A previous study from this laboratory (Feigl, 1968) and investigations by DiSalvo et al. (1971) and Limet et al. (1975) demonstrated a reflex coronary vasoconstriction in response to carotid sinus hypotension. Kirchheim (1976) has questioned the interpretation of the results obtained in the previous study by Feigl (1968), pointing out that they might be explained by coronary autoregulation (relatively constant flow despite changing perfusion pressure). In the previous study, both calculated diastolic coronary vascular resistance and aortic pressure increased during the carotid sinus reflex in animals treated with propranolol. The increased coronary resistance was abolished by cardiac sympathectomy, but the reflex rise in aortic pressure was reduced as well. Thus, the difference in the
coronary vascular response caused by the carotid sinus reflex before and after sympathectomy might have been due to autoregulation.

The purpose of the present study was to determine the magnitude of the coronary vasoconstriction caused by the carotid sinus reflex in a closed-chest preparation in which reflex changes in aortic pressure and cardiac oxygen metabolism were carefully matched before and after interruption of the reflex arc with the intracoronary administration of an α-adrenergic receptor blocking agent. The results indicate that sympathetic α-receptor coronary vasoconstriction is a part of the carotid sinus reflex, independent of coronary autoregulation or myocardial oxygen metabolism.

Methods

Animal Preparation

Male mongrel dogs (25–29 kg) were sedated with morphine sulfate (2.5 mg/kg, sc) and anesthetized 1 hour later with α-chloralose (50 mg/kg, iv, initially and 10 mg/kg per hour thereafter). The dogs were intubated and ventilated with a positive-pressure respiration pump (Harvard model 607). End-expiratory carbon dioxide was measured continuously by an infrared absorption analyzer (Beckman LB-2) and maintained between 4% and 5% throughout the experiment. Rectal temperature was maintained at 39°C by means of a heating pad. The right femoral vein was cannulated, and continuous sodium bicarbonate infusion was begun (5 ml/kg per hour of a 1.5% solution) to offset the acidosis accompanying chloralose anesthesia (Arfors et al., 1971). Blood pressure was measured with a strain gauge manometer (Statham P23Dd) via a polyethylene cannula advanced from the femoral artery to the ascending aorta. Both common carotid arteries were isolated, and blood from the proximal left carotid artery was supplied by a silastic Y tube to both the distal right and left carotid arteries. A side tube was used for the measurement of carotid sinus pressure. All dogs received propranolol hydrochloride, 1 mg/kg, iv, initially and 0.2 mg/kg per hour thereafter. They also were given atropine sulfate, 0.25 mg/kg, iv, prior to a midcervical bilateral vagotomy.

Measurement of Coronary Blood Flow

Total left coronary blood flow was measured by means of a cannula-tip transducer composed of a stainless steel tube with an inflatable balloon at the tip (Smith et al., 1974). The transducer was inserted into the right carotid artery with the balloon empty, advanced into the ascending aorta, and then the balloon was filled with water. The transducer then was positioned so that the tip wedged securely in the left coronary ostium with the balloon forming a seal (Fig. 1). At this time, blood flow through the probe was stopped for 10 seconds by means of the occluder. Coronary blood pressure was measured via the injection tube. In every experiment, coronary diastolic blood pressure was less than 25 mm Hg during occlusion, thereby verifying the integrity of the seal between the cannula tip and left coronary ostium. Blood entered the flowmeter from the aorta and flowed past a pair of piezoelectric crystals before entering the left coronary artery. Flow was measured by the ultrasound Doppler-shift technique. The injection tube was used for intracoronary artery administration of drugs. To verify the seal between the cannula tip and left coronary ostium, coronary blood flow was interrupted briefly and coronary blood pressure was measured via the injection tube.

Measurement of Myocardial Oxygen Consumption

An 8F Sones catheter was advanced from the right jugular vein into the coronary sinus under fluoroscopic observation. The position of the cannula tip was determined postmortem and ranged from 37 to 52 mm from the coronary sinus ostium among the seven dogs studied. Coronary sinus blood was withdrawn at a constant rate of 12 ml/min by means of a roller pump (Cole-Parmer model 4420).
The blood passed from the Sones catheter through the cuvette of a spectrophotometric oximeter (Waters model 0-600), through the pumping head, and through an oxygen electrode (Feigl and D’Alecy, 1971) for determination of blood oxygen tension. It was then returned to the dog via the jugular or femoral vein. A valve permitted sampling of either coronary sinus or arterial blood. Arterial oxygen tension was maintained between 125 and 150 mm Hg by supplementation of the inspired air with oxygen by means of a variable-demand valve. This level of oxygen tension ensured full saturation of the arterial blood (Dittmer, 1961). The oximeter was calibrated by drawing arterial and coronary sinus blood samples at frequent intervals throughout the experiment. Blood samples were collected anaerobically in glass syringes, and oxygen content was determined by the fuel-cell method (Lex-O-Con, Lexington Instruments) (Kusumi et al., 1973), and hemoglobin content was determined spectrophotometrically by the cyanmethemoglobin method (Ellman, 1967). The hemoglobin concentration (g/dl) multiplied by 1.34 ml O₂/g Hb was the calculated oxygen-carrying capacity of a given blood sample (Hufner, 1894).

**Arterial Pressure Control**

The most logical way to prevent changes in coronary artery resistance due to coronary autoregulation would be to keep arterial pressure constant during the carotid sinus reflex. This was done in pilot experiments, and a decrease in coronary blood flow was observed. However, so much blood had to be sequestered in an arterial reservoir to keep mean aortic pressure constant during the carotid sinus reflex that myocardial oxygen consumption decreased. Presumably, the mechanism was a diminution of the cardiac preload to the point that stroke work fell and cardiac oxygen consumption decreased. The fall in myocardial oxygen consumption resulted in a metabolically mediated coronary vasodilatation, which would be difficult to distinguish from the hypothesized neurogenic vasoconstriction to be studied. Accordingly, an increment in blood pressure was sought in pilot experiments such that the decrease in myocardial oxygen consumption due to diminished preload would be balanced by the augmented oxygen metabolism due to increased afterload. A reflex rise of 15 mm Hg in mean aortic pressure was found to result in small changes in myocardial oxygen consumption during the carotid sinus reflex.

Increases in arterial pressure were limited by a pressurized reservoir, connected to the dog by a large-bore polyethylene cannula inserted in the femoral artery. A pressurized air source maintained the pressure within the reservoir 15 mm Hg higher than the resting mean arterial pressure of the animal. When arterial pressure increased 15 mm Hg during an experimental maneuver, blood entered the reservoir and arterial pressure was controlled. The blood was contained in a plastic bag designed to eliminate a blood-to-air interface and exclude air from the arterial system. At the termination of an experimental maneuver, blood was returned to the dog.

**Experimental Protocol**

Carotid hypotension was achieved by clamping the base of the Y tube that supplied blood to both carotid sinuses and adjusting the mean pressure within the sinuses to 40 mm Hg with a screw clamp on a shunt between the carotid arteries and jugular vein. The reflex increase in aortic blood pressure that accompanied this maneuver was limited to 15 mm Hg by means of the pressure reservoir. Data points were obtained after the measured variables reached steady state. The duration of carotid sinus hypotension was approximately 1.5 to 3 minutes in the various experiments. Norepinephrine was infused into the coronary artery through a tube in the transducer in two doses (10 and 20 µg/min) in each experiment.

Alpha-adrenergic receptor blockade was achieved by slow (30-minute) intracoronary artery infusion of dibozane (1 mg/kg). Then 5 ml/kg of a 6% dextran solution (mol wt = 40,000) was given intravenously to elevate the arterial pressure, which had been reduced by dibozane. After α-receptor blockade, carotid hypotension and norepinephrine infusions were repeated.

At the termination of each experiment, a saturated solution of crystal violet dye in 3 N ammonium hydroxide was injected through the transducer into the left coronary artery. The dye produced an intense staining of the myocardium perfused by the left coronary artery. The average weight of the myocardium perfused by the left coronary artery was 168 ± 18 (SEM) g, which was 82 ± 2% (SEM) of the total heart weight.

**Experimental Criteria**

The following criteria were established for acceptance of an experiment in this study. First, without arterial pressure stabilization the increase in mean aortic pressure during the carotid sinus reflex must have been at least 65 mm Hg before α-adrenergic receptor blockade. Second, the reflex increase in aortic pressure was limited to 15 ± 3 mm Hg during the carotid sinus reflex before and after α-adrenergic receptor blockade. Additionally, in any given dog, the reflex rise in aortic pressure during the stabilization after the administration of dibozane had to be within 3 mm Hg of the reflex rise that occurred before α-receptor blockade. Third, the change in myocardial oxygen metabolism during the carotid sinus reflex before α-receptor blockade must have been within 10% of the value immediately before the reflex was elicited. Seven of 12 experiments met these criteria. The most com-
mon reason for the rejection of an experiment was inadequate aortic pressure control during the carotid sinus reflex.

Data Analysis

Data points were obtained immediately before and during an experimental maneuver when measured variables were not changing. Heart rate was obtained from the aortic pressure pulses by means of a tachometer. Diastolic coronary resistances were calculated to minimize the effects of systolic compression on the calculated coronary resistance (Denison, et al., 1956). Aortic pressure and coronary blood flow were measured in diastole for the calculation of resistance for 10 consecutive heart beats. The average of these 10 values was used as a single data point for diastolic resistance. Statistical comparisons before and during the carotid sinus reflex were made before and after α-receptor blockade, using two-tailed paired t-tests [degrees of freedom (d.f.) = n − 1, for n animals]. Since the t-test assumes a normal distribution, the results also were evaluated by means of the Wilcoxon signed rank test for paired data and a paired t-test on the log of the differences. These tests gave results very similar to the simple paired t-test; thus the probability values for the paired t-test are given in the text, tables, and figures. By use of these methods, each dog served as its own control. The values immediately preceding the carotid sinus reflex were used as control values, both before and after α-receptor blockade. The standard errors presented in the figures and tables represent the variability between animals (d.f. = n − 1).

Results

The effects of carotid sinus hypotension on coronary blood flow in an anesthetized dog treated with propranolol are shown in Figure 2. There was a reflex increase in aortic pressure that was limited to 15 mm Hg by the pressure-control reservoir. There was a small decrease in mean coronary blood flow during carotid sinus hypotension and an associated decrease in oxygen saturation of coronary sinus blood. The reduction in venous oxygen saturation represented an increase in oxygen extraction by the heart, since arterial oxygen saturation was constant. After α-receptor blockade with dibozane (Fig. 2), carotid artery pressure was again reduced to 40 mm Hg and aortic pressure allowed to increase by 15 mm Hg. Dibozane prevented the reduction in coronary blood flow and greatly attenuated the decreases in coronary sinus blood oxygen saturation. A summary of the effects of carotid sinus hypotension on coronary vascular resistance is shown in Figure 3. There was an average 21 ± 6% increase in diastolic coronary vascular resistance when carotid pressure was lowered to 40 mm Hg; that was reduced to less than 5% following α-receptor blockade. The difference before and after α-receptor blockade was statistically significant (P < 0.02). The righthand panel of Figure 3 illustrates the change in myocardial oxygen extraction that accompanied the change in coronary resistance during the carotid sinus reflex. Alpha-adrenergic receptor blockade tended to reduce the increase in myocardial oxygen extraction caused by the carotid sinus reflex, although this reduction was not statistically significant (P < 0.1).

The effects of carotid sinus hypotension on the determinants of coronary blood flow are summarized in Table 1. The effectiveness of the blockade of cardiac β-receptors by propranolol is evidenced by the small decrease in mean coronary blood flow in an anesthetized dog treated with propranolol.
by the absence of changes in heart rate during carotid sinus hypotension. The average myocardial oxygen consumption did not change during the carotid sinus reflex before α-adrenergic receptor blockade but increased by 8% following dibozane. Mean coronary blood flow was relatively unchanged, but myocardial oxygen extraction increased before α-adrenergic receptor blockade (P < 0.02). Alpha-receptor blockade abolished the increases in oxygen extraction and resulted in an increase in coronary blood flow during carotid hypotension. Dibozane also reduced arterial pressure and caused a reduction in coronary blood flow, myocardial oxygen consumption, and myocardial oxygen extraction.

In each experiment two doses of norepinephrine were infused into the left coronary artery. As shown in Table 2, both doses of norepinephrine increased aortic blood pressure and did not greatly change heart rate or myocardial oxygen consumption. The lower dose of norepinephrine slightly decreased mean coronary blood flow. The higher dose caused a larger reduction in blood flow, which was significantly attenuated by α-receptor blockade. Both doses of norepinephrine caused increases in myocardial oxygen extraction and coronary resistance (Fig. 4) that were greatly reduced following blockade of α-adrenergic receptors.

**Discussion**

The results indicate that carotid sinus hypotension produces a reflex coronary vasoconstriction mediated by α-adrenergic receptors that is independent of changes in myocardial oxygen metabolism or aortic pressure. The following discussion has been divided into sections dealing with the major determinants of coronary vascular resistance: coronary perfusion pressure, myocardial systolic compression of coronary vessels, myocardial oxygen metabolism, and neural control of coronary vessels.

**Coronary Perfusion Pressure**

The changes in mean aortic pressure during the carotid reflex were controlled carefully and matched to an increment of 15 mm Hg within a tolerance of 3 mm Hg. Further, the change in aortic pressure during the carotid sinus reflex in an individual animal did not differ by more than 3 mm Hg before and after α-receptor blockade. It is possible that a portion of the increased coronary vascular resist-

**Table 1** Effects of α-Adrenergic Receptor Blockade on the Coronary Vascular Response before and during Carotid Sinus Hypotension

<table>
<thead>
<tr>
<th></th>
<th>Control Before</th>
<th>Control During</th>
<th>α Block Before</th>
<th>α Block During</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean carotid artery pressure (mm Hg)</td>
<td>128 ± 5</td>
<td>44 ± 3</td>
<td>101 ± 8</td>
<td>40 ± 1</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>132 ± 5</td>
<td>148 ± 5</td>
<td>108 ± 9</td>
<td>122 ± 9</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>155 ± 9</td>
<td>157 ± 9</td>
<td>148 ± 7</td>
<td>151 ± 8</td>
</tr>
<tr>
<td>Myocardial O2 consumption (ml/min per 100 g)</td>
<td>10.9 ± 1.4</td>
<td>8.4 ± 1.1</td>
<td>9.1 ± 1 1</td>
<td></td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min per 100 g)</td>
<td>62 ± 9</td>
<td>59 ± 9</td>
<td>51 ± 6</td>
<td>55 ± 7*</td>
</tr>
<tr>
<td>Myocardial O2 extraction (%)</td>
<td>85 ± 1</td>
<td>89 ± 2</td>
<td>81 ± 1</td>
<td>81 ± 1*</td>
</tr>
</tbody>
</table>

* The response (before—during) was significantly different after α-receptor blockade compared to control (P < 0.05). The values are the mean of seven experiments ± SEM.

**Table 2** Effects of α-Adrenergic Receptor Blockade on the Coronary Vascular Response before and during Norepinephrine Infusion

<table>
<thead>
<tr>
<th>Norepinephrine (10 µg/min)</th>
<th>Control</th>
<th>α Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>135 ± 8</td>
<td>145 ± 8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>156 ± 9</td>
<td>156 ± 9</td>
</tr>
<tr>
<td>Myocardial O2 consumption, (ml/min per 100 g)</td>
<td>11.5 ± 1.5</td>
<td>11.8 ± 1.7</td>
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<tr>
<td>Mean coronary blood flow (ml/min per 100 g)</td>
<td>63 ± 8</td>
<td>60 ± 8</td>
</tr>
<tr>
<td>Myocardial O2 extraction (%)</td>
<td>86 ± 1</td>
<td>91 ± 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Norepinephrine (20 µg/min)</th>
<th>Control</th>
<th>α Block</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>127 ± 5</td>
<td>141 ± 6</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>153 ± 9</td>
<td>157 ± 9</td>
</tr>
<tr>
<td>Myocardial O2 consumption, (ml/min per 100 g)</td>
<td>10.8 ± 1.4</td>
<td>10.4 ± 1.5</td>
</tr>
<tr>
<td>Mean coronary blood flow (ml/min per 100 g)</td>
<td>59 ± 8</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Myocardial O2 extraction (%)</td>
<td>86 ± 1</td>
<td>85 ± 1</td>
</tr>
</tbody>
</table>

* The response (before—during) was significantly different after α-receptor blockade compared to control (P < 0.05). The values are the mean of seven experiments ± SEM.
Myocardial Systolic Compression

Extravascular compression of the coronary circulation is related to heart rate, systolic pressure, and the inotropic state of the heart. The use of atropine and propranolol in this study prevented autonomic changes in heart rate and contractility, and the increment in aortic pressure during the carotid sinus reflex was controlled with an arterial reservoir. Diastolic coronary vascular resistance was calculated to evaluate coronary vasomotion during the period of the cardiac cycle when systolic compressive forces are minimal. Mean coronary resistance measurements gave similar results. In the control situation, mean coronary resistance increased by 17.4 ± 2.8% during the carotid sinus reflex. After dibozane there was a 5.6 ± 2.0% increase. The attenuation of the increased coronary resistance during the carotid sinus reflex by dibozane was significant (P < 0.01). It is unlikely that alterations of myocardial systolic compression can account for the findings in these experiments.

Myocardial Metabolism

An arterial pressure increment of 15 mm Hg during the carotid sinus reflex was chosen so that there would be little change in myocardial oxygen consumption. An additional criterion for an acceptable experiment was that myocardial oxygen consumption increase or decrease no more than 10% from the preocclusion value during the carotid sinus reflex. Under control conditions without α-receptor blockade, the average myocardial oxygen consumption was 19.5 ml/min per 100 g and did not change during the carotid sinus reflex (Table 1). Thus the 21% increase in coronary vascular resistance and 4% increase in myocardial oxygen extraction probably were not due to an increase or decrease in myocardial oxygen consumption. This suggests that reflex neurogenic coronary vasoconstriction was the mechanism involved. The validity of this hypothesis is borne out by the loss of the effect when the reflex arc was interrupted by α-receptor blockade. Following α-receptor blockade, the reflex increase in aortic blood pressure again was limited to 15 mm Hg to provide similar conditions for myogenic autoregulation. The reflexly induced increase in coronary diastolic vascular resistance was only 5%, and myocardial oxygen extraction was unchanged (Fig. 3; Table 1). However, average myocardial oxygen consumption increased from a prereflex value of 8.4 to 9.1 ml/min per 100 g during the reflex under these conditions. Thus it could be argued that the blunted resistance response after α-receptor blockade was due to a metabolic vasodilation effect related to increased myocardial oxygen consumption rather than blockade of sympathetic coronary vasoconstrictor fibers.

If the original criterion—that myocardial oxygen consumption change no more than 10%—is applied be – nd after α-receptor blockade, three dogs were excluded. In the remaining four, diastolic coronary resistance increased 28 ± 5% and myocardial oxygen consumption was unchanged (9.0 ± 1.6 before vs. 8.9 ± 1.8 ml/min per 100 g during the
reflex) with the carotid sinus reflex under control conditions without a-receptor blockade. After a-receptor blockade in these same four dogs, diastolic coronary vascular resistance increased only 6 ± 3% during the carotid sinus reflex and myocardial oxygen consumption was unchanged (7.4 ± 0.9 before vs. 7.7 ± 1.0 ml/min per 100 g during the reflex). The reduction in the reflex increase in coronary vascular resistance by a-receptor blockade (28%, vs. 6%) was significant (P < 0.025). The contrast in coronary vascular responses before and after a-receptor blockade in these dogs, in which the changes in aortic blood pressure and myocardial oxygen consumption were so closely matched, indicates reflex neurogenic coronary vasoconstriction during carotid sinus hypotension.

**Neural Control**

Parasympathetic effects were prevented by vagotomy and atropine, and β-adrenergic receptor effects were blocked by propranolol in these experiments. That portion of the increase in coronary vascular resistance during the carotid sinus reflex that was attenuated by dibozine indicates the reflex activation of coronary a-adrenergic receptors. The small coronary vasoconstriction that persisted after dibozine may have been due to incomplete blockade of coronary a-receptors, since intracoronary norepinephrine still caused a small increase in coronary vascular resistance after a-receptor blockade (Fig. 4). In the previous study from this laboratory (Feigl, 1968), the reflex arc was interrupted by cardiac sympathectomy, and it was demonstrated that coronary vasoconstriction during carotid sinus hypotension is primarily due to coronary innervation and not circulating catecholamines.

Biscoe et al. (1970) found in cats that the reduction of carotid sinus pressure to below 50–60 mm Hg caused a firing of chemoreceptor fibers. It is possible that carotid body chemoreceptors were stimulated during carotid sinus hypotension to 40 mm Hg employed in the present study. However, it is unlikely that a chemoreceptor reflex contributed to the reflex coronary vasoconstriction observed in these experiments, because chemoreceptor activation produces reflex coronary vasodilation. Hackett et al. (1972) and Vatner and McRitchie (1975) observed reflex vagal parasympathetic coronary vasodilation secondary to carotid body chemoreceptor activation. This effect was prevented by atropline and vagotomy in the present experiments. Vatner and McRitchie (1975) also observed in unanesthetized dogs a reflex coronary vasodilation due to inhibition of sympathetic a-receptor coronary vasoconstrictor tone in a two-step reflex, when chemoreceptor stimulation with nicotine produced pulmonary hyperinflation which led to coronary vasodilation. This effect is unlikely in these experiments in anesthetized animals with controlled ventilation. Even if such a reflex were present in these experiments, it would produce coronary vasodilation and tend to make the observed reflex vasoconstriction smaller.

The pathway for cardiac sympathetic afferent fibers remained intact in these experiments (Malliani et al., 1972, 1973). It is possible that the sequestration of blood in the external pressure control reservoir due to carotid sinus hypotension could be a stimulus to sympathetic cardiac afferent fibers, and this may have contributed to the reflex response observed here in a secondary way.

Limet and co-workers (1975) examined the effects of increasing and decreasing carotid sinus pressure in a right-heart bypass preparation in which aortic blood pressure was partially stabilized at a rather low level of 40–50 mm Hg. Under these conditions, lowering carotid sinus pressure from 70 to 30 mm Hg resulted in small changes in myocardial oxygen consumption and a consistent increase in coronary vascular resistance. These results are similar to the findings in the first part of the present study before a-receptor blockade and suggest that the increased coronary vascular resistance during carotid sinus hypotension is not dependent on increases in coronary perfusion pressure. Limet et al. did not determine whether the increase in coronary resistance during carotid sinus hypotension was neurogenic by interrupting the reflex arc.

In conclusion, the results of this study indicate that the carotid sinus reflex elicited by lowering carotid blood pressure results in sympathetic a-adrenergic receptor coronary vasoconstriction that is independent of autoregulation and changes in myocardial metabolism.

**Acknowledgments**

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