygen consumption by division of the oxygen delivery (coro-
nary flow times arterial oxygen content) by the change in myocardial oxygen consumption per 100 g of myocardium. Before a-receptor blockade, either intracoronary norepinephrine infusion or reflex sympathetic activation from the carotid sinus resulted in an increase of only 0.85 ml/100 g min⁻¹ in oxygen delivery for each increase of 1 ml/100 g
min⁻¹ in cardiac oxygen consumption. Under these circumstances, myocardial oxygen extraction increased and coron-
ary venous oxygen content fell. After a-receptor blockade, either intracoronary norepinephrine infusion or a carotid sinus reflex resulted in an increase of 1.23 ml/100 g min⁻¹ in oxygen delivery for each increase of 1 ml/100 g min⁻¹ in cardiac oxygen consumption. Myocardial oxygen extraction and coronary venous oxygen content changed only slightly after a-receptor blockade. The greater coronary vasodilation and lesser change in cardiac oxygen extraction after a-receptor blockade were significantly different (P < 0.001) from the values before blockade. It is concluded that the coronary a-receptor constrictor mechanism competes with metabolic vasodilation during sympathetic activation even when there are large increases in myocardial metabolism. The net effect of the a-receptor constrictor influence is to restrict the metabolically related flow increase by about 30%, thus increasing oxygen extraction and decreasing coronary venous oxygen content.

IT HAS LONG been known that stimulation of the sympathetic innervation of the heart results in tachycardia and augmented contractility, accompanied by increased myocardial oxygen consumption, increased coronary blood flow, and decreased coronary sinus oxygen content.1-4 Coronary sinus oxygen content decreases because coronary blood flow responses do not quite match alterations in myocardial oxygen metabolism. The imbalance may reflect the normal operation of the local metabolic control of coronary flow, or it may be due to a limiting effect of sympathetic coronary vasoconstriction on the extent of local metabolic vasodilation. The cardiac vessels have autonomic innervation, and the direct result of sympathetic activation is coronary vasoconstriction.5, 8, 9, 13, 14, 16 Sympathetic vasoconstriction is mediated through a-receptors.5, 11, 12, 14, 16 A previous study in this laboratory demonstrated that sympathetic a-receptor coronary vasoconstriction is capa-
bale of competing with local metabolic control and lowering coronary sinus oxygen tension after adrenergic β-receptor blockade.17 In that study the positive inotropic and chron-
otropic effects of sympathetic stimulation were blunted by propranolol, so that there was little increase in myocardial oxygen consumption, and coronary α-receptor vasoconstriction was unmasked. Because of the β-receptor blockade, the previous study did not show whether the effects of sympathetic coronary vasoconstriction would be overwhelmed in the presence of the large increase in cardiac oxygen metabolism that normally results from sympathetic activation.

The objective of the present study was to determine whether sympathetic coronary α-receptor vasoconstriction is capable of modulating coronary blood flow and thus oxygen delivery to the heart in the absence of β-receptor blockade. A comparison of coronary blood flow normalized against myocardial oxygen consumption before and after α-receptor blockade indicated that a direct coronary vasoconstrictor effect significantly limits oxygen delivery to myocardium during sympathetic activation.

Methods

General Preparation

Twelve male closed-chest dogs weighing 21–30 kg were studied. Each dog was anesthetized with an initial injection of α-chloralose (100 mg/kg, iv) approximately 1 hour after sedation with morphine sulfate (2.5 mg/kg, sc) and a continuous infusion of additional α-chloralose (10 mg/kg per hour, iv) during the experiment. Each dog was atropinized (0.5 mg/kg, iv) following completion of surgery and cannula placement. Ventilation was with room air enriched with a mixture of 40% oxygen in nitrogen gas supplied from a positive-pressure pump (Harvard 601) operating with a 5-cm H 2O end-expiratory back pressure. Oxygen enrichment 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 held between 4.5% and 5% by adjustment of respiration rate and tidal volume. Blood coagulation in the extracorporeal circuits was prevented by infusion of sodium heparin (750 U/kg plus 250 U/kg per hour, iv), and the metabolic acidosis associated with chloralose anesthesia was counteracted by a continuous infusion of 150 mEq sodium bicarbonate (5 ml/kg per hour, iv). Rectal temperature was held at 37°C with a heating pad and temperature controller. (Yellow Springs 73A).

A schematic diagram of the experimental preparation appears in Figure 1. A Y cannula arrangement (not illustrated) was used to accept blood from the central left common carotid artery and direct it to both the cranial left and right common carotid arteries. This arrangement ensured perfusion of both carotid sinuses under control conditions and enabled simultaneous experimental reduction of both carotid sinus pressures.

Perfusion of Left Coronary Artery

Blood was supplied to the left coronary artery at constant pressure through the special cannula shown in Figure 1, a modification of the transducer described by Smith et al. The cannula was advanced through the right carotid artery into the ascending aorta, and a balloon near its tip was inflated. The cannula tip was then inserted into the left coronary artery ostium until the balloon sealed the tip of the ostium. Left coronary artery pressure at the cannula tip was measured through a small, stainless steel internal auxiliary tube. Blood was obtained from the left femoral artery and passed a servo-controlled roller pump (modified Sarnes 3500), an extracorporeal electromagnetic flow transducer (Zepeda SWF-3RD), and an infusion site before entering the coronary cannula. The roller pump was connected in a servo loop to pump automatically at the rate necessary to maintain 90 mm Hg pressure at the tip of the cannula in the left coronary ostium.

The seal at the left coronary ostium was tested at the beginning of each experiment and considered to be secure against leakage from the ascending aorta, and a balloon near its tip was inflated. The cannula tip was then inserted into the left coronary artery ostium until the balloon sealed the tip of the ostium. Left coronary artery pressure at the cannula tip was measured through a small, stainless steel internal auxiliary tube. Blood was obtained from the left femoral artery and passed a servo-controlled roller pump (modified Sarnes 3500), an extracorporeal electromagnetic flow transducer (Zepeda SWF-3RD), and an infusion site before entering the coronary cannula. The roller pump was connected in a servo loop to pump automatically at the rate necessary to maintain a mean left coronary artery pressure of 90 mm Hg. The electromagnetic flowmeter was fully calibrated at the end of each experiment with blood from the experimental animal. Occlusive zero flow determinations were repeated frequently throughout the experiment.

The seal at the left coronary ostium was tested at the beginning of each experiment and considered to be secure against leakage from the ascending aorta if the pressure at the cannula tip during complete occlusion of the inflow tubing dropped to below 20 mm Hg. The possibility of outward leakage was tested at the termination of the
experiment by adjustment of the servo-controlled perfusion pump to maintain mean left coronary artery pressure 25 mm Hg above mean aortic pressure and injection of approximately 1.5 ml of an intense blue dye (crystal violet in 1 N ammonia) into the perfusion cannula. Any leakage from the left coronary artery into the ascending aorta caused dye streaks in the aorta that were easily detected post-mortem. All dogs in which leakage occurred were excluded from the study. The dye also served to mark the area of the myocardium perfused during the experiment; this area was separated from the rest of the myocardium and weighed at the end of each experiment and was found to have an average weight of 81.3 ± 3.7% (SE) of the total myocardial weight in the 12 dogs studied.

Oxygen Measurements
A Sones catheter (USCI no. 007538) was advanced into the coronary sinus via the right jugular vein and right atrium under fluoroscopy. Measurements of the exact placement of the catheter tip post-mortem ranged from 31 to 44 mm into the coronary sinus in the 12 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 cannula tip placement was chosen to prevent contamination of the coronary sinus sample with blood from the right atrium. Coronary sinus blood passed a spectrophotometric oximeter cuvette (Waters 0-500), the withdrawal pump, a sampling site, and an oxygen tension cuvette before returning to the left jugular vein. Provision was made for either coronary sinus blood or arterial blood to be drawn through the oxygen-measuring and -sampling circuit.

Blood samples were taken for generating the oximeter calibration curve and establishing the current hemoglobin concentration. Each sample was analyzed for oxygen content (Lexington Instruments Lex-O2-Con) and for hemoglobin content by the cyanmethemoglobin method. The oxygen-carrying capacity of each blood sample was calculated by multiplying the measured hemoglobin content by 1.34 ml O2/g Hb.

Experimental Protocol
The responses to a series of intracoronary norepinephrine infusions and carotid artery occlusions were recorded before and after \(\alpha\)-receptor blockade with either dibozane or phenoxybenzamine. Each experimental maneuver lasted from 1 to 3 minutes and was terminated when left coronary artery flow and coronary sinus oxygen saturation reached steady values.

In the dibozane experiments (four dogs), intracoronary norepinephrine (10 \(\mu\)g/ml saline) was administered with a syringe pump at infusion rates of 1.0, 1.5, 2.0, 3.1, 4.1, and 6.2 \(\mu\)g/min. Alpha-receptor blockade was effected by the intravenous infusion of dibozane (3 mg/kg, iv).

In the phenoxybenzamine experiments (eight dogs), both vagus nerves were cut in the neck. Intracoronary norepinephrine was administered at infusion rates of 1.7, 3.4, and 6.8 \(\mu\)g/min, and the reflex effects of two levels of carotid sinus hypotension were recorded. Alpha-receptor blockade was effected by a slow intracoronary infusion (0.74 ml/min) of phenoxybenzamine (0.5 mg/ml saline) in an attempt to maximize coronary blockade and minimize peripheral blockade. The total dose of phenoxybenzamine was 0.5 mg/kg.

Data Analysis
Data were analyzed from two time points associated with each norepinephrine infusion or carotid occlusion response. Control values were read from the period immediately before each experimental maneuver. Final response values were read during the steady period near the end of each norepinephrine infusion or carotid occlusion. Changes in myocardial oxygen delivery (flow) were plotted against changes in myocardial oxygen consumption. For quantitative analysis it was useful to characterize individual responses by a single dimensionless measure, the response slope, defined as the change in oxygen delivery divided by the change in oxygen consumption. This procedure has the effect of normalizing coronary flow responses against metabolic changes, so that discrepancies between oxygen supply and demand of the myocardium are readily apparent.

All reported standard error values are measures of variability between dogs and were derived from data sets containing one value from each dog studied. When multiple determinations for the value of a particular variable were made within a single experiment, the average of these represented that dog in the overall data analysis. The statistical significance of differences observed for a variable before and after \(\alpha\)-receptor blockade was evaluated with a two-tailed, paired \(t\)-test (df = n - 1, for n animals).

Results
The responses to intracoronary norepinephrine infusion before and after \(\alpha\)-receptor blockade are shown in Figure 2. Norepinephrine infusion increased left coronary artery flow and decreased coronary sinus hemoglobin-oxygen saturation. Note that the norepinephrine infusion before \(\alpha\)-receptor blockade produced a lesser rise in coronary flow and a greater fall in coronary sinus oxygen saturation than the norepinephrine infusion following \(\alpha\)-receptor blockade. The slight flow overshoot at the offset of infusion before \(\alpha\)-blockade was observed in all 12 dogs studied. Flow overshoot was not observed following \(\alpha\)-receptor blockade. In these experiments, changes in coronary arterial flow indicate changes in coronary artery vascular conductance, since coronary perfusion pressure was held at 90 mm Hg by the servo system regardless of changes in aortic pressure.

The reflex responses to carotid artery occlusion before and after \(\alpha\)-receptor blockade are shown in Figure 3. Carotid artery occlusion increased coronary flow, decreased coronary sinus oxygen saturation, and increased aortic pressure both before and after \(\alpha\)-receptor blockade. As with norepinephrine infusion, the carotid occlusion before \(\alpha\)-receptor blockade produced a lesser increase in flow and a greater decrease in coronary sinus oxygen saturation than did the carotid occlusion following \(\alpha\)-receptor blockade.
Myocardial responses to intracoronary norepinephrine infusion before and after α-receptor blockade with phenoxybenzamine (0.5 mg/kg, intracoronary). Norepinephrine infusion (NE) caused a lesser increase in coronary blood flow and a greater decrease in coronary sinus hemoglobin oxygen saturation before α-receptor blockade than after blockade. Changes in coronary flow are due to changes in coronary vascular conductance, since coronary perfusion pressure was servo controlled at 90 mm Hg. Atropine, administered at the onset of the experiment, was responsible for the high heart rate. The norepinephrine infusion rate was 6.8 μg/min in each case, and 148 g of myocardium were perfused.

Figure 4 illustrates, for a single experiment, how α-receptor blockade affected the relationship between changes in coronary flow (expressed as arterial oxygen delivery) and changes in myocardial oxygen consumption induced by intracoronary norepinephrine infusion and carotid artery occlusion. An arrow in Figure 4 represents the response to a single norepinephrine infusion or carotid occlusion. The tail of each arrow indicates the control values of oxygen delivery and oxygen consumption before norepinephrine infusion or carotid occlusion, whereas the head indicates the steady values during the experimental maneuver. Norepinephrine infusion and carotid occlusion increased oxygen consumption and oxygen delivery in all instances. However, the differences between the slopes of the arrows before and after α-receptor blockade indicate an altered relationship between oxygen consumption and delivery. Coronary blood flow (oxygen delivery) increased less in relation to oxygen consumption before α-receptor blockade than after blockade. Before α-receptor blockade, increased oxygen consumption was accompanied by increased oxygen extraction; however, following blockade, oxygen extraction remained nearly constant (at about 70%) even during substantial increases in oxygen consumption. As a consequence of increased extraction,
coronary sinus oxygen levels fell to low values when oxygen consumption was increased before \( \alpha \)-receptor blockade.

Figure 5 shows the change in oxygen delivery accompanying the change in oxygen consumption for all the trials with norepinephrine infusion and carotid occlusion in this study. Each point represents one norepinephrine infusion or carotid occlusion, and closed and open symbols represent trials before and after \( \alpha \)-receptor blockade, respectively. The magnitude of the change in oxygen consumption was purposely modulated in this study by variation of the rate of norepinephrine infusion or the degree of lowering carotid sinus pressure. The changes in oxygen consumption shown in Figure 5 represent increases over the control oxygen consumption (Table 1), ranging from a few percent to more than 100%. For a particular set of experimental conditions, the response slope was quite independent of the magnitude of the change in oxygen consumption. It is evident from Figure 5 that the change in oxygen delivery associated with a given change in oxygen consumption (the response slope) was consistently less before \( \alpha \)-receptor blockade than after blockade. For the same norepinephrine-induced change in oxygen consumption, the oxygen delivery increased 39% more after dibozane \((P < 0.001)\) and 46% more after phenoxybenzamine \((P < 0.001)\). For equal carotid sinus reflex-induced changes in myocardial oxygen consumption, oxygen delivery increased 51% more after coronary \( \alpha \)-receptor blockade with phenoxybenzamine \((P < 0.001)\). No statistically significant differences in response slope were detected between norepinephrine infusions before dibozane, norepinephrine infusions before phenoxybenzamine, or carotid occlusions before phenoxybenzamine. Neither were there statistically significant differences between the response slopes for norepinephrine infusions after dibozane, norepinephrine infusions after phenoxybenzamine, or carotid occlusions after phenoxybenzamine.

Systolic blood pressure and heart rate are factors that influence the systolic compression of myocardial vessels and, thus, coronary blood flow. Since changes in heart rate and systolic blood pressure were not identical before and after \( \alpha \)-receptor blockade, we evaluated the possible roles of these factors by plotting them against changes in myocardial oxygen consumption (the normalizing variable used in this study) produced by intracoronary norepinephrine infusion or carotid occlusion before and after \( \alpha \)-receptor blockade (Fig. 6). The changes in heart rate and systolic pressure that accompanied a given change in myocardial oxygen consumption were highly variable. No significant effect of \( \alpha \)-receptor blockade upon the relationships indicated in Figure 6 was detected.

Figure 7 summarizes the results from this study. Since no significant differences were found between the effects of \( \alpha \)-receptor blockade by phenoxybenzamine and dibozane on response slopes, the results are combined in

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**Table 1** Effect of \( \alpha \)-Receptor Blockade on Control Values

<table>
<thead>
<tr>
<th></th>
<th>Intracoronary phenoxybenzamine blockade ((n = 8))</th>
<th>Intravenous dibozane blockade ((n = 4))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Left coronary flow</td>
<td>87.7 ± 10.4 (ml/100 g/min)</td>
<td>80.9 ± 9.5</td>
</tr>
<tr>
<td>Oxygen delivery</td>
<td>18.4 ± 1.9 (ml/100 g/min)</td>
<td>17.2 ± 1.3</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>15.7 ± 1.1 (ml/100 g/min)</td>
<td>12.6 ± 1.3</td>
</tr>
<tr>
<td>Oxygen extraction</td>
<td>75.9 ± 3.6</td>
<td>73.9 ± 2.8</td>
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<tr>
<td>Coronary sinus PO2</td>
<td>17.2 ± 1.1</td>
<td>18.1 ± 1.0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>196 ± 7</td>
<td>188 ± 13</td>
</tr>
<tr>
<td>Mean aortic pressure</td>
<td>120 ± 3</td>
<td>108 ± 4</td>
</tr>
</tbody>
</table>

*Data are expressed as mean ± SEM.*
Heart rate and aortic pressure responses before and after alpha-blockade

Figure 6 Changes in heart rate (upper panel) and systolic aortic blood pressure (lower panel) in relation to changes in myocardial oxygen consumption produced by intracoronary norepinephrine infusion and carotid occlusion before (solid symbols) and after (open symbols) alpha-receptor blockade. Alpha-receptor blockade had no consistent or statistically detectable effect on the magnitude of the change in heart rate or systolic blood pressure that accompanied a given change in myocardial oxygen consumption. (In contrast, note the extremely consistent effect of alpha-receptor blockade on the relationship between oxygen delivery and oxygen consumption shown in Figure 5.)

Discussion

The data indicate that coronary vessels are simultaneously subjected to an alpha-receptor constrictor influence and a metabolic vasodilator influence during either intracoronary norepinephrine infusion or carotid occlusion. Effects of alpha-blockade on myocardial responses to intracoronary norepinephrine infusion and carotid occlusion for all dogs of this study. Crossed brackets at left indicate mean ± se. (n = 12) of the control values of oxygen consumption, oxygen delivery, and oxygen extraction before (solid) and after (broken) alpha-receptor blockade. These control values were not significantly altered by alpha-receptor blockade. The shaded areas show the direction of change (mean response slope ± se, n = 12) produced by norepinephrine infusion or carotid occlusion. Before alpha-receptor blockade, a sympathetic coronary alpha-constrictor influence limited, by about 30%, the increase in oxygen delivery accompanying an increase in oxygen consumption; thus, oxygen extraction increased rapidly with augmented oxygen consumption.
Coronary sympathetic and metabolic competition

Coronary sympathetic and metabolic competition is a complex interplay between the autonomic nervous system and metabolic factors that regulate coronary blood flow. This balance is critical to maintaining myocardial oxygen supply and demand, and alterations in this balance can lead to pathological conditions such as myocardial ischemia.

**Perfusion Pressure**

The arterial pressure driving coronary blood flow is a major determinant of myocardial perfusion. It is influenced by factors such as coronary artery pressure, systemic blood pressure, and the resistance of the coronary vascular bed. In the context of sympathetic activation, the increase in arterial pressure due to sympathetic vasoconstriction can counteract the metabolic vasodilator influence, leading to a balance between sympathetic and metabolic control of coronary blood flow.

**Systolic Compression**

During systole, the myocardium is subjected to compressive forces that can impede coronary blood flow. The extent of systolic compression is influenced by factors such as myocardial contractility, arterial pressure, and the geometry of the coronary arteries. In the presence of sympathetic vasoconstriction, the compressive forces during systole can be augmented, further reducing coronary blood flow.

**Metabolic Control**

Coronary blood flow is strongly linked to myocardial metabolism through local metabolic control. The myocardium is a metabolically active tissue that requires a constant supply of oxygen and nutrients to maintain its function. Changes in myocardial metabolism can directly influence coronary blood flow, with factors such as myocardial oxygen extraction and oxygen consumption playing key roles.

**Neural Control**

The autonomic nervous system, particularly the sympathetic and parasympathetic branches, plays a crucial role in regulating coronary blood flow. Sympathetic stimulation can increase coronary vasoconstriction, which reduces coronary blood flow, while parasympathetic stimulation can have opposing effects.

**Coronary Sympathetic and Metabolic Competition/Afo/i/yiwi and Feigl**

In the study by Mohrman and Feigl, the authors investigated the competition between sympathetic vasoconstriction and metabolic vasodilation in the coronary circulation. They found that the balance between these two forces is critical in determining coronary blood flow and myocardial oxygen supply. The results of their study highlight the importance of understanding the complex interplay between sympathetic nervous system activity and metabolic factors in the regulation of coronary blood flow.
nary β-receptors would have been a factor both before and after β-receptor blockade.

Sympathetic α-receptor coronary vasoconstriction is well recognized and has been demonstrated in numerous laboratories. When β-receptor blockade is used to blunt changes in myocardial metabolism, sympathetic activation produces coronary vasoconstriction and decreased coronary venous oxygen levels. The coronary vasoconstriction and depressed venous oxygen tension due to sympathetic nerve stimulation observed in a β-receptor blocked preparation are prevented by α-receptor blockade. In the absence of β-receptor blockade, electrical stimulation of the stellate ganglion has been reported to produce a lesser coronary vasodilatation than that resulting when coronary sinus oxygen levels are reduced to similar levels by systemic hypoxia.

The present results with intracoronary norepinephrine infusion are very similar to those obtained by Imai et al. with catecholamine infusions in an isolated, supported heart-lung preparation. Oxygen extraction and coronary venous oxygen tension were not reported by Imai et al., but myocardial oxygen consumption was low (3 ml/100 g min⁻¹) in their preparation.

Reflex sympathetic α-receptor coronary vasoconstriction in response to carotid sinus hypotension has been reported previously in β-receptor-blocked preparations. Electrical stimulation of the carotid sinus nerve, which mimics increased carotid sinus pressure, produces inhibition of coronary sympathetic constrictor tone. In the present experiments a restriction of flow and oxygen delivery was observed before α-receptor blockade but not afterwards; the most probable interpretation of these results is that an α-receptor vasoconstrictor mechanism limits coronary blood flow during reflex sympathetic activation from the carotid sinus baroreceptors.

In conclusion, this study indicates that a coronary α-receptor constrictor mechanism is important even when competing with the metabolic vasodilator influence of large increases in myocardial metabolism produced by intracoronary norepinephrine or carotid sinus reflex sympathetic activation. The net effect of the α-receptor constrictor influence is to restrict the metabolically related increase in coronary flow by about 30%, thus increasing oxygen extraction and decreasing coronary venous oxygen content.

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