**α-Adrenoceptor Attenuation of the Coronary Vascular Response to Severe Exercise in the Conscious Dog**

**PAUL A. MURRAY AND STEPHEN F. VATNER**

**SUMMARY** The hypothesis that α-adrenergic vasoconstriction could limit the extent of coronary vasodilation during spontaneous strenuous exercise was tested in normal mongrel dogs instrumented for the measurement of left circumflex coronary blood flow, aortic pressure, and left ventricular pressure. These signals were radiotelemetered at rest and during free-ranging exercise with dogs either in the unblocked condition, or after β-receptor blockade (propranolol, 1 mg/kg), α-receptor blockade (phentolamine, 1-2 mg/kg), or combined β- and α-receptor blockades. Heart rate was held constant by electrical stimulation throughout the exercise period. After α-receptor blockade alone, late diastolic coronary resistance decreased during exercise to a significantly lower (P < 0.01) level (0.36 ± 0.06 mm Hg/ml per min) than in the unblocked condition (0.52 ± 0.04 mm Hg/ml per min). In the presence of β-adrenergic blockade, exercise induced insignificant increases in mean left circumflex coronary blood flow and decreases in late diastolic coronary resistance. In contrast, after pretreatment causing combined α and β blockade, both the increase (P < 0.05) in mean left circumflex coronary blood flow (22 ± 4 ml/min) and the decrease (P < 0.01) in late diastolic coronary resistance (0.35 ± 0.07 mm Hg/ml per min) during exercise were significantly greater. This enhanced coronary vascular dilation during exercise following α-receptor blockade could not be attributed to increased metabolically induced vasodilation secondary to changes in aortic pressure, heart rate, left ventricular systolic pressure, or left ventricular dP/dt. These observations strongly support the hypothesis that α receptors in the coronary circulation can act to attenuate alterations in coronary vascular resistance, even during periods of high sympathetic discharge, as occurs during severe exercise. *Circ Res* 45: 884–890, 1979

**BECAUSE** of the striking ability of the heart to match an increase in metabolic demand with an increase in nutrient supply, it has been presumed that control of the coronary circulation is primarily an intrinsic phenomenon involving the release of vasoactive metabolites from myocardial cells (Berne, 1964). In recent years, however, work by a number of investigators supports the concept that the coronary circulation is also under direct neural control. For instance, it has become increasingly apparent that sympathetic activation can result in α-adrenergic-mediated coronary vasoconstriction, which in turn can compete with metabolic vasodilator influences, and thus modulate alterations in coronary vascular resistance (Mohrman and Feigl, 1978).

Although the existence of sympathetic coronary vasoconstrictor activity appears to be well documented, the physiological importance of such a mechanism remains unresolved. Previous work in our laboratory (Vatner et al., 1970a) indicates that the coronary dilation observed with carotid sinus nerve stimulation at rest, and even during moderate exercise, is due to a reflex reduction in resting sympathetic constrictor tone. Moreover, results from recent clinical studies suggest that α-adrenergic constriction may be responsible for the generation of spontaneous coronary vasospasm and associated anginal pain (Hillis and Braunwald, 1978).

The objective of this present study, therefore, was to determine whether sympathetic adrenergic vasoconstriction might also exert a controlling influence on the coronary circulation by attenuating decreases in coronary vascular resistance associated with periods of sympathetic discharge, such as occurs during spontaneous strenuous exercise.

**Methods**

**Surgical Preparation**

Nine mongrel dogs, ranging in weight from 25 to 34 kg, were anesthetized with sodium pentobarbital (30 mg/kg, iv), intubated, and artificially ventilated. A left thoracotomy was performed through the 5th intercostal space using sterile surgical technique. A solid state pressure transducer (P22: Konigsberg Instruments) was inserted in the descending thoracic aorta through a 1-cm longitudinal incision and secured with three to five sutures (4-0 silk, Ethicon Co.). The pericardium was incised, and the circum-
flex branch of the left main coronary artery was dissected carefully and isolated for placement of a Doppler ultrasonic flow transducer and hydraulic occluder. In eight of the dogs, a second solid state pressure gauge was inserted into the left ventricular (LV) cavity via a stab wound in the apex. Pacing electrodes were sutured to the surface of the left atrium and right ventricle. Heparin-filled Tygon catheters (Norton Co.) were placed in the left atrium and in the thoracic aorta just distal to the aortic pressure gauge. Connections to the instrumentation were exteriorized between the scapulae, and the dogs were placed on a 1-week regimen of antibiotics.

**Measurements**

Left circumflex coronary blood flow was measured by the Doppler ultrasonic flow technique (Franklin et al., 1966). The rate of blood flow was calculated as the product of vessel cross-sectional area at autopsy and blood flow velocity. The accuracy and reliability of this method of measuring regional blood flow has been described previously in detail (Vatner et al., 1970b). Aortic and LV pressures were measured and telemetered from the implanted gauges (Baig et al., 1977). These gauges were calibrated both in vitro and in vivo using the implanted aortic and left atrial catheters attached to a Statham P23Db strain gauge manometer (Statham Instruments), which in turn was calibrated against a mercury manometer.

**Experimental Protocol**

A period of at least 3 weeks was allowed for full recovery from the effects of anesthesia and surgery. During the exercise periods, instrumentation necessary for the continuous transmission of aortic pressure, LV pressure, and left circumflex coronary blood flow signals by radiotelemetry (described below) was carried by each dog in a backpack. The exercise regimen consisted of each dog running freely behind a mobile recording van over a hilly half-mile course in the absence of any pharmacological blocking agent (unblocked condition), or 3-5 minutes after the intravenous administration of a β-receptor blocker (propranolol-HCl, 1 mg/kg; Ayerst Laboratories, Inc.), an α-receptor blocker (phenolamine-HCl, 1-2 mg/kg; Ciba Pharmaceuticals), or after combined β and α blockades. Heart rate was held constant during exercise by battery-powered electrical pacing (Medtronics Corp.). The entire exercise protocol for each dog usually was completed over a 1-week period, with a maximum of two exercise periods per day. Three- to 5-hour rest intervals were allowed between exercise periods on a given day. The order of the exercise regimen was randomized in an effort to avoid the potentially confounding influences of dog training or altered sensitivity to the adrenergic antagonists that may accompany multiple exercise periods. Moreover, duplicate exercise runs were performed in selected dogs to assess the consistency of the responses of the measured variables during exercise.

**System for Telemetry of Data**

Continuous measurements of left circumflex coronary blood flow, heart rate, aortic pressure, and LV pressure were radiotelemetered while the dogs were standing quietly at rest or running freely in the field behind a mobile recording van. Speeds of 25-35 miles/hour (mph) were achieved routinely by these dogs in the absence of any blocking agent. Whereas running speeds generally were slower in the presence of the adrenergic antagonists (10-20 mph), in all cases, the severity of the exercise period (as reflected by the time required to traverse the exercise course) after blockade of α-receptor activity was either less than or equal to the level of exercise with α-receptor activity intact. Descriptions of the instrumentation and techniques used to transmit continuously the left circumflex coronary blood flow (Franklin et al., 1966; Vatner et al., 1970b), aortic pressure, and LV pressure (Vatner et al., 1971; Patrick et al., 1974; Baig et al., 1977) signals by radiotelemetry have been reported previously in detail. Briefly, the signals from the aortic and LV pressure implant systems were transmitted from the dogs to the remote recording unit via an FM/FM sub-carrier telemetry system. The Doppler ultrasonic flowmeter signal was frequency modulated on the carrier frequency and did not require an additional subcarrier. The mobile recording unit consisted of a van carrying FM communication receivers, subcarrier discriminators, signal processing electronics, and a multichannel tape recorder (Honeywell model 5600-C). A commercial whip antenna mounted on the roof of the van received the signals transmitted from the dog. Power for the equipment was obtained from two DC-to-AC inverters (Heathkit model MP-14 and Wilmore model 1057-12). Each of these units was powered by one 12-V battery. The FM tuners (Heathkit model AJ-15) were modified to disable the FM deemphasis network and multiplex circuitry thus providing video response sufficient to recover the modulated subcarrier signals. The output of the FM tuners was applied directly to the input of the two subcarrier frequency discriminators (Airpax model FDS-30). These discriminators converted the frequency modulation signals to DC voltages proportional to the signals measured in the dog. These DC voltages then were applied to FM channels of the instrumentation tape recorder. During the experiment, commentary was recorded on a voice channel of the tape recorder.

**Data Analysis**

The experimental data were played back from magnetic tape on a multichannel, direct-writing oscillograph. A continuous record of LV dP/dt was...
Figure 1. Characteristic responses of the measured variables to a period of severe, free-ranging exercise over a hilly course 0.5 miles in length in the absence of any pharmacological blocking agent. Maximum speed of 30 miles/hour was attained by this dog during the course of the exercise period. Heart rate was held constant at approximately 300 beats/min by electrical pacing.

Values derived from the pressure signal with an LV 301 operational amplifier (National Semiconductor) connected as a differentiator. In addition, the effects of exercise on the quotient of dP/dt and developed pressure, P (where P equals LV isovolumic minus end-diastolic pressure), were examined. Mean aortic pressure and mean left circumflex coronary blood flow were derived using passive electronic filters with a 2-second time constant. Late diastolic coronary resistance was calculated as the quotient of late diastolic aortic pressure and late diastolic coronary blood flow. A cardiotachometer (Beckman type 985), triggered by the electrical signal from the aortic pressure pulse, provided instantaneous and continuous records of heart rate.

The measured variables were evaluated for data analysis over a period of at least 15-30 seconds while the dog was standing quietly just prior to exercise, and at three separate points during the exercise run, corresponding to two-tenths, three-tenths, and four-tenths of a mile of the exercise course, and 10 and 20 minutes after the exercise period. All changes in the measured variables during exercise occurred spontaneously. Duplicate exercise runs performed in selected dogs were averaged before inclusion in the final data pool, so that all dogs were weighted equally. The sample sizes (n) presented in the figures and tables represent the number of dogs from which a single respective value for each of the measured variables was obtained. Changes in the measured variables during exercise and differences in the measured variables, (1) between the unblocked and a-blocked protocols, and (2) between the β-blocked and combined a- and β-blocked protocols, were analyzed by the method of two-way analysis of variance and the method of least significant differences (Armitage, 1974). Values presented represent mean ± 1 SEM. The values of the measured variables during exercise presented in the tables represent the steady state values of those variables at four-tenths of a mile of the exercise course.

Table 1: Preexercise and Steady State Exercise Levels of Variables in the Absence of Blocker and after α Blockade

<table>
<thead>
<tr>
<th>Variable</th>
<th>No block</th>
<th>Exercise</th>
<th>α block</th>
<th>Exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>141 ± 10</td>
<td>199 ± 8*</td>
<td>107 ± 7†</td>
<td>124 ± 9‡</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>4.4 ± 0.9</td>
<td>18.1 ± 2.5*</td>
<td>4.8 ± 0.8</td>
<td>9.0 ± 2.6§</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3653 ± 482</td>
<td>11495 ± 981*</td>
<td>3004 ± 770</td>
<td>7154 ± 1366†</td>
</tr>
<tr>
<td>LV dP/dt/P (sec⁻¹)</td>
<td>41.9 ± 2.7</td>
<td>121.7 ± 19.4*</td>
<td>49.4 ± 7.6</td>
<td>87.7 ± 18.4†</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>126 ± 5</td>
<td>144 ± 8*</td>
<td>86 ± 3‡</td>
<td>96 ± 5‡</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>304 ± 2</td>
<td>304 ± 2</td>
<td>303 ± 2</td>
<td>303 ± 2</td>
</tr>
<tr>
<td>Mean left circumflex blood flow (ml/min)</td>
<td>89 ± 9</td>
<td>143 ± 10*</td>
<td>119 ± 13§</td>
<td>150 ± 12†</td>
</tr>
<tr>
<td>Late diastolic coronary resistance (mm Hg/ml per min)</td>
<td>0.81 ± 0.11</td>
<td>0.52 ± 0.04*</td>
<td>0.57 ± 0.10‡</td>
<td>0.36 ± 0.06*‡</td>
</tr>
</tbody>
</table>

n = number of dogs.
* Exercise significantly different from control, P < 0.01.
† Exercise significantly different from control, P < 0.05.
‡ Control or exercise after α block significantly different from no block, P < 0.01.
§ Control or exercise after α block significantly different from no block, P < 0.05.
Results

Spontaneous Exercise (No Block)

Typical responses of the measured variables to free-ranging exercise in the field in the absence of any pharmacological blocker and with heart rate held constant at approximately 300 beats/min are illustrated in Figure 1 and summarized in Table 1. Exercise was associated with average steady state increases (P < 0.01) in LV systolic pressure, LV end-diastolic pressure, LV dP/dt, LV dP/dt/P, mean aortic pressure, and mean left circumflex coronary blood flow, and a decrease (P < 0.01), in late diastolic coronary resistance (0.52 ± 0.04 mm Hg/ml per min from a preexercise level of 0.81 ± 0.11).

α-Receptor Blockade during Exercise

Preexercise and steady state exercise levels of the measured variables after pretreatment with the α blocker are summarized in Table 1. Administration of the α blocker resulted in preexercise decreases (P < 0.01) in LV systolic and mean aortic pressures, as well as late diastolic coronary resistance and an increase (P < 0.05) in mean left circumflex coronary blood flow, as compared to the unblocked condition. Whereas LV dP/dt (P < 0.01), LV dP/dt/P (P < 0.05), mean aortic pressure (P < 0.05), and mean left circumflex coronary blood flow (P < 0.05) all increased significantly during exercise with α-receptor activity blocked, the levels of LV systolic pressure (P < 0.01), LV end-diastolic pressure (P < 0.05), LV dP/dt (P < 0.01), and mean aortic pressure (P < 0.01) achieved during exercise were all significantly lower than with α-receptor activity intact. Moreover, the level to which late diastolic coronary resistance decreased during steady state exercise, 0.36 ± 0.06 mm Hg/ml per min, was significantly lower (P < 0.01) following blockade of α-receptor activity, and, as shown in Figure 2, this lower level of late diastolic coronary resistance, as compared to the unblocked condition, was sustained over the entire duration of the exercise period.

Combined α- and β-Receptor Blockades during Exercise

To delineate more clearly the direct effects of an α-adrenergic activity on the coronary vascular response to exercise, the positive inotropic effects of exercise were blunted by pretreating the dogs with propranolol. As summarized in Table 2, the admin-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Exercise</th>
<th>Change (Δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>150 ± 8</td>
<td>10 ± 8</td>
<td>5.5 ± 1.0</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>4.9 ± 0.6</td>
<td>13.7 ± 2.9</td>
<td>13.5 ± 2.6</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>2918 ± 216</td>
<td>900 ± 265</td>
<td>2357 ± 195</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>46.3 ± 3.2</td>
<td>28.8 ± 8.5</td>
<td>30.6 ± 6.5</td>
</tr>
<tr>
<td>Mean left circumflex blood flow (ml/min)</td>
<td>136 ± 5</td>
<td>-10 ± 4</td>
<td>-8 ± 3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>198 ± 4</td>
<td>0 ± 0</td>
<td>199 ± 2</td>
</tr>
<tr>
<td>Mean left circumflex blood flow (ml/min)</td>
<td>74 ± 4</td>
<td>5 ± 5</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>Late diastolic coronary resistance (mm Hg/ml per min)</td>
<td>1.04 ± 0.09</td>
<td>-0.02 ± 0.03</td>
<td>-0.35 ± 0.07</td>
</tr>
</tbody>
</table>

n = number of dogs.

† Change (Δ) with exercise significantly different from control, P < 0.01.
‡ Change (Δ) with exercise significantly different from control, P < 0.05.
§ Control or change (Δ) with exercise after α and β block significantly different from β block alone, P < 0.01.

$Control or change (Δ) with exercise after α and β block significantly different from β block alone, P < 0.05.
The coronary vasculature is innervated by autonomic nerves (Gregg and Fisher, 1963). In addition, although a previous report (Zuberbuhler and Bohr, 1965) demonstrated that isolated vascular smooth muscle strips from large (1.5–2.4 mm in diameter) coronary vessels demonstrated more frequent a-adrenergic-mediated contractions than did small (0.25–0.50 mm) coronary arteries, a more recent study (Kelly and Feigl, 1978) indicates that a-receptor stimulation can modulate coronary vascular resistance throughout the coronary bed. a-receptor-mediated alterations in coronary vascular resistance, induced either directly by intravenous (Vatner et al., 1974) or intracoronary (Mohrman and Feigl, 1978) norepinephrine infusions and stellate ganglion stimulation (Nayler et al., 1973) or reflexly by carotid sinus nerve stimulation (Vatner et al., 1970a; Hackett et al., 1972) and bilateral carotid occlusion (Feigl, 1968; DiSalvo et al., 1971; Mohrman and Feigl, 1978), have been reported. Moreover, the sympathetic nervous system appears to exert a tonic constrictor influence on the coronary circulation, since stellate ganglion ablation results in an augmented coronary reactive hyperemic response, as well as improved endocardial perfusion (Schwartz and Stone, 1977). Sympathetic a-receptor-induced coronary vasoconstriction unmasked by β-receptor blockade also has been shown to be capable of competing with local metabolic control by decreasing coronary sinus oxygen tension (Feigl, 1975).

In the clinical setting, patients with coronary artery disease have been shown to respond to cutaneous cold with an a-adrenergic-mediated reflex increase in coronary vascular resistance (Mudge et al., 1976), even in the presence of a superimposed increase in myocardial oxygen consumption induced by rapid atrial pacing (Mudge et al., 1979). Furthermore, several recent studies imply a causal role for a-adrenergic vasoconstriction in the genesis of spontaneous coronary vasospasm (Yasue et al., 1974; Yasue et al., 1976; Levene and Freeman, 1976). The primary objective of the present study was to determine in a conscious animal model, where the mitigating direct and indirect effects of anesthesia on myocardial performance and the coronary circulation (Vatner and Braunwald, 1975) are avoided, whether a-receptor-mediated alterations in coronary vascular resistance could be demonstrated during periods of sympathetic discharge associated with strenuous free-ranging exercise. The major finding of this study is that a-adrenergic coronary vasoconstriction can limit the extent of hyperemia in the coronary circulation of the conscious dog during spontaneous exercise. Observations that support this conclusion are (1) coronary vascular resistance decreased to a significantly lower level during exercise following blockade of a-receptor activity (Table 1 and Fig. 2), and (2) increases in coronary blood flow and decreases in coronary vascular resistance associated with exercise in propranolol-pretreated dogs were significantly greater after blockade of a-receptor activity (Table 2 and Fig. 3).

Alternative explanations for these results can be discussed in the context of those factors that are primary determinants of coronary blood flow, i.e., coronary perfusion pressure, myocardial systolic ex-
travascular compression, myocardial oxygen consumption, and direct neurohumoral control of the coronary circulation.

The enhanced coronary vascular response during exercise following inhibition of $\alpha$-receptor activity is not due to an elevated coronary perfusion pressure. The administration of the $\alpha$ blocker alone, or in combination with propranolol, resulted in a significant diminution in preexercise levels of mean aortic pressure. Moreover, during exercise, mean aortic pressure was significantly lower after blockade of $\alpha$-receptor activity, compared to either the unblocked or the $\beta$-blocked protocols, respectively (Tables 1 and 2). It is also unlikely that the more pronounced decreases in coronary vascular resistance during exercise following $\alpha$-receptor blockade could be the result of a decrease in extravascular compression of intramural coronary vessels during systole (Sabiston and Gregg, 1957), since coronary vascular resistance was calculated from pressure and flow measurements late in diastole, when the effects of systolic compression are minimal.

The enhanced coronary vascular response to exercise after $\alpha$-receptor blockade probably is not due to greater levels of local metabolic vasodilators secondary to an increased myocardial oxygen consumption in this condition. Direct measurements of myocardial oxygen consumption were not possible with this type of severe, free-ranging exercise in the field. However, three primary determinants of myocardial oxygen consumption, i.e., heart rate, myocardial contractility, and aortic pressure, were monitored continuously throughout the exercise periods. Although heart rate was held constant under all conditions, changes in aortic pressure during exercise were similar, whether $\alpha$-receptor activity was intact or blocked, and changes in LV $dP/dt$ and LV $dP/dt/P$ during exercise were either significantly less ($\alpha$ block alone) or not different ($\alpha$ block following propranolol pretreatment) than changes in these variables with $\alpha$-receptor activity intact (Tables 1 and 2). It should be noted that differential changes in LV end-diastolic pressure also could be responsible for the enhanced coronary vascular response during exercise. However, after propranolol pretreatment, the levels of LV end-diastolic pressure achieved during exercise were virtually identical with $\alpha$-receptor activity intact or blocked. These results strongly suggest that metabolic vasodilation secondary to changes in these variables cannot be responsible for the observed vascular responses.

Activation of parasympathetic cholinergic nerve fibers has been demonstrated to result in direct coronary vasodilation (Feigl, 1969). However, it is unlikely that this factor is responsible for the enhanced coronary vascular response during exercise after blockade of $\alpha$-receptor activity, since exercise is associated with a withdrawal of parasympathetic nervous system activity. Activation of vascular $\beta$ receptors also results in coronary vasodilation (Klocke et al., 1965; McRaven et al., 1971; Mark et al., 1972; Hamilton and Feigl, 1976). However, this mechanism is not responsible for the enhanced coronary dilation during exercise following $\alpha$-receptor blockade, since this occurred in propranolol-pretreated dogs in which $\beta_2$ as well as $\beta_1$ receptors were blocked.

When amounts of norepinephrine released from adrenergic nerve terminals during neural activation reach threshold levels, further release of the neurotransmitter is inhibited by a negative feedback mechanism involving binding of the neurotransmitter to presynaptic $\alpha$ receptors (Langer, 1974). The $\alpha$-receptor antagonist, phentolamine, blocks both presynaptic and postsynaptic $\alpha$ receptors and, thus, prevents this feedback inhibition of norepinephrine release (Starke, 1972). Presumably then, under the conditions of these experiments, norepinephrine release would be enhanced during spontaneous exercise after pretreatment with phentolamine. However, it is unlikely that the greater coronary vascular dilation during exercise following $\alpha$-receptor blockade can be attributed to increased $\beta$-adrenergic receptor activation subsequent to the increased release of norepinephrine, since (1) the enhanced coronary vascular response was observed following combined $\alpha$ and $\beta$-receptor blockade (Table 2), and (2) $\beta$-receptor activation actually appeared to be diminished during exercise after $\alpha$-receptor blockade alone, as reflected by significantly smaller increases in left ventricular systolic pressure and left ventricular $dP/dt$, as compared to the unblocked condition (Table 1).

The fact that coronary $\alpha$-receptor vasoconstrictor influence can compete with metabolic vasodilation during sympathetic activation has been demonstrated most conclusively by Mohrman and Feigl (1978). In studies on anesthetized, closed-chest dogs, these investigators estimate that $\alpha$-receptor vasoconstriction restricts metabolically related flow increases associated with intracoronary norepinephrine infusions or carotid sinus hypotension by approximately 30%. It is interesting to note the similarity of their results with the results of this study, since we observed approximately a 27% greater increase in coronary blood flow and a 32% greater decrease in late diastolic coronary resistance during exercise following blockade of $\alpha$-receptor activity in propranolol-pretreated dogs (Fig. 3).

In conclusion, the results of the present investigation indicate that $\alpha$-adrenergic activation can exert a controlling influence on the coronary circulation, even during periods of high sympathetic discharge, by attenuating the reductions in coronary vascular resistance associated with spontaneous strenuous exercise.

Acknowledgments

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