Effect of $\alpha$-Adrenergic Blockade With Prazosin on Large Coronary Diameter During Exercise

Kenneth W. Baran, MD; Robert J. Bache, MD; Xue-Zheng Dai, MD; and Jeffrey S. Schwartz, MD

Background. Exercise-induced dilation of coronary resistance vessels is limited by $\alpha$-adrenergic mechanisms. However, the effect of $\alpha$-adrenergic mechanisms on large coronary arteries during exercise is not known.

Methods and Results. In the present study, sonomicrometry was used to measure circumflex coronary arterial diameter during treadmill exercise before and after $\alpha_1$-adrenergic blockade with prazosin in eight instrumented dogs. Before infusion of prazosin, exercise caused a fall in coronary vascular resistance (2.1±0.4 to 1.6±0.2 units, $p<0.05$) and dilation of the circumflex coronary artery (4.66±0.37 to 4.79±0.34 mm, $p<0.05$). Intracoronary infusion of prazosin during exercise caused a further decrease in coronary vascular resistance (1.6±0.2 to 1.4±0.2 units, $p<0.05$) and a further increase in circumflex coronary arterial diameter (4.79±0.34 to 4.83±0.34 mm, $p<0.05$). Intracoronary infusion of vehicle without prazosin during exercise did not cause a further decrease in coronary vascular resistance or increase in coronary diameter. Prazosin caused no significant increase in heart rate, aortic pressure, or coronary blood flow. Therefore, both small coronary resistance vessels and large epicardial coronary arteries dilated during exercise and dilated further after $\alpha$-adrenergic blockade.

Conclusions. This finding indicates that $\alpha_1$-adrenergic activity during exercise limits dilation of both large and small coronary arteries. *(Circulation 1992;85:1139–1145)*

Key Words • coronary vasomotion • exercise • prazosin

Previous studies have demonstrated that $\alpha$-adrenergic tone limits the normal increase in coronary artery blood flow that accompanies exercise.1,2 Gwirtz et al1 demonstrated that bolus administration of prazosin, a selective $\alpha_1$-adrenergic receptor blocker, directly into the canine coronary artery during treadmill exercise caused an increase in coronary blood flow. Similarly, Dai et al2 found that during graded treadmill exercise in dogs, coronary blood flow was higher and coronary resistance was lower after $\alpha_1$-adrenergic blockade produced by intracoronary infusion of prazosin. These results indicate that $\alpha_1$-adrenergic vasoconstrictor tone limits vasodilation of the coronary resistance vessels during exercise.

Because different segments of the coronary vascular tree may exhibit differing responses to physiological stimuli, it is uncertain whether $\alpha$-adrenergic tone would also modify the response of large coronary arteries during exercise. The present study was designed to determine whether epicardial coronary artery vasoconstrictor tone during exercise is modulated by $\alpha$-adrenergic influences. Specifically, the study protocol tested whether local, selective $\alpha_1$-adrenergic blockade with prazosin augments exercise-induced dilation of epicardial coronary arteries.

Methods

Surgical Preparation

Eight adult mongrel dogs of either sex were trained to run on a motor-driven treadmill. Before surgery, the dogs were sedated with morphine sulfate (0.5 mg/kg i.m.) and anesthetized with sodium pentobarbital (30 mg/kg i.v.). No muscle relaxants were used.

Respiration was maintained through a cuffed endotracheal tube with a Harvard respirator. A thoracotomy was performed in the fourth left intercostal space. The heart was suspended in a pericardial cradle. Polyvinyl chloride catheters (3.0-mm o.d.) filled with heparin-saline solution were placed into the ascending aorta via the internal mammary artery, into the left ventricle via the apical dimple, and into the left atrium via the left atrial appendage. Catheters were secured in place with purse-string sutures. The left circumflex coronary artery was dissected free, and a Silastic heparin-filled catheter (0.3-mm o.d.) was implanted into the proximal segment of the artery.3 Miniature 5-MHz piezoelectric ceramic crystals affixed to Silastic/Dacron patches were positioned on opposite sides of the artery. A length of 6-0 rapid-absorbing plain gut suture was passed beneath the coronary artery and then through the Silastic/Dacron patches, which were then positioned on opposite sides of the artery. Before the suture was secured, nitroglycerin (200 μg) was infused intravenously to ensure that the sutures did not constrict the artery during maximal vasodilation. The suture was then secured snugly.
around the artery (Figure 1). A Doppler flowmeter probe was positioned around the artery at least 1 cm distal to the ultrasonic crystals, and a hydraulic occluder was positioned distal to the flowmeter probe (Figure 2). The pericardium was closed loosely, and the catheter tubing, flowmeter, and crystal wires were tunneled subcutaneously to exit the skin dorsally. The thoracotomy was repaired, and the dogs were allowed to recover from the effects of surgery. The catheters were protected by a nylon vest that the dog had been trained to wear and were flushed daily to ensure patency.

Experimental Measurements

Studies were performed 1–3 weeks after surgery in the unsedated state. Aortic pressure was measured with a Gould P23ID pressure transducer at midchest level. Coronary blood flow velocity was measured with a Doppler flowmeter (Craig Hartley, Houston, Tex.). Instantaneous coronary artery diameter was measured with a sonomicrometer (Sonomicrometer 120, Triton Technology, San Diego, Calif.) calibrated in 0.2-mm steps. The calibration was checked frequently during the course of each experiment. The resolution of the sonomicrometry system is at least ±0.04 mm. Data were recorded on a Model 8800 Hewlett-Packard eight-channel, direct-writing oscillograph.

Coronary artery reactivity, expressed as percent increase above the resting baseline diameter, was determined for each dog by intravenous or intracoronary injection of nitroglycerin (10–200 μg). A minimum 2% dilation in response to nitroglycerin was required for inclusion in the study. The mean increase in coronary artery diameter in response to a maximally vasodilating dose of nitroglycerin for the eight dogs in the study was 7.0±1.5%. Coronary flow reserve, expressed as percent increase of blood flow above baseline during the reactive hyperemia after release of a 15–20-second complete arterial occlusion, was determined for each dog. A minimum 300% flow reserve (3:1 peak hyperemia to baseline flow) was required to be included in the study. The mean flow reserve for the eight dogs in the study was 380±20%.

At least 1 day before the exercise study, intracoronary phenylephrine (1–2 μg/kg) was given to assess the adrenergic vasoconstrictor response of the proximal epicardial artery. An intracoronary bolus of prazosin (25 μg/kg) was then given, followed by another dose of phenylephrine. This was done to demonstrate that this dosage and route of administration of prazosin produced selective α1-adrenergic blockade of the proximal epicardial coronary artery.

Protocol

Studies were performed with the dogs standing on a motor-driven treadmill. The experimental protocol consisted of two separate sequential exercise trials. In stage 1, the treadmill speed was 4.8 km/hr, and the incline was 0%. In stage 2, the speed was increased to 6.4 km/hr, and the incline was increased to 5%. For stage 3, the incline was increased to 10%, but the speed was maintained at 6.4 km/hr. The first two stages were each 3 minutes long, whereas stage 3 was 6 minutes long. Midway through stage 3, when hemodynamic variables had achieved a steady state, an intracoronary infusion was given. During the control run, 1 ml of vehicle (deionized water) was infused via the intracoronary catheter over 15–20 seconds. The dog continued to exercise for at least 3 minutes after infusion. Dogs were allowed to rest for 1 hour after the control run. The exercise protocol was then repeated, but midway through stage 3, prazosin (25 μg/kg) was infused via the intracoronary catheter in an equal volume of vehicle, and exercise continued for 3 minutes after prazosin administration. After completion of the second exercise protocol, a bolus of intracoronary phenylephrine was given to assess the adequacy of α1-adrenergic blockade.

Data Analysis

Heart rate, aortic pressure, mean and phasic coronary blood flow velocities, and mean and phasic coronary artery diameters were measured directly from the strip chart recordings. Mean coronary vascular resistance was computed as mean aortic pressure divided by mean coronary blood flow. All data shown are mean±SEM values. Significant differences were determined by Student’s t test for paired observations. Probability values were adjusted by the Bonferroni method to correct for performing multiple tests on correlated data.4

Only seven of the eight dogs were used to calculate the data before and after infusion of vehicle because of technical difficulties during the vehicle run in one dog.

Results

The intracoronary phenylephrine bolus did not cause a significant change in mean arterial pressure or coronary blood flow either before or after prazosin. Before administration of prazosin, coronary artery diameter decreased 2.0±0.7% (p<0.05). After prazosin, the
second exercise trial, the mean decrease in diameter was 0.3±0.3% (*p=NS).

Table 1 summarizes the effects of exercise before the infusions on aortic pressure, heart rate, coronary blood flow, coronary diameter, and coronary vascular resistance. As expected, aortic pressure, heart rate, and coronary blood flow increased significantly with exercise. Coronary arterial diameter also increased significantly in response to exercise. The mean percent increase in diameter in response to exercise was 2.6% before vehicle and 2.8% before prazosin. This confirms that the response of the coronary artery to this level of exercise was nearly identical in the two sequential runs. As expected, coronary vascular resistance decreased significantly in response to exercise.

Table 2 shows the effects of intracoronary infusion of vehicle and prazosin during exercise. After intracoronary infusion of vehicle, none of the parameters changed significantly. After intracoronary infusion of prazosin, a trend toward a decrease in aortic pressure and increase in heart rate was seen. Neither of these changes reached statistical significance. A trend toward an increase in coronary blood flow was also seen but was not statistically significant.

After intracoronary prazosin, coronary vascular resistance decreased significantly, indicating dilation of coronary resistance vessels. In addition, intracoronary prazosin caused significant dilation of the epicardial coronary artery. A tracing from one dog is shown in Figure 3.

In Figures 4–8, individual data points are shown for aortic pressure, heart rate, coronary blood flow, coronary vascular resistance, and coronary arterial diameter. The first point on each graph represents the difference between the control measurement and the exercise preinfusion measurement. The second point represents the difference between the control measurement and the exercise postinfusion measurement. Mean values are indicated by the dashed line in each graph. For example, in Figure 8, coronary arterial diameter increased by a mean of 0.13±0.3 mm from control to exercise before infusion. After infusion of prazosin, the difference from control increased to 0.17±0.04 mm (*p<0.025). Therefore, intracoronary prazosin caused a significant increase in coronary arterial diameter.

The data have therefore been analyzed in two ways. In Tables 1 and 2, the absolute measurements are compared. In Figures 4–8, the changes from control before and after the intracoronary infusions are compared. The analysis of significance of differences by the two methods is in agreement in all cases except one. In response to intracoronary prazosin, aortic pressure fell from 113±5 to 107±6 mm Hg (Table 2), which was not significant. As shown in Figure 4, however, the mean change in aortic pressure from control to exercise before prazosin was 16.3 mm Hg, whereas the difference between the control measurement and the exercise postprazosin measurement was 10.5 mm Hg (*p<0.05). Therefore, from this point of view, aortic pressure fell significantly after intracoronary prazosin.

**Discussion**

The most important finding of this study was that intracoronary infusion of an α1-adrenergic blocking agent during exercise caused further dilation of the coronary artery. This suggests that α-adrenergic activity limits exercise-induced vasodilation of the epicardial coronary artery.

This finding parallels the response of small coronary vessels (arterioles) to exercise after α-blockade, where it has been shown that α-adrenergic-mediated vascular tone opposes exercise-induced vasodilation. Gwirtz et al3 and Dai et al2 demonstrated that administration of prazosin directly into a coronary artery during exercise increased blood flow and decreased calculated coronary vascular resistance. Presumably, this resulted from a

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**Table 1. Effect of Exercise on Hemodynamics and Coronary Diameter**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle run</th>
<th>Prazosin run</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rest</td>
<td>Exercise before infusion</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>98±4</td>
<td>115±4*</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>115±10</td>
<td>192±5*</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>45±7</td>
<td>79±11*</td>
</tr>
<tr>
<td>Coronary vascular resistance (units)</td>
<td>2.5±0.4</td>
<td>1.7±0.3*</td>
</tr>
<tr>
<td>Coronary diameter (mm)</td>
<td>4.64±0.43</td>
<td>4.76±0.4*</td>
</tr>
</tbody>
</table>

*p<0.05 vs. rest in the same run.

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**Table 2. Effect of Vehicle and Prazosin on Hemodynamics and Coronary Diameter During Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle run</th>
<th>Prazosin run</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exercise before infusion</td>
<td>Exercise after infusion</td>
</tr>
<tr>
<td>Aortic pressure (mm Hg)</td>
<td>115±4</td>
<td>115±4</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>192±5</td>
<td>189±7</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min)</td>
<td>79±11</td>
<td>81±10</td>
</tr>
<tr>
<td>Coronary vascular resistance (units)</td>
<td>1.7±0.3</td>
<td>1.6±0.3</td>
</tr>
<tr>
<td>Coronary diameter (mm)</td>
<td>4.76±0.4</td>
<td>4.78±0.39</td>
</tr>
</tbody>
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*p<0.05 vs. exercise before infusion of prazosin.
blockade of \( \alpha_1 \)-adrenergic receptors, causing relaxation of vascular smooth muscle at the arteriolar level.

In the present study, intracoronary prazosin during exercise caused a significant decrease in coronary vascular resistance, which is consistent with previous studies. Coronary blood flow did not increase significantly in response to intracoronary prazosin, possibly because of the decrease in aortic pressure after prazosin.

The neurohumoral regulation of small resistance vessels of the canine coronary circulation has been studied extensively,\(^5\,\text{6}\) whereas study of the neurohumoral regulation of large conductance vessels has been limited by the lack of a suitable method of continuous in vivo measurement of large coronary artery tone. In 1980, Vatner et al\(^7\) introduced the ultrasonic technique for continuous measurement of epicardial coronary artery caliber. This technique has been used in numerous studies in the past decade that have

**Figure 3.** Tracings show effect of intracoronary prazosin on circumflex coronary diameter, aortic pressure, and blood flow during exercise. After intracoronary prazosin, coronary diameter increased.
improved our understanding of factors regulating large artery tone.

The model used in this study has several distinct advantages over previous experimental models. The intracoronary catheter allows direct infusion of relatively low doses of vasoactive substances, which minimizes confounding systemic effects. Placing this catheter proximal to the ultrasonic dimension crystals facilitates direct interaction between the proximal vessel wall and the study drug at the site where coronary caliper is measured. Because a flow probe or hydraulic occluder can produce a stenosis, which may cause a pressure drop across the area of narrowing, placing the ultrasonic crystals proximal to these instruments ensures that the measured aortic pressure is the same as the distending pressure where coronary caliper is measured. A major limitation of the ultrasonic technique is the potential for causing damage to the vessel wall at the time of surgical implantation of the piezoelectric crystals. In previously described techniques, the proximal circumflex artery is dissected free and the ultrasonic crystals are sutured directly to the adventitia with nonabsorbable suture. This is technically difficult in the beating heart. If the full thickness of the vessel wall is penetrated by the suture needle, a hematoma usually results, and subsequent vasomotion in the segment may be impaired. Perivascular fibrosis from the surgical dissection may also reduce vascular dilation.

We have developed a technique that uses minimal dissection of the proximal coronary artery without suturing the crystals directly to the artery (Figure 1). This method has yielded excellent ultrasonic crystal signals with good vascular reactivity. Epicardial artery dilation in response to nitroglycerin was seen within 4–6 days of surgery. Several dogs in this series had coronary artery diameter increases from 12% to 17% above baseline after intravenous nitroglycerin infusions, which is comparable to the magnitude of coronary artery dilation observed in humans after nitroglycerin administration. This technique may help reduce concern that normal epicardial artery vasomotion is impaired in studies that use ultrasonic crystal measurement techniques.

Gerova et al demonstrated that electrical stimulation of the stellate ganglion caused constriction of epicardial coronary arteries in an open-chest canine model. Histological studies confirm that large epicardial coronary arteries are innervated with sympathetic adrenergic nerve fibers. It is likely, therefore, that sympathetic nervous system outflow may contribute to tone of the vascular smooth muscle of epicardial arteries.

Circulating catecholamines have been shown to contribute to the vasoconstrictor tone of coronary resistance vessels during exercise. In a similar way, circulating catecholamines may contribute to the tone of vascular smooth muscle in large epicardial coronary arteries. Therefore, a-adrenergic vasoconstrictor tone during exercise could result from direct sympathetic nerve outflow, circulating catecholamines, or both sources.

Previous studies have shown that large epicardial coronary arteries contain both $\alpha_1$- and $\alpha_2$-adrenergic receptors. In the present study, an $\alpha_1$-adrenergic blocking agent was infused into the coronary artery during exercise and resulted in dilatation. This finding indicates that $\alpha_1$-receptors are involved in vasoconstriction of large coronary arteries during exercise. We cannot comment on the role of $\alpha_2$-adrenergic receptors during exercise because no $\alpha_2$-adrenergic blocking agents were studied.
Previous data from our laboratory\(^2\) indicated that intracoronary administration of an \(\alpha\)-adrenergic blocking agent dilated coronary resistance vessels during exercise. The results of the present study showed that intracoronary infusion of the \(\alpha\)-adrenergic blocking agent prazosin caused a decrease in coronary vascular resistance during exercise. Total coronary blood flow did not increase, probably because of the fall in aortic pressure. The results of the present study, therefore, are consistent with previous data concerning the effect of \(\alpha\)-adrenergic blockade on coronary resistance vessels during exercise. We cannot comment on the role of \(\alpha_2\)-adrenergic receptors on resistance vessels during exercise because we did not study \(\alpha_2\)-adrenergic blockade.

Causes of epicardial coronary arterial dilation after prazosin other than direct \(\alpha\)-adrenergic blockade should be considered. Guth et al\(^3\) found that infusion of prazosin into the left atrium during exercise caused an increase in wall thickening, heart rate, and left ventricular contractility. These effects were postulated to result from augmented norepinephrine release caused by prazosin. In the present study, prazosin was administered directly into the coronary artery. It is possible that increased regional release of norepinephrine could have occurred in response to intracoronary prazosin. Norepinephrine is a constrictor of large coronary arteries\(^1\) and therefore could not have directly contributed to the dilation that was observed in response to prazosin.

Norepinephrine could, however, have indirectly contributed to dilation of the large coronary arteries. It could have increased myocardial oxygen demands, causing an increase in coronary blood flow, which would augment release of endothelium-derived relaxing factor,\(^15\) causing dilation of the artery. However, coronary blood flow did not increase significantly after prazosin (Table 2, Figure 5), which makes this mechanism unlikely.

Although coronary blood flow did not increase significantly after the intracoronary infusion of prazosin, a trend toward increased flow was observed. It is possible that this trend contributed to flow-mediated dilation because of release of endothelium-derived relaxing factor. In three of the eight dogs, however, coronary blood flow did not increase at all after intracoronary prazosin (76±16 to 76±16 ml/min). As mentioned above, the lack of increase in flow may have been a result of the fall in aortic pressure that occurred in these dogs (109±6 to 99±6 mm Hg). However, although flow did not change in these three dogs, coronary arterial diameter increased in each dog. The mean diameter in the three dogs increased from 4.76±0.41 to 4.80±0.4 mm. Therefore, flow-mediated dilation caused by augmented release of endothelium-derived relaxing factor could not have contributed to the coronary dilation seen in these three dogs and cannot be the complete explanation for the dilation seen in the total group of dogs.

Aortic pressure fell after administration of prazosin (Figure 4), which could have induced a baroreflex. The reflex response to a fall in aortic pressure would have been increased sympathetic outflow. The direct effect of increased sympathetic outflow would have been constriction of the large coronary artery, which is the opposite of the effect that was seen. An indirect effect could have been increased myocardial metabolic demand, which would have increased coronary blood flow, causing release of endothelium-derived relaxing factor and resulting in dilation of the artery. Because no increase in coronary blood flow was seen, it is unlikely that this latter mechanism played a role in the observed large artery dilation after prazosin.

The present study demonstrates that normal dilation of large epicardial coronary arteries in response to exercise is opposed by \(\alpha\)-adrenergic receptor-mediated mechanisms. The magnitude of this opposition appears to be relatively small compared with the predominant vasodilation of the large artery during exercise. It is possible, however, that when normal vasodilator mechanisms are impaired, this effect may play a more significant role. For example, Furchgott\(^16\) demonstrated that acetylcholine causes constriction of isolated bovine coronary segments when the endothelium is removed, but it causes vasodilation when the endothelium is intact. In humans with mild to moderate coronary stenoses, intracoronary infusion of acetylcholine causes constriction of the diseased coronary segments.\(^17\) Presumably, the presence of coronary atherosclerosis impairs endothelial cell function, precluding normal endothelium-dependent vasodilation at the stenosis. Thus, the increase in \(\alpha\)-mediated vasoconstrictor tone during exercise may be capable of causing constriction of a diseased arterial segment when endothelium-dependent, flow-induced vasodilator mechanisms are impaired. Active narrowing of a stenosis by this mechanism could contribute significantly to reduced coronary blood flow and subsequent myocardial ischemia. This mechanism could at least partly explain the results of Gage et al,\(^18\) who performed serial coronary angiograms in humans at rest and during supine bicycle exercise. These investigators observed narrowing of stenotic segments of human coronary arteries during exercise but simultaneous dilation of normal coronary segments. Pretreatment with nitroglycerin prevented the exercise-induced narrowing of the stenotic segments, implying that exercise-induced narrowing was caused by an active, vasoconstricting process rather than passive collapse of the stenotic segment.

**Clinical Implications**

Coronary artery vasomotion may have a significant role in the pathogenesis of ischemic myocardial syndromes, including rest and exercise-induced angina, unstable angina, and myocardial infarction. The development of coronary atherosclerosis, aside from the potential to cause obstruction to coronary blood flow, may upset a balance between endogenous vasoconstrictor and vasodilator mechanisms. Whether the mechanism is a result of disruption of normal endothelial cell function is not known. More studies are needed to determine whether \(\alpha\)-adrenergic mechanisms play a significant role in the development of myocardial ischemia in humans and whether pharmacological intervention can ameliorate any clinically deleterious effects.

**References**

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