The Role of $\alpha_1$- and $\alpha_2$-Adrenergic Receptors in Mediation of Coronary Vasoconstriction in Hypoperfused Ischemic Myocardium During Exercise

David D. Laxson, Xue-Zheng Dai, David C. Homans, and Robert J. Bache

This study was carried out to test the hypothesis that adrenergic coronary vasoconstriction limits blood flow to hypoperfused regions of myocardium during exercise. The vasoconstrictor influence of $\alpha_1$-adrenergic receptor subtypes was assessed by use of selective adrenergic blocking agents. Dogs chronically instrumented with a circumflex coronary artery hydraulic occluder and an intra-arterial catheter underwent treadmill exercise in the presence of a coronary stenosis that decreased distal perfusion pressure to 40 mm Hg. Myocardial blood flow was measured with radioactive microspheres (15 $\mu$m) before and during selective $\alpha_1$- or $\alpha_2$-adrenergic receptor blockade produced by intracoronary infusion of prazosin (1 $\mu$g/kg/min $\times$ 10 min) or idazoxan (1 $\mu$g/kg/min $\times$ 10 min), respectively. Coronary perfusion pressure was held equal before and during receptor blockade with the hydraulic occluder. Compared with control exercise, subendocardial blood flow increased during $\alpha_1$-receptor blockade with prazosin from $0.60\pm0.14$ to $1.12\pm0.17$ ml/min/g ($p<0.05$), and mean transmural flow increased from $1.07\pm0.19$ to $1.60\pm0.22$ ml/min/g ($p<0.05$). In contrast, subendocardial and mean transmural blood flow were not different from control during selective $\alpha_2$-adrenergic receptor blockade with idazoxan ($0.48\pm0.10$ vs. $0.67\pm0.14$ ml/min/g, $p=0.33$, and $0.82\pm0.15$ vs. $1.02\pm0.20$ ml/min/g, $p=0.45$, respectively). These data indicate that even in the presence of a coronary stenosis that causes substantial myocardial underperfusion during exercise, residual coronary vasoconstrictor tone is present in ischemic myocardium, and this vasoconstriction is mediated predominantly by the $\alpha_2$-adrenergic receptor. (Circulation Research 1989;65:1688-1697)

Autoregulatory adjustment of coronary vaso-motor tone has traditionally been thought to maintain myocardial blood flow in the face of decreasing perfusion pressure until vasodilator capacity is exhausted. Further reductions in perfusion pressure are associated with decreased blood flow and the development of ischemia. However, recent evidence indicates that the coronary vascular bed may not be maximally vasodilated during myocardial ischemia. Thus, persistent coronary vasodilator reserve during ischemia has been reported in both open-chest$^1$-$^4$ and exercising canine studies.$^5$-$^6$ While the mechanisms responsible for residual vasoconstrictor activity are not clear, there is evidence for sympathetic $\alpha$-adrenergic receptor-mediated coronary vasoconstriction, even during hypoperfusion, when there is a strong metabolic stimulus for vasodilation.$^7$-$^9$

This study was carried out to test the hypothesis that adrenergic vasoconstrictor tone limits blood flow distal to a coronary artery stenosis which results in exercise-induced myocardial ischemia. Since the coronary resistance vessels, which are the main source of coronary vascular resistance, have both postsynaptic $\alpha_1$- and $\alpha_2$-adrenoceptors,$^{10}$-$^{12}$ the contributions of adrenergic receptor subtypes in mediation of coronary vasoconstriction during exercise-induced ischemia were examined by use of the selective $\alpha_1$-receptor antagonist prazosin and the selective $\alpha_2$-receptor antagonist idazoxan. The antagonists were infused directly into the circumflex coronary artery to avoid systemic and central effects of these agents on hemodynamics and sympathetic tone.
Materials and Methods

Adult mongrel dogs of either sex weighing 23–30 kg were premedicated with fentanyl (0.4 mg i.m.) and droperidol (20 mg i.m.), anesthetized with sodium pentobarbital (30 mg/kg i.v.), intubated, and ventilated with a mechanical respirator with supplemental oxygen. A sterile left fifth interspace thoracotomy was made, and a heparin-filled polyvinyl chloride catheter (3.0 mm o.d.) was advanced through the left internal thoracic artery into the ascending aorta. The pericardium was then opened and the heart suspended in a pericardial cradle. Heparin-filled polyvinyl chloride catheters were also placed into the left atrium through the atrial appendage and into the left ventricle though the apical dimple and secured with purse-string sutures. A solid-state micromanometer (model P5, Koningsberg Instruments, Pasadena, California) was also inserted into the left ventricle at the apex and secured with a purse-string suture. Pairs of 5-MHz miniature piezoelectric crystals for measurement of myocardial segment shortening were implanted 1–2 cm apart into the inner third of the anterior and posterior left ventricular wall in the region of the left anterior descending and left circumflex coronary artery perfusion beds. Pairs of crystals were aligned so that their axes were parallel to the expected subendocardial fiber orientation. A segment of the proximal left circumflex coronary artery was dissected free, and a 10-MHz Doppler ultrasonic flow probe was fitted around the artery. A hydraulic occluder constructed of 2.7-mm o.d. polyvinyl tubing was then placed around the artery immediately distal to the flow probe. A heparin-filled catheter constructed of a 5-cm length of silastic tubing (0.3 mm i.d.) bonded to a larger silastic tube (1.6 mm i.d.) was introduced into the left circumflex artery just distal to the hydraulic occluder after the method of Gwirtz. The pericardium was then loosely closed, an indwelling chest tube was placed, and all catheters and leads were brought out between the ribs, tunneled subcutaneously, and externalized dorsally at the base of the neck. The chest was then closed, and the pneumothorax was evacuated. Catheters and leads were protected by a nylon vest the animals were trained to wear. The intracoronary catheter was flushed daily with heparin, and all other fluid-filled catheters were flushed every second to third day with heparinized saline. Animals were allowed at least 14 days to recover from surgery.

Hemodynamic Measurements

Phasic and mean aortic pressure and coronary perfusion pressure were measured using Model P22XL pressure transducers (Gould, Cleveland, Ohio). Left ventricular pressure was obtained from the micro-manometer, which was calibrated with the fluid-filled left ventricular catheter. Left ventricular rate of change of pressure (dP/dt) was obtained by differentiation of the left ventricular pressure signal. All pressure and segment shortening data were recorded on a Model 8800 direct-writing eight-channel oscillograph (Hewlett-Packard, Palo Alto, California).

Regional Myocardial Function Measurements

Segment-length measurements were obtained by activation of the implanted piezoelectric crystals with a Model 120 ultrasonic dimension system (Triton, San Diego, California). Crystals separation for each channel was sampled at 1 kHz and converted to an analog voltage. Minimum resolution using 5-MHz crystals was approximately 0.07 mm. End-diastolic segment length was measured just before the onset of the upstroke of the left ventricular pressure tracing, while end-systolic segment length was taken at 20 msec before peak negative left ventricular dP/dt. Percent segment shortening was defined as (end-diastolic length - end-systolic length)/end-diastolic length×100. A minimum of 10 beats were averaged for each determination of regional function.

Myocardial Blood Flow Measurements

Distribution of blood flow across the wall of the left ventricle was estimated, after the method of Domenech et al, with tracer microspheres, 15 ?m in diameter, labeled with one of the following radionuclides: 125I, 55Nb, 51Cr, 57Co, 85Sr, 133Sn, or 46Sc. Microspheres were agitated in an ultrasonic mixer for 15 minutes before injection. Approximately 3×10^6 microspheres were injected into the left atrial catheter and flushed with 5 ml of normal saline for each measurement. A reference arterial blood specimen was withdrawn via the aortic catheter at a rate of 15 ml/min beginning 5 seconds before the injection and continuing for 120 seconds. Radioactivity in myocardial and blood reference specimens was determined by use of a Model 5912 gamma spectrometer with multichannel analyzer (Packard Instrument, Downers Grove, Illinois) at window settings appropriate for the combination of radioisotopes used during the study. The activity in each energy window, background activity, and sample weight were entered into a digital computer programmed to correct the counts recorded in each window for contaminant activity contributed by the associated isotopes, as well as for background activity, and to compute the corrected counts per minute per gram of myocardium. Knowing the rate of withdrawal of the reference sample (Q_r), the radioactivity in the reference sample (C_r), and the fact that complete mixing of the microspheres in the left ventricle and aortic root resulted in a uniform ratio of blood flow to radioactivity in the myocardium, we used myocardial radioactivity (C_m) to compute myocardial blood flow (Q_m) as Q_m=Q_r(C_m/C_r). Blood flows were expressed as milliliters per minute per gram of myocardium.
Study Protocol

Conditioned dogs were trained to run on a motor-driven treadmill before instrumentation and again after recovery from surgery. Studies were performed only after animals were able to exercise satisfactorily and the coronary reactive hyperemia response, as determined with the flow probe after a 10-second coronary occlusion, had returned to normal. At the time of study, dogs underwent exercise on a motor-driven treadmill until a heart rate of 200–220 beats/min (approximately 6.5 km/hr, 6% grade) was reached. After stable hemodynamics were achieved, an acute circumflex coronary artery stenosis was produced by inflation of the hydraulic occluder with saline from a micrometer-driven syringe that allowed precise control of the degree of stenosis. The occluder was adjusted as necessary to maintain coronary perfusion pressure distal to the stenosis at approximately 40 mm Hg. After 1–2 minutes of exercise in the presence of a coronary stenosis, when hemodynamics and myocardial segment shortening had stabilized, a microsphere injection was made into the left atrium for measurement of myocardial blood flow. When collection of reference flows from the aorta was completed, the stenosis was released and exercise discontinued.

After a 90-minute recovery period, the dogs were randomized to receive either the selective α1-adrenergic receptor antagonist prazosin (1 μg/kg/min×10 min) (group 1) or the α2-adrenergic receptor antagonist idazoxan (1 μg/kg/min×10 min) (group 2) as an intracoronary infusion. Prazosin (Pfizer, Groton, Connecticut) was dissolved in distilled water and diluted to an appropriate concentration. Idazoxan (Reckitt and Colman, Hull, England) was dissolved in normal saline and diluted to an appropriate concentration. This dose of prazosin has been previously found to completely inhibit the response to intracoronary bolus doses of phenylephrine (0.3 and 3.0 μg/kg) in awake chronically instrumented dogs, even though the higher dose resulted in a 15% increase in mean aortic pressure. Idazoxan in this dose has been demonstrated to completely inhibit the response to an intracoronary bolus of B-HT933, a selective α2-adrenergic agonist (Boehringer-Ingelheim, Ridgefield, Connecticut) at doses of 0.1, 1.0, and 10.0 μg/kg. Furthermore, in the initial four animals in the current study the coronary responses to the same bolus intracoronary doses of phenylephrine and B-HT933 were studied immediately before the intracoronary infusion of prazosin or idazoxan. The dogs then underwent the exercise protocol. After exercise the coronary response to intracoronary phenylephrine and B-HT933 was repeated after coronary flow had returned to baseline. The results confirmed the previous finding that these doses of prazosin and idazoxan blocked the coronary response to intracoronary phenylephrine and B-HT933, respectively.

Immediately upon completion of the intracoronary infusion of the α-adrenergic receptor antagonist, treadmill exercise was begun. When stable exercising hemodynamics were present, an acute coronary stenosis was again produced and the occluder adjusted to maintain coronary pressure equal to the coronary pressure during the first exercise. After 1–2 minutes of exercise in the presence of the coronary stenosis and with stable hemodynamics, a second injection of microspheres was made into the left atrium for measurement of myocardial blood flow. Upon completion of reference blood withdrawal, the stenosis was released and exercise was discontinued. A 150-minute rest period was then allowed to permit the effects of the selective α-adrenergic blockade to subside. The α-adrenergic receptor antagonistic effects of the doses of intracoronary idazoxan and prazosin used were lost within less then 2 hours. An intracoronary infusion of the selective α-adrenergic receptor antagonist the animal had not yet received (either prazosin or idazoxan) was then begun. After completion of this infusion the exercise protocol was carried out as described above in the presence of a coronary stenosis sufficient to match coronary perfusion pressure distal to the stenosis with the previous exercise periods.

Data were also collected from four control dogs in which myocardial blood flow was measured with microspheres during two separate exercise periods in the presence of a coronary stenosis that maintained coronary perfusion pressure equal during both runs, but without α-adrenergic blockade.

Upon completion of all studies, the animals were sacrificed with a lethal dose of pentobarbital and the hearts removed and fixed in 10% buffered formalin. After fixation the left ventricle was cut into four rings from base to apex, and each ring was divided into seven regions circumferentially. Each region was then divided into four transmural layers of equal thickness from epicardium to endocardium, weighed on an analytical balance, and placed in counting vials. Myocardial and reference blood sample radioactivity and myocardial blood flow were then determined as described above. Non-ischemic (anterior) region flows were determined as the mean of anterior left ventricular region samples for at least two myocardial rings. Ischemic region myocardial flows were determined as the mean of the posterior region from at least two rings of the left ventricle.

Statistical comparisons were made by use of Student's t test for paired data; p values were adjusted with the Bonferroni correction for multiple simultaneous comparisons. Significance was defined as p<0.05. All values are reported as mean±SEM.

Results

Results of the preliminary study in four dogs without adrenergic blockade are shown in Table 1. Subepicardial, subendocardial, and mean myocard-
Hemodynamic data are presented in Table 2. Compared with exercise in the absence of a coronary stenosis, heart rate, mean aortic pressure, left ventricular systolic pressure, and left ventricular dP/dt were unchanged, while left ventricular end-diastolic pressure was higher during exercise in the presence of a coronary stenosis. Circumflex coronary perfusion pressure was lower during coronary stenosis. During exercise in the presence of a coronary stenosis with α₁- or α₂-adrenergic receptor blockade, these variables were not different from control exercise with coronary stenosis, although left ventricular end-diastolic pressure tended to be slightly lower during exercise plus stenosis in the presence of α₂-adrenergic receptor blockade with prazosin. Coronary perfusion pressure in the presence of a stenosis was not different from control with either α₁-adrenergic receptor blockade (control 41.6±0.9 vs. idazoxan 41.6±1.3).

Myocardial Blood Flow

Myocardial blood flows measured with microspheres are shown in Table 3. Nonischemic region (anterior wall) myocardial flows were unchanged during selective α₁-adrenergic receptor blockade of the posterior wall with both prazosin and idazoxan as compared with control. In comparison with the anterior wall, during control exercise blood flow in the posterior wall was significantly decreased in all layers, and the subendocardial to subepicardial flow ratio was reversed. α₁-Adrenergic receptor blockade with prazosin resulted in increases of posterior region myocardial blood flow in all transmural layers; this increase was statistically significant for the inner three layers and for mean myocardial flow (Table 3 and Figure 1). The subendocardial/subepicardial flow ratio was also modestly increased after prazosin, but this increase was only of borderline significance (p=0.07). While the relative increase in flow was greater to the inner layers, the absolute increase in blood flow was similar to all layers (Table 3).

In contrast with α₁-adrenoceptor blockade, α₂-adrenergic blockade with idazoxan caused no significant change in myocardial blood flow to any layer of the myocardium during exercise in the presence of a coronary stenosis compared with exercise plus stenosis alone in that group (Table 3 and Figure 2).

### Table 1. Myocardial Blood Flow in Four Dogs During Separate Exercise Periods Without α-Adrenergic Receptor Blockade

<table>
<thead>
<tr>
<th>Group 1 (n=8)</th>
<th>Myocardial blood flow (ml/min/g)</th>
<th>END/O/EP</th>
<th>Group 2 (n=8)</th>
<th>Myocardial blood flow (ml/min/g)</th>
<th>END/O/EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>EX</td>
<td>209±6</td>
<td>107±4</td>
<td>EX+ST</td>
<td>215±6</td>
<td>105±4</td>
</tr>
<tr>
<td>EX+ST+Pr</td>
<td>214±7</td>
<td>100±4</td>
<td>EX</td>
<td>206±3</td>
<td>102±5</td>
</tr>
<tr>
<td>EX+ST+Id</td>
<td>205±4</td>
<td>100±5</td>
<td>EX+ST</td>
<td>211±5</td>
<td>101±5</td>
</tr>
<tr>
<td>EX+ST+Id</td>
<td>205±4</td>
<td>100±5</td>
<td>EX+ST+Pr</td>
<td>214±7</td>
<td>100±4</td>
</tr>
<tr>
<td>EX+ST+Id</td>
<td>205±4</td>
<td>100±5</td>
<td>EX+ST+Id</td>
<td>211±5</td>
<td>101±5</td>
</tr>
</tbody>
</table>

AOP, aortic pressure; CPP, coronary perfusion pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; LV+dP/dt, first derivative of left ventricular systolic pressure rise; EX, exercise; ST, coronary stenosis; Pr, prazosin; Id, idazoxan.

* †p < 0.05 compared with exercise without stenosis.
Myocardial blood flow was slightly higher in group 1 (prazosin) than group 2 (idazoxan) in both the anterior and posterior regions during control exercise with a stenosis as well as during selective α-adrenergic receptor blockade plus stenosis. This difference was due mainly to the presence of four nonoverlapping animals (two in each group) and was not statistically significant.

Regional Myocardial Function

Posterior (ischemic) left ventricular region myocardial segment shortening was determined in a subgroup of animals in each group. Results are shown in Figure 3. Hemodynamic and blood flow results were not different in these subgroups than in the groups as a whole. Posterior regional segment shortening during control exercise was 17.7±2.2% in group 1 (n=4) and 18.3±2.7% (n=5) in group 2. Segment shortening decreased significantly during exercise in the presence of coronary artery stenosis in both groups. Selective α₂-adrenergic blockade with prazosin tended to blunt the decrease in systolic segment shortening that occurred during exercise in the presence of a coronary stenosis, although this difference was only of borderline statistical significance (p=0.06); systolic shortening was still significantly less than shortening during exercise without coronary stenosis.

Selective α₂-adrenergic receptor blockade with idazoxan did not alter posterior region segment shortening during exercise in the presence of coronary stenosis, so that shortening remained significantly decreased compared with exercise without a coronary stenosis.

Discussion

The most important findings of this study are that adrenergic coronary vasomotor tone is present in regions of hypoperfused myocardium during exercise in the presence of a coronary stenosis, and that this vasoconstriction is mediated principally via α₂-adrenergic mechanisms. Coronary resistance vessels undergo vasoconstriction in response to both postsynaptic α₁-receptors and α₂-receptors.

![Figure 1](http://circres.ahajournals.org/)

**FIGURE 1.** Posterior (ischemic) region myocardial blood flow measured with radionuclide-labeled microspheres in eight dogs during exercise with an acute coronary stenosis (control) and during exercise plus selective α₂-adrenergic receptor blockade with prazosin in presence of a coronary stenosis. Flow to four layers of myocardium from subepicardium (EPI) to subendocardium (ENDO), as well as mean flow and ratio of subendocardial to subepicardial layer flow (ENDO/EPI) are shown. Values are mean±SEM. *p<0.05.
adrenergic mechanisms in a number of species, including dogs and humans.7 The relative importance of $\alpha_1$- versus $\alpha_2$-receptors in mediation of adrenergic vasoconstriction is unclear, however, and may depend on the experimental model and specific stimulus for sympathetic activation. Thus, coronary vasoconstriction in response to electrical stimulation of cardiac sympathetic nerves in open-chest dogs has been reported to be mediated mainly through $\alpha_2$-receptor mechanisms both in the absence and in the presence of myocardial ischemia.10,16,17

In chronically instrumented awake dogs, however, $\alpha_1$- and $\alpha_2$-receptors participate approximately equally in the coronary vasoconstrictor response to intravenous7 and intracoronary12 administration of norepinephrine. Gwirtz et al11 reported that in chronically instrumented dogs undergoing treadmill exercise, $\alpha_2$-receptor blockade with intracoronary bolus administration of prazosin increased coronary blood flow and myocardial oxygen consumption by 20–25%. Blockade of both $\alpha_1$- and $\alpha_2$-receptors by intracoronary infusion of the nonselective $\alpha$-adrenergic antagonist phentolamine did not produce greater coronary vasodilation than prazosin, suggesting that in this setting $\alpha_1$-, but not $\alpha_2$-, receptors mediate coronary vasoconstriction. Dai et al15 studied the effect of selective $\alpha$-receptor blockade in the chronically instrumented exercising dog using intracoronary infusions of prazosin and idazoxan alone and in combination. Selective $\alpha_2$-receptor blockade with prazosin significantly increased coronary blood flow by 30% and decreased coronary resistance by 30% compared with control exercise. In contrast, selective $\alpha_1$-receptor blockade with idazoxan did not change coronary blood flow or coronary vascular resistance, and the addition of idazoxan to prazosin did not increase coronary blood flow or decrease coronary vascular resistance beyond that seen with prazosin alone. An important consideration in both of these studies is that intracoronary dosing of $\alpha$-receptor blockers prevented systemic or central effects of $\alpha$-blockade that might have confounded the results. The above studies indicate important differences in adrenergic mechanisms depending on the experimental model. In open-chest animals exposed to intense adrenergic stimulation, coronary vasoconstriction is mediated principally by postjunctional $\alpha_2$-mechanisms. In contrast, in intact animals in the setting of a physiological stimulus (i.e., exercise) that results in modest generalized sympathetic activation, $\alpha_1$-receptors predominate in mediation of adrenergic coronary vasoconstriction.

The present study demonstrates that even during exercise in the presence of myocardial hypoperfusion, which would be expected to result in ischemia, residual coronary vasoconstrictor tone is present that is mediated primarily through $\alpha_1$-adrenergic receptor mechanisms. Alternative explanations for the observed myocardial blood flow increase seen after intracoronary prazosin infusion include changes in loading conditions or direct myocardial effects of prazosin. In this study, after prazosin infusion the left ventricular end-diastolic pressures tended to be lower during exercise with a stenosis, though this result was not statistically significant. The decrease occurred in five of the eight dogs. The decrease in left ventricular end-diastolic pressure could have been due to changes in loading conditions as a result of the systemic effects of prazosin, or to a lesser degree of ischemia secondary to improved myocardial blood flow. If the former were true, then the improved gradient between coronary perfusion pressure and ventricular filling pressure might have contributed to the improved myocardial blood flow.
However, neither arterial nor left ventricular systolic pressure was significantly changed by intracoronary prazosin in the dose used. Additionally, anterior region flows were unchanged after prazosin administration into the circumflex coronary artery. These observations argue against a significant systemic effect of the prazosin that would alter loading conditions and, thus, affect ventricular end-diastolic pressure. Additionally, no direct effect of intracoronary prazosin on left ventricular filling pressures, systolic pressure, or contractile function, independent of enhanced myocardial perfusion, was observed in this study or other studies.4,8 Thus, direct augmentation of myocardial performance as the result of prazosin causing increased oxygen consumption with subsequent further metabolic vasodilation, rather than a direct vasodilator effect through \( \alpha \)-receptor blockade, is unlikely.

Several recent studies have supported the concept of "paradoxical" coronary vasoconstriction during myocardial hypoperfusion and ischemia in both anesthetized open- chest and chronically instrumented awake canine models.1-5 The implication of such residual coronary vasoconstrictor tone has been investigated by Nathan and Feigl,9 who used a constant coronary blood flow preparation in an open-chest dog model. Transmural distribution of blood flow during hypoperfusion that resulted in ischemia was measured in myocardial regions with and without nonselective \( \alpha \)-adrenergic receptor blockade produced by intracoronary infusion of phenoxybenzamine. They found greater subendocardial flow in the \( \alpha \)-receptor–intact region than in the \( \alpha \)-receptor–blocked region. On the basis of this finding, they postulated that residual \( \alpha \)-receptor–mediated vasoconstriction acts to lessen the degree of subepicardial "steal" that occurs during intense coronary vasodilation. Huang and Feigl19 studied dogs with unimpeded coronary flow undergoing treadmill exercise during regional nonselective \( \alpha \)-receptor blockade produced by intracoronary phenoxybenzamine infusion. While mean transmural flow was less in the \( \alpha \)-receptor–intact region, at high levels of exercise the absolute inner myocardial blood flow and the ratio of inner layer flow to outer layer flow was greater in the \( \alpha \)-receptor–intact than in the \( \alpha \)-receptor–blocked region. They concluded that \( \alpha \)-receptor–mediated vasoconstriction helps to maintain more uniform transmural blood flow distribution despite limiting total myocardial flow.

Chilian and Ackell20 measured myocardial blood flow distal to a flow-limiting stenosis during exercise in myocardial regions with and without sympathetic denervation produced by epicardial application of phenol. While subepicardial flow was greater in the denervated than in the innervated stenotic region, subendocardial blood flow (and the ratio of inner layer flow to outer layer flow) was greater in the innervated than in the sympathectomized stenotic region during both control conditions and after \( \beta \)-adrenergic blockade with intravenous propranolol. The addition of \( \alpha \)-adrenergic blockade with intravenous phentolamine abolished these differences. However, it appeared to do so by increasing subendocardial layer flow in the sympathectomized region, raising the issue of enhanced \( \alpha \)-receptor–mediated vasoconstriction in the denervated region (i.e., supersensitivity following denervation). They concluded that \( \alpha \)-adrenergic vasomotor tone distal to a flow-limiting stenosis results in redistribution of blood flow toward the subendocardium due to preferential \( \alpha \)-adrenergic coronary constriction in the outer layers of the ventricular wall. These previous studies suggest that \( \alpha \)-adrenergic vasoconstriction may act to enhance subendocardial perfusion, possibly by limiting blood flow to the subepicardium. This mechanism could be of functional importance, since myocardial contractile function has been found to be closely related to subendocardial myocardial blood flow but not to subepicardial blood flow.21 In the present study, \( \alpha \)-receptor blockade resulted in a significant increase inner layer flow, while the increase in subepicardial layer flow was not significant. However, mean myocardial flow did increase, and there was a trend toward increased subepicardial layer flow during \( \alpha \)-adrenergic receptor blockade. Thus, the present data do not resolve the issue of an "anti-steal" effect of \( \alpha \)-adrenergic–mediated vasoconstrictor tone in the setting of hypoperfusion.

The results of the present study contrast with the previous report of Seitelberger et al.6 who found that \( \alpha \)-adrenergic blockade increased myocardial blood flow distal to a coronary stenosis during exercise. They studied chronically instrumented dogs during treadmill exercise after nonselective \( \beta \)-blockade and in the presence of an acute coronary stenosis sufficiently severe to reduce regional systolic wall thickening by 75%. They determined myocardial blood flow before and after intracoronary infusion of an average of 80 \( \mu \)g/kg of the selective \( \alpha \)-receptor blocker idazoxan. After idazoxan infusion subendocardial and mean transmural flow increased significantly with no change in subepicardial flow. Ischemic region systolic wall thickening also increased significantly after idazoxan. From these results, they concluded that postjunctional \( \alpha \)-adrenergic coronary vasoconstriction limited myocardial blood flow during ischemia and further impaired contractile function. They suggested that the distribution of \( \alpha \)-receptors varies across the left ventricular wall, with greatest receptor density in the subendocardium. These results are at variance both with the present study and with several previously mentioned studies examining the role of \( \alpha_1 \) and \( \alpha_2 \)-receptor–mediated coronary vasoconstriction.

Several substantive differences exist between the study of Seitelberger et al.6 and the present study, which make direct comparisons of these differing results difficult. The degree of coronary hypoperfu-
sion and ischemia was substantially greater in the study of Seitelberger et al than in the present study or the studies of Liang and Jones and Nathan and Feigl. Subendocardial flow before selective \( \alpha \)-adrenergic blockade was considerably lower in Seitelberger's study \((0.17 \pm 0.05 \text{ ml/min/g})\) than in the current study \((0.60 \pm 0.14 \text{ ml/min/g})\), and regional myocardial contractile function was reduced to 25\% of baseline as compared with 50–60\% of baseline function in the present study. It is possible that the different degree of myocardial ischemia might result in a different level of sympathetic stimulation between the studies. The intensity of exercise was less in the study of Seitelberger et al than in the present study. Another difference between these two studies was the use of systemic \( \beta \)-adrenergic blockade by Seitelberger et al; \( \beta \)-blockade was not used in the current study. \( \alpha_2 \)-Adrenergic receptors that inhibit nerve terminal norepinephrine release are present at presynaptic sites, so that presynaptic \( \alpha_2 \)-blockade may result in augmented norepinephrine release due to the loss of feedback inhibition. Thus, \( \alpha_2 \)-blockade could result in increased norepinephrine release, and the increased local \( \beta \)-receptor stimulation could magnify local metabolic vasodilation. Therefore, \( \beta \)-blockade might have had an "unmasking" effect on \( \alpha_2 \)-adrenergic–mediated vasoconstriction in their study. The study of Gwirtz et al and studies in our laboratory have failed, however, to find evidence for an important effect of the unmasking of \( \alpha_2 \)-adrenergic–mediated coronary vasoconstriction by \( \beta \)-adrenergic blockade in the exercising dog.

Another important difference between the report of Seitelberger et al and the present study is that coronary perfusion pressure was maintained constant through the current study. By maintaining coronary perfusion pressure equal between conditions, we were able to ensure that differences in flow rates were due to a change in vascular resistance and to obviate differences in collateral inflow into the stenotic bed due to the differences in driving pressure for collateral flow. In the study of Seitelberger et al, coronary perfusion pressure was not measured; the degree of stenosis was set according to its initial effect on contractile function and was not further adjusted. In such an experimental model coronary perfusion pressure distal to the stenosis may rise and fall in parallel with changes in aortic pressure, in part because of compliance of the hydraulic occluder. In their preliminary studies Seitelberger et al reported that idazoxan increased aortic pressure. In our laboratory doses of idazoxan in excess of 10 \( \mu \text{g/kg/min} \) intracoronary have caused an increase in aortic pressure. Such an increase in aortic pressure could have increased coronary perfusion pressure distal to the occluder. In addition, with the severe stenosis used in their study, small changes in the stenosis-distending pressure could have substantially altered blood flow through the stenosis; without monitoring distal coronary pressure, it is difficult to maintain a fixed degree of stenosis throughout the study period, and it cannot be clearly ascertained whether a change in flow is due to a change in resistance at the level of the coronary microvasculature or at the level of the arterial stenosis. Furthermore, blood flow distal to a "fixed" coronary stenosis has been shown to decrease in response to vasodilation of the distal coronary vasculature due to passive collapse of the stenosis consequent to the decrease in distending pressure accompanying vasodilatation distal to the stenosis.

While current evidence suggests that adrenergic vasoconstriction in large coronary arteries is predominantly mediated by \( \alpha_1 \)-receptors, it is possible that the dose of idazoxan employed by Seitelberger et al, which was substantially larger than the dose used in the current study, may have had some vasodilating effect at the level of the stenosis. Finally, idazoxan is only a relatively selective \( \alpha_2 \)-receptor blocker, and even at a dose of 10 \( \mu \text{g/kg} \) it exhibits weak \( \alpha_1 \)-adrenergic receptor–blocking activity. Therefore, the dose of 80 \( \mu \text{g/kg} \) of idazoxan used in the study of Seitelberger et al may have produced some degree of \( \alpha_1 \)-receptor blockade, which could have contributed to the observed increase in coronary flow.

There are several potential limitations to the present study. The possible role of presynaptic \( \alpha_2 \)-blockade resulting in augmented norepinephrine release and the possibility of unmasking \( \alpha_2 \)-adrenergic–mediated coronary vasoconstriction by \( \beta \)-adrenergic blockade in the exercising dog. Failure to find increased myocardial blood flow in response to idazoxan could have resulted from incomplete \( \alpha_2 \)-adrenoceptor blockade. A small increase in flow was seen after idazoxan infusion, though this was not statistically significant. It is possible that this increase would have been greater if a larger dose of idazoxan had been used. However, the dose of intracoronary idazoxan employed in this study has been shown to abolish the vasoconstrictor response to intracoronary bolus injections of the selective \( \alpha_2 \)-receptor agonist B-HT933 at doses of 0.1, 1.0, and 10.0 \( \mu \text{g/kg} \). In addition, effective blockade of the response to intracoronary B-HT933 was confirmed in a subgroup of the animals used in this study. At the highest dose of B-HT933 a systemic pressor response to intracoronary agonist administration can be seen at a time when no coronary vasoconstriction occurs. There-
fore, it is unlikely that α₂-receptor blockade was inadequate.

A final consideration is whether the degree of stenosis used was sufficient to cause ischemic coronary vasodilation. While myocardial segment shortening was measured in only subsets of animals in this study, systolic dysfunction was observed. Additionally, a previous study with a similar protocol demonstrated that at similar levels of coronary perfusion pressure and myocardial blood flow, regional segment shortening measured with implanted ultrasonic microcrystals was reduced to 50% of normal. These findings indicate that the degree of hypoperfusion in this study was sufficient to produce ischemic dysfunction.

A previous study in this laboratory examined the effect of an intracoronary infusion of a supramaximally vasodilating dose of adenosine on myocardial blood flow during ischemia caused by exercise in the presence of a coronary stenosis. As in the current study, coronary perfusion pressure was held equal before and during adenosine infusion at approximately the same level as in the current study. The results of this previous study demonstrated a very similar level of absolute myocardial blood flow to the ischemic region and a very similar degree of increase in flow during adenosine-induced vasodilation, as was seen during α₁-receptor blockade in the present study. These results suggest that essentially all of the coronary vasoconstrictor tone present in the ischemic bed during exercise is mediated by α₁-adrenergic receptor mechanisms. This conclusion presumes that adenosine did indeed result in maximal coronary vasodilation in the setting of ischemia, as it is known to do under nonischemic conditions.

In summary, this study demonstrated that coronary vasoconstrictor tone exists distal to a flow-limiting arterial stenosis, even during exercise that results in ischemic myocardial systolic dysfunction. Blood flow to the region of hypoperfused myocardium was enhanced by selective α₁-adrenergic receptor blockade with prazosin but not by selective α₂-adrenergic receptor blockade with idazoxan. These findings indicate that α₁-adrenergic receptor-mediated coronary vasodilatation may worsen myocardial hyperperfusion at the reduced perfusion pressures that exist distal to a coronary stenosis during exercise.

Acknowledgments

The authors gratefully acknowledge the valuable technical assistance of Eugene Sublett, Paul Lindstrom, Melanie Crampton, and Todd Pavek; and Pfizer (prazosin), Reckitt and Colman (idazoxan), and Boehringer-Ingelheim (B-HT933) pharmaceutical companies for providing drugs.

References


KEY WORDS • α-adrenergic receptors • coronary circulation • prazosin • myocardial ischemia • idazoxan
The role of alpha 1- and alpha 2-adrenergic receptors in mediation of coronary vasoconstriction in hypoperfused ischemic myocardium during exercise.

D D Laxson, X Z Dai, D C Homans and R J Bache

Circ Res. 1989;65:1688-1697
doi: 10.1161/01.RES.65.6.1688

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/65/6/1688

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/