Effect of \( \alpha \)-Adrenergic Stimulation on Regional Contractile Function and Myocardial Blood Flow With and Without Ischemia

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**Background.** The effect of \( \alpha \)-adrenergic receptor activation on regional contractile function and transmural myocardial blood flow is controversial. Accordingly, the effects of selective \( \alpha_1 \)- (methoxamine) and \( \alpha_2 \) (BHT 933) receptor stimulation on regional contractile function and transmural myocardial blood flow distribution were studied in 15 anesthetized open-chest dogs.

**Methods and Results.** The \( \alpha \)-adrenergic agonists were separately infused into the cannulated left circumflex coronary artery during control and ischemic conditions in the same animal. Mean coronary perfusion pressure was held constant by a servocontrolled pump in an extracorporeal circuit. Ischemia was created by reducing coronary perfusion pressure to the level at which percent systolic wall thickening (%WT) decreased by 54%. Contractile function during control conditions was unchanged, whereas under ischemic conditions a further significant decrease in %WT of 27% occurred with either \( \alpha_1 \) - or \( \alpha_2 \)-receptor stimulation without any change in the anterior (control) wall function. Both \( \alpha_1 \) - and \( \alpha_2 \)-receptor stimulations during control conditions resulted in a relatively uniform transmural decrease in blood flow with no change in the subendocardial-to-subepicardial blood flow ratio. With \( \alpha_1 \)-stimulation during ischemia \((n = 13)\), there was a tendency toward decreased subepicardial blood flow with no change in subendocardial flow, resulting in an increased subendocardial-to-subepicardial blood flow ratio \((0.61 \pm 0.23 \text{ to } 0.82 \pm 0.40, p < 0.05)\). \( \alpha_2 \)-Receptor stimulation during ischemia \((n = 12) \) produced a significant decrease in subepicardial blood flow \((0.45 \pm 0.20 \text{ to } 0.35 \pm 0.12 \text{ ml/min/g, } p < 0.01)\) with no change in subendocardial blood flow, also resulting in an increased subendocardial-to-subepicardial blood flow ratio.

**Conclusions.** These results indicate that selective vasoconstriction in outer wall layers during ischemia mediated by either \( \alpha_1 \) - or \( \alpha_2 \)-receptors can cause a decrease in regional contractile function despite unchanged subendocardial blood flow and improved subendocardial-to-subepicardial flow ratio. This suggests an adverse effect of \( \alpha \)-adrenergic vasoconstriction during ischemia in this coronary perfusion pressure-controlled canine model. (Circulation 1991;84:1715-1724)

Although \( \alpha \)-adrenergic coronary vasoconstriction is a well-documented phenomenon,\(^1\) \( \alpha \)-receptor activation and its effect on the transmural distribution of regional myocardial blood flow are highly controversial. The physiological significance of sympathetic vasoconstriction under conditions of myocardial ischemia remains unclear. Laboratory studies in open-chest\(^2\) and exercising\(^3,4\) dogs with and without ischemia suggest that \( \alpha \)-receptor-
mediated vasoconstriction occurs predominantly in outer layers, resulting in a beneficial antitransmural steal effect with a possible redistribution of blood flow to inner layers. Other studies performed during either cardiac sympathetic nerve stimulation in anesthetized dogs or exercise in conscious dogs suggest that α-adrenergic vasoconstriction is deleterious and may exacerbate ischemia, perhaps by selectively decreasing subendocardial blood flow.

Accordingly, the present study was undertaken to examine the effect of selective α-receptor–mediated vasoconstrictor activity on regional myocardial blood flow distribution and regional contractile wall function under controlled conditions in anesthetized dogs.

Methods

Fifteen mongrel dogs (weight, 15–28 kg) were studied under anesthesia. Each animal was handled in accordance with the animal welfare regulations of the University of California San Diego, and the experimental protocol was approved by the animal subjects committee of this institution.

Animal Model

Dogs were premedicated with morphine (1 mg/kg i.m.), and anesthesia was induced with thiamylal (8 mg/kg) administered through a superficial leg vein. Anesthesia was maintained throughout the experiment by isoflurane (1–2%) with oxygen, and ventilator manipulations were performed as necessary to maintain arterial PCO₂, PO₂, and pH within the ranges of PCO₂, 35±5 mm Hg; PO₂, >95 mm Hg; and pH, 7.35±0.05. Both femoral arteries and one femoral vein were cannulated. One arterial line was used for withdrawal of reference blood samples during microsphere injections, and the other was used for recording of systemic arterial pressure (model P23Db, Statham, Hato Rey, P.R.). Isotonic saline solution (0.9%) was administered through the venous catheter for volume replacement. The right carotid artery was cannulated to serve as the blood supply for an extracorporeal circuit. Rectal temperature was measured periodically, and the dogs were kept on a circulating hot water pad to maintain body temperature above 36°C.

A left lateral thoracotomy was performed in the fifth intercostal space, and the heart was suspended in a pericardial cradle. Electrodes were sutured to the left atrial appendage for pacing (model 5800, Medtronic, Inc., Minneapolis, Minn.), and a catheter was introduced into the left atrium for microsphere injections. A micromanometer (Konigsberg Instruments, Pasadena, Calif.) was placed in the left ventricle through the apex for measurement of left ventricular (LV) pressure. This high-fidelity transducer was calibrated by pressure measurements from a saline-filled catheter placed in the LV chamber through the same apical stab wound.

Ultrasound crystals were implanted in the postero-lateral wall within the perfusion bed of the left circumflex coronary artery (LCx) and in the anterior (control) wall within the left anterior descending artery perfusion zone using standard techniques.

The crystals were configured to measure transmural wall thickness in the two perfusion areas by the transit time technique (Triton Technologies, San Diego, Calif.). End diastole was defined as the zero crossing point of the first derivative of LV pressure (LV dP/dt) before its maximum value, and end systole was defined as the time of maximum excursion of the sonomicrometer tracing occurring within 20 msec before peak negative LV dP/dt. Myocardial wall function was assessed by calculating the percent change in wall thickness from end diastole to end systole (%WT).

The proximal LCx was dissected free from the surrounding tissue for a distance of approximately 1.5 cm. After heparinization (15,000 units initial dose, followed by 10,000 units/hr), the exposed LCx segment was ligated proximally and rapidly cannulated. Blood was supplied as previously described by an extracorporeal circuit that included an occlusive roller pump (Masterflex, Cole-Parmer Instrument Co., Chicago), a windkessel that trapped air bubbles, an ultrasonic flow probe (model T-201, Transonic, Ithaca, N.Y.), and one side port for drug infusions. Coronary perfusion pressure was measured through a distal side arm of the cannula, with the pressure drop from cannula tip to the side arm previously determined to be less than 1 mm Hg for flows in the range observed in this experiment. The transducer (model 1290C, Hewlett-Packard) used to measure the coronary perfusion pressure was placed at the level of the cannula tip, which provided the zero reference level.

Blood Flow Measurements

Regional blood flow distribution was measured by microspheres (15-μm diameter) labeled with one of the following radionuclides: 125I (3M, St. Paul, Minn.), 103Ce, 114In, 51Cr, 113Sn, 109Ru, 85Nb, and 46Sc (DuPont—New England Nuclear, Boston). For each measurement, approximately 3×10⁶ microspheres in a volume of 1 ml were infused into the left atrium approximately 15 seconds after the initiation of a 90-second arterial blood reference withdrawal. The microsphere injections were rapidly followed by three 3-ml flushes of saline.

At the conclusion of the study, the hearts were removed and placed in 10% formalin for at least 1 day. The accuracy of ultrasound crystal placement was verified visually, and LV tissue samples from the myocardium between the subepicardial and subendocardial crystals were divided into transmural thirds. Tissue samples were placed into glass tubes for gamma radioactivity counting by means of a multichannel gamma counter (model 5912, Packard Instruments, Downers Grove, Ill.), and gamma radioactivity of blood samples from the reference withdrawals were similarly counted by previously described methods. Regional myocardial blood flow...
corrected for wet weight of the tissue was calculated by using the following equation:

\[
\text{Blood flow to tissue sample} = \text{counts per sample} \times \frac{\text{reference flow}}{\text{reference counts}}
\]

The reference withdrawal flow was calculated by weighing the withdrawal syringe before and after the 90-second withdrawal as previously described.\(^{10}\)

**Study Protocol**

After the LCx was isolated and proximally cannulated, the level of coronary inflow was adjusted so that the coronary perfusion pressure matched the mean systemic arterial pressure. Pacing was then initiated at a rate above the intrinsic level, and control of the pump was switched to a servosystem to maintain mean coronary perfusion pressure constant at a level preset to approximate the mean systemic arterial pressure. %WT in the posterolateral wall was averaged over six beats and automatically calculated and displayed on the strip-chart recorder. After posterolateral %WT had recovered to precannulation values, the first myocardial blood flow and hemodynamic measurements were performed. Intracoronary methoxamine (3–12 μg/kg/min, Burroughs-Wellcome) or BHT 933 (BHT, 6 μg/kg/min, Boehringer Ingelheim), selected at random, was then continuously administered through the infusion port on the extracorporeal circuit (infusion rate, 1.5 ml/min). Three minutes later, after a steady state had been achieved during drug administration, another set of measurements was made. Immediately after the 90-second withdrawal period, the drug infusion was stopped, and sufficient time was allowed for return to baseline (approximately 20 minutes). Total drug infusion time averaged 4:16 minutes. After recovery, the LCx perfusion pressure was gradually reduced so that posterolateral %WT fell to approximately 50% of the control value. After a brief period of stabilization at this level of ischemia, pre–drug infusion hemodynamic and blood flow measurements were made. Infusion of the same α-agonist at the same infusion rate (1.5 ml/min) was then initiated. Hemodynamic and myocardial blood flow measurements were made 3 minutes later, when a steady state had been achieved. Again, total drug infusion time averaged 4:16 minutes. After completion of the reference withdrawal, the drug infusion was stopped and flow was restored so that perfusion pressure again matched systemic arterial pressure, with subsequent full recovery of function. After recovery from the drug effects and hypoperfusion, the protocol was repeated using the other α-agonist.

Methoxamine was infused first in eight of the 15 dogs. Because the magnitude of the coronary flow responses to methoxamine was found to vary among dogs, a test dose (6 μg/kg/min) was administered. This dose was chosen because it had been previously shown to cause significant coronary vasoconstriction.\(^{11}\) If after 3 minutes, the mean systemic arterial pressure response (due to drug recirculation) exceeded 10 mm Hg, one half of the test dose was used for the remainder of the study. If, on the other hand, the test infusion resulted in no coronary flow effect, a 12-μg/kg/min methoxamine dosage was used. In all cases, baseline flow and pressure levels were restored before proceeding with the protocol. One dog was given the 3-μg/kg/min dosage, and another dog was given the 12-μg/kg/min dosage. All other dogs received a 6-μg/kg/min dosage. As the responses to BHT were observed to be much less variable, no test infusion of this drug was routinely carried out. The 6-μg/kg/min dosage of BHT was selected because it did not produce appreciable systemic effects and other studies have demonstrated the ability of similar dosages to cause significant coronary vasoconstriction.\(^{12}\) The complex study design comparing different drugs under both control and ischemic conditions in the same animals included the maximum number of radioisotopes that can be analyzed in our system (eight); therefore, assessment of flow distribution at multiple dose levels was not feasible. We found in pilot studies that subendocardial flow did not change with α-agonist infusions during ischemia and elected to maintain the same drug infusion rates, recognizing that at the level of reduced perfusion that was induced, drug concentrations in the perfusion line were approximately twice those under nonischemic conditions. The experiment was terminated by thiamylal overdose, and hearts were immediately excised and preserved as previously described.

**Data Analysis and Statistics**

Data from two control methoxamine infusions and two infusions during ischemia were excluded because of intractable arrhythmias or unexplained persistent postcannulation hyperemia. Data from two control BHT infusions and three infusions during ischemia were excluded for similar reasons.

Data were recorded on an eight-channel recorder (model 200, Gould, Cerritos, Calif.) and in digitized form on computer disk for beat averaging (CODAS, Dataq Instruments Inc., Akron, Ohio). Ten sequential beats were averaged for each measurement (CORDAT, Essen, Germany). Calculated hemodynamic parameters included LV peak and end-diastolic pressures, peak positive LV dP/dt, mean coronary inflow, mean coronary perfusion pressure, and mean systemic arterial pressure.

The effect of each drug infusion on the variables measured was analyzed with a paired Student's t test with Bonferroni's correction for four comparisons. Data are reported as mean±SD.

**Results**

Before and after drug infusions, coronary perfusion pressure was held constant by the servocontrol system. After recovery from drug infusions at normal perfusion, coronary perfusion pressure was reduced to create regional ischemia with an average decrease
in %WT of the posterolateral wall of 54±19%. During ischemia, coronary perfusion pressure was held constant before and after each α-agonist drug infusion (Tables 1 and 2).

**Hemodynamic Changes**

Infusion of the α-agonists methoxamine (α₁) or BHT (α₂) under both control and ischemic conditions resulted in small increases in mean aortic pressure, probably the result of drug recirculation (Tables 1 and 2). Left ventricular end-diastolic pressure rose significantly upon α₁-receptor stimulation during ischemia. No changes in LV dP/dt were observed. Infusions of either drug under both normal and ischemic conditions resulted in significant decreases in mean total coronary inflow (Tables 1 and 2).

**Regional Wall Function**

**Control conditions.** Intracoronary infusion of methoxamine or BHT did not result in a change in regional systolic wall function during nonischemic conditions (Tables 1 and 2).

**Ischemic conditions.** In contrast, both α₁- and α₂-receptor stimulation under ischemic conditions resulted in a further significant decrease in systolic wall thickening of the posterior (ischemic) wall by 27% without any change in the anterior (control) wall function (Tables 1 and 2 and Figure 1).

**Regional Transmural Blood Flow Distribution**

Regional transmural blood flows in the control anterior wall before and after selective LCx coronary drug infusion remained unchanged during either normal perfusion or ischemia.

**α₁-Adrenergic stimulation: Control conditions.** Infusion of methoxamine under control conditions resulted in a uniform decrease in blood flow to all three myocardial layers (subepicardial, midmyocardial, and subendocardial) with no change in the subendocardial-to-subepicardial blood flow ratio (Figure 2, top panel).

**α₂-Adrenergic stimulation: Ischemic conditions.** During ischemia, α₁-receptor stimulation resulted in a tendency toward decreased subepicardial blood flow.

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**Table 1. Hemodynamic and Regional Wall Function Before and After α₁-Adrenergic Agonist Infusion During Normal Perfusion and Ischemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal perfusion</th>
<th>Normal perfusion + α₁</th>
<th>Ischemia</th>
<th>Ischemia + α₁</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>136±9</td>
<td>136±9</td>
<td>136±10</td>
<td>137±10</td>
</tr>
<tr>
<td>Left ventricular systolic pressure (mm Hg)</td>
<td>87±12</td>
<td>92±10*</td>
<td>84±14</td>
<td>86±14*</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>11±4</td>
<td>12±4</td>
<td>13±3</td>
<td>13±3</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>72±14</td>
<td>78±12†</td>
<td>71±17</td>
<td>75±15†</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>1,693±362</td>
<td>1,696±323</td>
<td>1,463±314</td>
<td>1,459±285</td>
</tr>
<tr>
<td>Wall thickening (posterior) (%)</td>
<td>23±6</td>
<td>23±7</td>
<td>11±6</td>
<td>8±6†</td>
</tr>
<tr>
<td>Wall thickening (anterior control) (%)</td>
<td>23±10</td>
<td>23±9</td>
<td>25±12</td>
<td>25±12</td>
</tr>
<tr>
<td>LCx mean pressure (mm Hg)</td>
<td>76±10</td>
<td>77±9</td>
<td>38±10</td>
<td>38±9</td>
</tr>
<tr>
<td>LCx mean flow (ml/min)</td>
<td>48±13</td>
<td>35±6†</td>
<td>16±9</td>
<td>12±7*</td>
</tr>
</tbody>
</table>

α₁, methoxamine; LCx, left circumflex coronary artery. Values are given as mean±SD. n=13 for normal perfusion; n=13 for ischemia. *p<0.05 and †p<0.01 vs. normal perfusion or ischemia.

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**Table 2. Hemodynamic and Regional Wall Function Before and After α₂-Adrenergic Agonist Infusion During Normal Perfusion and Ischemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal perfusion</th>
<th>Normal perfusion + α₂</th>
<th>Ischemia</th>
<th>Ischemia + α₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>135±9</td>
<td>135±9</td>
<td>136±9</td>
<td>135±9</td>
</tr>
<tr>
<td>Left ventricular systolic pressure (mm Hg)</td>
<td>89±15</td>
<td>92±12</td>
<td>79±13</td>
<td>82±13</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>11±3</td>
<td>11±3</td>
<td>12±3</td>
<td>13±3†</td>
</tr>
<tr>
<td>Aortic mean pressure (mm Hg)</td>
<td>74±15</td>
<td>78±12*</td>
<td>64±13</td>
<td>68±14*</td>
</tr>
<tr>
<td>+dP/dt (mm Hg/sec)</td>
<td>1,647±338</td>
<td>1,591±260</td>
<td>1,351±310</td>
<td>1,325±258</td>
</tr>
<tr>
<td>Wall thickening (posterior) (%)</td>
<td>23±7</td>
<td>22±7</td>
<td>11±5</td>
<td>8±5†</td>
</tr>
<tr>
<td>Wall thickening (anterior control) (%)</td>
<td>21±12</td>
<td>21±12</td>
<td>24±15</td>
<td>22±15</td>
</tr>
<tr>
<td>LCx mean pressure (mm Hg)</td>
<td>83±7</td>
<td>84±6</td>
<td>37±9</td>
<td>37±9</td>
</tr>
<tr>
<td>LCx mean flow (ml/min)</td>
<td>44±11</td>
<td>31±7†</td>
<td>15±8</td>
<td>11±7†</td>
</tr>
</tbody>
</table>

α₂, BHT 933; LCx, left circumflex. Values are given as mean±SD. n=13 for normal perfusion; n=12 for ischemia. *p<0.05 and †p<0.01 vs. normal perfusion or ischemia.
(decrease observed in 10 of 13 animals; 0.53±0.25 to 0.45±0.25 ml/min/g, Figures 2, bottom panel and 3, left panel) with no such trend observed in subendocardial blood flow (0.30±0.12 to 0.32±0.13 ml/min/g, Figures 2, bottom panel and 3, right panel). Drug infusion was associated with an increased subendocardial-to-subepicardial flow ratio (0.61±0.23 to 0.82±0.40, p<0.05, Figure 2, bottom panel).

α2-Adrenergic stimulation: Control conditions. Infusion of BHT under control conditions caused blood flow reductions in all three myocardial layers in a nonuniform fashion, reflected by an increased subendocardial-to-subepicardial flow ratio (0.94±0.29 to 1.11±0.38, p<0.01, Figure 4, top panel).

α2-Adrenergic stimulation: Ischemic conditions. During ischemia, BHT infusion resulted in a significant decrease in subepicardial blood flow (0.45±0.20 to 0.35±0.12, p<0.01) with no change in midmyocardial or subendocardial layers, resulting in an increased subendocardial-to-subepicardial flow ratio (0.73±0.30 to 0.97±0.32, p<0.01, Figure 4, bottom panel).

Discussion

Results from the present study demonstrate a transmural decrease in myocardial blood flow upon selective activation of either α1- or α2-adrenergic receptors under nonischemic conditions. During ischemia, stimulation of either α1- or α2-receptors resulted in a decrease in regional contractile function and a nonuniform transmural blood flow reduction with an increase in the subendocardial-to-subepicardial blood flow ratio. The increased subendocardial-to-subepicardial blood flow ratio during ischemia was the result of vasoconstriction in the subepicardium, with no change in midwall or subendocardial blood flow. Under either control or ischemic conditions, total coronary inflow was decreased significantly by either drug.

In the constant coronary perfusion pressure model used in the present study, assuming a parallel array of coronary perfusion beds, blood flow to an individual bed is independent of resistance changes in all other perfusion beds. This system was selected to enable us to monitor resistance changes in each myocardial layer resulting from α-receptor activation independent of resistance changes occurring in other layers. It follows that during ischemia, a selective decrease in subepicardial blood flow induced through α-adrenergic vasoconstriction could occur without any change in subendocardial flow.

Our results are consistent with those of previous studies in conscious13 and anesthetized resting
dogs\textsuperscript{11,12} under nonischemic conditions, in which constriction of coronary resistance vessels was found to be mediated by both \(\alpha\)-receptor subtypes. Although Woodman and Vatner\textsuperscript{13} measured late dia-

stolic total coronary vascular resistances, we have extended their observations to show that this increase in coronary resistance is due to vasoconstrictor activity present across the whole myocardial wall. Our

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2}
\caption{Plots of effect of \(\alpha\)-receptor stimulation on regional blood flow and subendocardial-to-subepicardial blood flow ratio during normal (top panel) and ischemic (bottom panel) conditions. EPI, subepicardium; MID, mid-myocardium; ENDO, subendocardium; ENDO/EPI, subendocardial-to-subepicardial blood flow ratio. \#p<0.05 vs. control or ischemia. ##p<0.01 vs. normal perfusion or ischemia. Values are given as mean\(\pm\)SD.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure3}
\caption{Plots of individual regional blood flow data demonstrating (left panel) trend toward decreased subepicardial perfusion in 10 of 13 dogs, with (right panel) no change in subendocardial perfusion on \(\alpha\)-receptor stimulation. BEFORE, before \(\alpha\)-receptor stimulation; AFTER, during \(\alpha\)-receptor stimulation.}
\end{figure}
results are also consistent with those of Chen et al., who demonstrated uniform transmural vasoconstriction in the open-chest dog in response to intracoronary phenylephrine (α1-agonist) or BHT 933.

Although α-adrenergic stimulation during ischemia has been extensively studied, the effect on regional transmural blood flow distribution is still unclear. Heusch and Deussen demonstrated increased end-diastolic resistance upon cardiac sympathetic nerve stimulation during ischemia. In their study, coronary stenosis was produced in anesthetized open-chest dogs with and without β-adrenergic receptor blockade and was defined as being intermediate or severe by the reduction of reactive hyperemia following a test coronary occlusion. Subgroups of dogs were given intravenous phentolamine (non-selective α-receptor antagonist), prazosin (selective α1-antagonist), or rauwolscine (selective α2-antagonist). The α-adrenergic vasoconstrictive effects of left cardiac sympathetic nerve stimulation were monitored by measuring end-diastolic coronary resistances distal to the coronary stenosis. During sympa-

thetic stimulation, they observed a shift from a decrease in resistance in the intact vessel to a significant increase in resistance with severe coronary stenosis. They concluded that the increased resistance was largest during severe stenosis due to the exhaustion of vasoconstriction and resultant unmasking of α-receptor-mediated sympathetic vasoconstriction. The observed vasoconstrictor effect was blocked by rauwolscine (α2) and phentolamine but not by prazosin (α1), suggesting that sympathetic vasoconstriction in the presence of a severe coronary stenosis is primarily mediated by postjunctional α2-receptors. The relative contribution of the individual myocardial layers to the total resistance increase observed with cardiac sympathetic nerve stimulation during ischemia was not studied.

We have extended the above findings of Heusch and Deussen in showing that the increase in coronary resistance with humoral α-adrenergic stimulation during moderate ischemia mainly occurs in the outer myocardial layers, as evidenced by the flow reduction in the subepicardium without changes in
midwall and subendocardial blood flows. Although direct electrical nerve stimulation and intracoronary drug infusions do not necessarily mimic normal endogenous neural activation, our studies nevertheless show the potential for both α₁- and α₂-receptors to play a role in causing coronary vasoconstriction during myocardial ischemia. In our experiments, it appears possible that metabolic vasoilation of the ischemic inner layers prevented significant α-adrenergic vasoconstrictor effects, because vasoconstrictor activity in the subendocardium was evident only under control conditions. It is also possible that the observed lack of inner wall vasoconstriction during ischemia was related to reduced drug delivery to inner layers relative to delivery to outer layers; however, this appears unlikely because, as mentioned earlier, we elected not to change drug infusion rates during ischemia, resulting in an approximate twofold increase in drug concentration in the perfusate (blood flow to the inner third of the wall during ischemia was approximately 50% of control flow) and because despite this not even a tendency toward drug-induced vasoconstriction in the subendocardium was observed.

In the present study, α-receptor stimulation during ischemia resulted in a decrease in regional wall function. These results are similar to the observations of Heusch and Deussen⁵ showing sympathetic vasoconstriction to adversely affect myocardial wall function. It has been hypothesized that the decrement in function in these and other studies may have been the result of selective α₁-receptor–mediated vasoconstriction in the subendocardium, resulting in reduced blood flow to the inner myocardial layers.¹ Although the small increase in aortic pressure and afterload may in part explain our findings, our results suggest a different explanation. It appears more likely that alterations in subepicardial perfusion may have indeed been the important determinant of regional contractile function because subendocardial blood flow did not change at the level of ischemia used here (54% of control %WT). Gallagher et al.¹⁵ observed in conscious dogs that although transmural contractile function is strongly dependent on subendocardial blood flow, subepicardial blood flow becomes an important determinant of segmental function when systolic wall thickening is reduced to levels less than 50% of control function. Thus, our observations suggest that α-adrenergic receptor–mediated subepicardial vasoconstriction during moderate-to-severe ischemia effected a significant decline in transmural contractile function.

Nathan and Feigl² studied open-chest anesthetized dogs subjected to β-adrenergic blockade in which intracoronary norepinephrine produced α-adrenergic stimulation. In studies with constant flow ischemia, α-adrenergic blockade with phenoxybenzamine was produced in one portion of the coronary bed, whereas the other region remained unblocked. It was found that the subendocardial-to-subepicardial flow ratio was higher in the absence than in the presence of α-blockade, suggesting a beneficial effect of α-adrenergic constrictor tone during ischemia. However, absolute regional blood flows were not reported, and markers of the degree of ischemia such as regional function were not used. Thus, it is possible (as in our experiments) that the subendocardial-to-subepicardial blood flow ratio could have been higher with intact α-receptors even though subendocardial blood flow was unchanged.

The present data emphasize that subendocardial-to-subepicardial blood flow ratios are not sufficient to assess regional myocardial ischemia because an improved subendocardial-to-subepicardial blood flow ratio would not necessarily be beneficial, as was observed in the present study. In another study, Huang and Feigl¹ demonstrated a potential role for α-adrenergic receptor stimulation in maintaining uniform transmural distribution of blood flow in nonischemic dogs during exercise. In their study, α-adrenergic blockade with phenoxybenzamine increased total transmural myocardial blood flow but decreased the subendocardial-to-subepicardial blood flow ratio compared with regions with intact α-receptors. Interpretation of these results is complicated by the lack of absolute regional blood flow data in that report. In addition, phenoxybenzamine has been shown to cause complete blockade of α₁-receptors but only partial blockade of α₂-receptors, raising the possibility of heterogeneous effects.¹ The near-maximal sympathetic stimulation under which this antitransmural steal effect has been proposed to exist is also clearly different from that of the anesthetized preparation used in the present study.

To study the role of neurally mediated α-adrenergic vasoconstriction, Chilian and Ackell⁴ studied conscious exercising dogs with one area of a region rendered ischemic and subjected to phenol denervation while the other area was spared. Coronary perfusion pressure beyond a coronary stenosis during exercise was maintained constant. The innervated region exhibited lower subepicardial blood flow, higher subendocardial flow, and higher subendocardial-to-subepicardial ratio than the denervated region. These differences between the innervated and denervated regions were eliminated by intravenous phentolamine. Although the effect on outer wall blood flow is consistent with the present study, the improvement in inner wall flow observed in the innervated region was not seen in the present study. In a pressure constant system, an increase in vascular resistance (as in the subepicardium) must result in reduced total flow (as observed in the present study), unless another region has an appropriate reduction in vascular resistance to accommodate the flow. Thus, it is not clear how the transmural shift observed by Chilian and Ackell could have occurred at a constant perfusion pressure. Nevertheless, as pointed out by these authors, most of the coronary adrenergic constrictor tone in exercising dogs is due to circulating, not neuronally released, catechol-
amines. Because in the present study α-adrenoceptor activation was accomplished by the administration of α-agonists through the coronary artery and not by neuronal release of catecholamine, a direct comparison between these studies is not possible.

Other studies in experimental models using conscious exercising dogs in which selective α-blocking agents were used during ischemia have suggested that α1- and α2-receptors in the subendocardium may be responsible for mediating vasoconstriction and therefore worsening inner wall ischemia during exercise, although increased subepicardial flow after α2-blockade was not observed in our previous study. Thus, potential benefits of regional α-receptor blockade were postulated to result from improvement of subendocardial blood flow under conditions of very high sympathetic tone induced by exercise. These studies in complex, intact animal models during exercise clearly differ from those in the open-chest anesthetized preparation used in the present study, and differences in the preparation, degree of ischemia, and intensity and mode of α-adrenergic stimulation may account for some of the variability in results.

Potential Clinical Implications

It is difficult to compare these experiments with the more complex clinical setting in which a proximal lesion may be present in a coronary artery. In such a setting, α-adrenergic stimulation could affect the lesion itself as well as the more distal resistance vessels. An example of a relevant clinical setting may be postulated to occur if enhanced sympathetic stimulation results in increased resistance of the proximal stenosis associated with a significant increase in aortic pressure, resulting in no net change in coronary perfusion pressure, as might occur during exercise or emotional stress. Under these conditions of constant coronary perfusion pressure and increased α-adrenergic activation during ischemia, vasoconstriction of subepicardial vessels without a change in subendocardial resistance could occur as observed in the present experiments. In such a situation, increased α-adrenergic tone would be detrimental, causing decreased regional function, whereas α-receptor blockade could be of benefit.

Limitations

Admittedly, neither the constant flow nor the constant pressure models completely simulate the physiological situation of ischemia due to a proximal coronary stenosis. It should also be noted that isoflurane anesthesia has been reported to functionally inhibit α-adrenergic vascular responses, raising the possibility that the present data underestimate the magnitude of responses to α-adrenergic agonists at the dosages used in the present study. Another limitation of the canine model involves the presence of collateral vessels to the experimental posterior wall. It has been variously reported that α-adrenergic receptors are present and absent from these collateral vessels. α-Adrenergic receptors in collateral vessels could exaggerate the responses observed in these experiments, but such an effect does not appear likely because drug recirculation effects were minimal. Although the pig has fewer coronary collateral vessels, α-receptor activity in the porcine coronary circulation is minimal, making it an inappropriate model for these studies. Humoral delivery of the α-agonists in this study does not simulate the complex effects of adrenergic nerve stimulation. Prior β-adrenergic blockade was not used in our experiments because any stimulatory effect on prejunctional α-adrenergic receptors would probably be small in the absence of a high degree of sympathetic neuronal tone. If such an effect did occur, it would have resulted in less norepinephrine release and a less intense vasoconstrictor response, which would only have lessened the substantial direct vasoconstrictor effects observed. Furthermore, we saw no effects on myocardial contractility after infusion of α-agonists under control conditions, whereas a mild negative inotropic effect might have been expected if significant prejunctional α-receptor stimulation had occurred with α-agonist infusion. Finally, the technique used did not allow determination of the role of constriction at the larger epicardial vessels compared with the smaller vessels. It is clear, however, that α1- and α2-adrenergic effects could be demonstrated in both the inner and outer walls of the canine left ventricle.

Summary

With normal perfusion, stimulation of either α-subtype resulted in a transmural decrease in regional blood flow, whereas during ischemia, subepicardial blood flow decreased with no change in midwall or subendocardial blood flow. During ischemia, the observed decrease in wall function in response to α-receptor stimulation appeared to be the result of decreased subepicardial perfusion, suggesting an adverse effect of α-adrenergic vasoconstriction during ischemia in this perfusion pressure–controlled canine model.

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References


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