Adrenergic Coronary Vasoconstriction in the Presence of Coronary Stenosis in the Dog

CHARLES W. BUFFINGTON AND ERIC O. FEIGL

SUMMARY Previous studies have demonstrated competition between sympathetic α-receptor-mediated coronary vasoconstriction and local metabolic vasodilation during sympathetic activation. The present study tested if this competition also occurs in the presence of coronary stenosis. In closed-chest dogs, the left coronary artery was cannulated, and blood flow from the aorta was restricted by a moderate stenosis (70% area reduction). Intracoronary norepinephrine infusion produced coronary vascular α-receptor and myocardial β-receptor activation. Norepinephrine infusion was repeated following a receptor blockade with phenoxybenzamine (0.25 mg/kg, injected into the coronary artery). Myocardial oxygen and lactate extraction, coronary sinus blood oxygen tension, and coronary resistance were compared at equal levels of myocardial oxygen consumption before and after coronary α-receptor blockade. In the presence of coronary stenosis, intracoronary norepinephrine infusion decreased coronary sinus oxygen content and increased myocardial oxygen extraction. At comparable myocardial oxygen consumptions coronary vascular resistance was greater with α receptors intact than after a receptor blockade. The increase in myocardial oxygen extraction was prevented by α receptor blockade. We conclude that a sympathetic α-receptor-mediated coronary vasoconstrictor influence operates, even in the presence of coronary stenosis, to limit oxygen delivery to the heart and increase myocardial oxygen extraction up to the point of cardiac failure, but that this vasoconstrictor effect does not result in net myocardial lactate production. Circ Res 48: 416-423, 1981

SYMPATHETIC coronary vasoconstriction has been demonstrated in a number of laboratories (Szentiványi and Juhász-Nagy, 1959; Berne et al., 1965; Granata et al., 1965; Feigl, 1967; Ross, 1976) and is of the α receptor type (Feigl, 1967; Pitt et al., 1967; McRaven et al., 1971). There is also evidence for resting sympathetic vasoconstrictor tone (Vatner et al., 1970; Holtz et al., 1977; Schwartz and Stone, 1977; Orlick et al., 1978). Previous studies from this laboratory demonstrated that sympathetic α-receptor-mediated coronary vasoconstriction competes with local metabolic control of the coronary circulation. This vasoconstrictor influence limits oxygen delivery to the heart, increases myocardial oxygen extraction, and decreases coronary venous oxygen tension (Feigl, 1975; Mohrman and Feigl, 1978). The present investigation was designed to determine whether sympathetic coronary vasoconstriction is capable of limiting oxygen delivery to the myocardium in the presence of coronary artery stenosis; a situation in which local metabolic vasodilation might overwhelm sympathetic effects, or even a modest vasoconstriction could have a harmful effect on myocardial oxygenation. The results indicate that α receptor-mediated coronary vasoconstriction limits oxygen delivery to the heart and increases myocardial oxygen extraction in the presence of coronary artery stenosis, but the sympathetic vasoconstriction is not severe enough to push the myocardium into net lactate production.

Methods

General Preparation

Thirteen closed-chest dogs weighing 25–31 kg were studied. Approximately 1 hour after sedation with morphine sulfate (2.5 mg/kg, sc), each dog was anesthetized with an initial injection of α-chloralose (100 mg/kg, iv). Anesthesia was maintained with a continuous infusion of α-chloralose (10 mg/kg per hour, iv) during the experiment. Ventilation was with room air enriched with a mixture of 40% oxygen in nitrogen gas supplied from a positive-pressure pump (Harvard 601) operating with a 5-cm H2O end-expiratory back pressure. Oxygen enrichment was adjusted by means of a variable demand valve so that arterial blood oxygen tension was kept between 125 and 150 mm Hg throughout the experiment. End-expiratory carbon dioxide was monitored continuously with an infrared absorption meter (Beckman LB-2) and held between 4.5% and 5% by adjustment of rate of ventilation and tidal volume. Blood coagulation in the extracorporeal circuits was prevented by infusion of sodium heparin (750 U/kg plus 250 U/kg per hour, iv), and the metabolic acidosis associated with chloralose anes-
themia was counteracted by a continuous infusion of 150 mM sodium bicarbonate (5 ml/kg per hour, iv) (Arfors et al., 1971). Rectal temperature was held at 37°C with a heating pad and temperature controller (Yellow Springs 73A). Femoral arteriovenous shunts with an adjustable screw clamp were installed. Arterial blood pressure was measured with a catheter-tip transducer (Millar) introduced into the arch of the aorta via the left brachial artery. Pulmonary artery wedge pressure was measured through a balloon-tip catheter inserted into the pulmonary artery via the left external jugular vein. A schematic diagram of the experimental preparation appears in Figure 1.

**Coronary Blood Flow Measurement and Coronary Stenosis**

Blood flow into the left coronary artery was measured and controlled with the cannula-tip flow transducer shown in Figure 1, which is a modification of the device described by Smith et al. (1974). The transducer was advanced through the right carotid artery into the ascending aorta, and a balloon near its tip was inflated. The tip then was inserted into the left coronary ostium until the balloon sealed at the lip of the ostium. Left coronary artery flow was measured using the ultrasonic Doppler shift technique. Blood from the aorta entered the stainless steel tube through a variable annular orifice and passed a pair of piezoelectric crystals before entering the coronary artery. Coronary artery pressure was measured distal to the imposed stenosis through a small stainless steel internal auxiliary tube, and a similar tube allowed direct intracoronary drug injection.

The seal at the left coronary ostium was tested at the beginning and end of each experiment by a 10-second complete occlusion. If the seal was adequate, pressure distal to the occluder fell below 20 mm Hg during occlusion and a marked reactive hyperemia followed re-opening. At the end of each experiment, approximately 1.5 ml of an intense blue dye (crystal violet in 1 N ammonia) was injected into the drug administration tube, and the heart was arrested by intravenous KCl a few moments later. The dye delineated the myocardium perfused during the experiment. The weight of dyed myocardium was used to calculate cardiac oxygen consumption per 100 g of myocardium.

A spherical occluder at the inflow port of the transducer was advanced during the experiment to reduce the cross-sectional area of the cannula lumen by approximately 70%. Flow through this annular stenosis produced a pressure gradient from aorta to coronary artery, as shown in Figure 2. The relationship between pressure gradient and flow resembled that of a moderately severe coronary stenosis (Gould, 1978). Reactive hyperemia following a 10-second complete occlusion was limited by the stenosis, as shown in Figure 3. The same degree of inflow restriction was used in all experiments.

**Oxygen Measurements**

A Sones catheter (USCI no. 007538) was advanced into the coronary sinus via the right jugular vein and right atrium with the aid of a fluoroscope. Postmortem measurements of the location of the catheter tip ranged from 35 to 52 mm into the coronary sinus in the 13 dogs studied. Blood was withdrawn continuously from the coronary sinus catheter at a rate of 12 ml/min with a roller pump (Cole-Parmer 4420). This combination of withdrawal rate and cannula tip placement was chosen to prevent contamination of the coronary sinus sample with blood from the right atrium (Koberstein et al., 1969). Coronary sinus blood passed a spectrophotometric oximeter cuvette (Waters 0-500), the withdrawal pump, a sampling site, and an oxygen tension cuvette (Feigl and D’Alecy, 1971).
FIGURE 2 Stenosis pressure gradient resulting from flow through the stenosis used in all 13 experimental animals. The values were obtained by an in vitro calibration. Resting coronary blood flow was approximately 70 ml/min and increased 2- to 3-fold with norepinephrine infusion.

before being returned to the right jugular vein. Provision was made for either coronary sinus blood or arterial blood to be drawn through the oxygen-measuring and sampling circuit.

Blood samples were drawn periodically throughout the experiment for generating the oximeter calibration curve and determining the hemoglobin concentration. Each sample was analyzed for oxygen content (Lexington Instruments Lex-O2-Con) and for hemoglobin content by the cyanmethemoglobin method (Bauer et al., 1974). The oxygen-carrying capacity of each blood sample was calculated by multiplying the measured hemoglobin content by 1.36 ml O₂/g Hb (Dijkhuizen et al., 1977). Arterial oxygen tension was maintained between 125 and 150 mm Hg, and arterial hemoglobin was assumed 100% saturated. Myocardial oxygen consumption was computed from steady state measurements of arterial and venous oxygen contents and coronary blood flow, and was expressed per 100 g of perfused left ventricular myocardium.

Myocardial Lactate Extraction

Plasma lactate extraction or production across the coronary circulation was determined by measurements of simultaneously drawn arterial and coronary venous samples. Samples were promptly chilled, precipitated with 8% perchloric acid, and centrifuged at 3°C. Lactate concentration was determined photometrically by the enzymatic method (Drewes, 1974). The lactate extraction ratio was calculated from the arterial-coronary sinus venous difference divided by the arterial concentration, [(Ca-Cv)/Ca], and expressed as a percent.

Experimental Protocol

Following imposition of the standard stenosis, intracoronary infusion of norepinephrine was used to increase myocardial oxygen consumption and activate coronary vascular α receptors. Graded doses of norepinephrine in the range of 1-3 μg/min provided step-wise increases in sympathetic stimulation. Prior to α receptor blockade, the femoral arteriovenous shunts were opened to offset increases in systemic vascular resistance caused by norepinephrine and maintain mean arterial pressure constant within ±5 mm Hg. It was necessary to stabilize arterial pressure in order to have comparable conditions before and after α receptor blockade. Norepinephrine infusion was stopped at the onset of left ventricular failure, as manifest by a fall in arterial pressure or a rise in pulmonary artery wedge pressure.

Alpha receptor blockade was produced by intracoronary infusion of phenoxybenzamine (0.25 mg/kg). A slow infusion (0.35 ml/min) of a 0.5 mg/ml saline solution was used to maximize coronary blockade and minimize peripheral blockade. After α receptor blockade, intracoronary norepinephrine was infused just as it was before blockade.

Data Analysis

Coronary vascular resistance was calculated as the quotient of mean coronary pressure (measured distal to the stenosis) and mean coronary blood flow. A downstream pressure of zero was assumed for these calculations. Left ventricular diastolic pressure, as reflected by pulmonary artery "wedge" pressure, was unchanged by α receptor blockade and did not exceed 10 mm Hg during norepinephrine infusion. Coronary resistance, oxygen extraction, lactate extraction, and coronary sinus blood oxygen tension were plotted vs. myocardial oxygen consumption.
Coronary resistance data for each animal and each condition (before and after alpha receptor blockade) were fit, using a quadratic equation: \( Y = A + BX + CX^2 \), where \( Y \) equals predicted coronary resistance and \( X \) equals the measured oxygen consumption. \( A, B, \) and \( C \) are the estimated parameters for the equation. The equation was fit by the least squares method using the SPSS (version 7.0) regression procedure (Nie et al., 1975).

Examples of regression curves for a single dog are shown in Figure 4. The computed curve was used to determine interpolated values of coronary resistance for each animal at 2.0 (\( ml \ O_2/\text{min per 100 g} \)) intervals of oxygen consumption. These curves were used only for interpolation between real data points—no extrapolations of the data were made.

The computed coronary resistance observations before and after alpha receptor blockade were tested using a two-tailed paired \( t \)-statistic at oxygen consumption intervals of 2.0 (as above). Each of the tests was based on \( n - 1 \) degrees of freedom for \( n \) paired dog comparisons.

A similar analysis of oxygen extraction, coronary sinus blood oxygen tension, and lactate extraction data was made. Oxygen extraction data were analyzed by means of the quadratic equation: \( Y = A + BX + CX^2 \), where \( Y \) equals predicted oxygen extraction and \( X \) is oxygen consumption. Coronary sinus blood oxygen tension data were analyzed using the equation: \( Y = A + BX \), where \( Y \) is predicted blood oxygen tension and \( X \) is oxygen consumption. Examples of these data and equations are given in Figure 4. Lactate extraction data were analyzed by use of linear interpolation because there was an insufficient number of data points to warrant curve fitting.

The number of paired comparisons at each interval of myocardial oxygen consumption differed from 13 because not all dogs had resting oxygen consumption values as low as 8 or achieved maximal values as high as 20 \( ml \ O_2/\text{min per 100 g} \). The number of paired comparisons for lactate extraction data was fewer than for other variables because only 3-4 lactate samples were drawn during each experimental run.

**Figure 4** Changes in myocardial lactate extraction, coronary sinus blood oxygen tension, oxygen extraction, and coronary resistance during norepinephrine infusion before (solid lines) and after (dashed lines) alpha receptor blockade. Coronary resistance was consistently greater prior to blockade with phenoxybenzamine over the range of oxygen consumption observed. Consequently, oxygen extraction was greater and coronary sinus blood Po2 less, prior to blockade. Lactate extraction is positive at low oxygen consumption values, signifying net uptake. Lactate extraction decreases during norepinephrine infusion in the presence of a stenosis. The solid (alpha receptors intact) and dashed (alpha receptors blocked) lines are curves fit to the data using the equations shown.
Results

Resting hemodynamic and metabolic data before and after α receptor blockade obtained prior to norepinephrine infusion are shown in Table 1. Small decreases in coronary sinus hemoglobin concentration and myocardial oxygen extraction following blockade were the only significant changes noted during resting conditions. Resting coronary blood flow was not detectably altered by imposition of the stenosis prior to α receptor blockade but fell slightly with stenosis following phenoxybenzamine administration.

The response of a single animal to intracoronary norepinephrine in the presence of stenosis is shown in Figure 5. Stepwise increases in norepinephrine infusion rate produced steady hemodynamic states with an elevation of heart rate, an increase in coronary flow and a fall in coronary artery pressure distal to the stenosis. Coronary sinus hemoglobin-oxygen saturation was lowered modestly during norepinephrine infusion. The right hand side of Figure 5 shows the response to norepinephrine infusions after a receptor blockade with phenoxybenzamine. Heart rate and coronary blood flow increased and coronary artery pressure fell. Coronary sinus hemoglobin-oxygen saturation was higher than before phenoxybenzamine administration and remained elevated until maximal levels of norepinephrine infusion were reached. Norepinephrine infusion was terminated at the onset of left ventricular failure as manifest by a fall in arterial pressure or a rise in pulmonary artery wedge pressure (not shown). The unstable hemodynamic conditions resulting from acute failure precluded reliable steady state measurements.

Table 1 Control Values without Norepinephrine Infusion

<table>
<thead>
<tr>
<th></th>
<th>α Receptors intact</th>
<th>α Receptors blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unrestricted</td>
<td>Stenosed</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>120 ± 3</td>
<td>121 ± 4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>93 ± 8</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>Mean coronary pressure (mm Hg)</td>
<td>119 ± 3</td>
<td>112 ± 3</td>
</tr>
<tr>
<td>Coronary blood flow (ml/min per 100 g)</td>
<td>59 ± 6</td>
<td>59 ± 6</td>
</tr>
<tr>
<td>Mean coronary resistance (mm Hg/ml per min per 100 g)</td>
<td>2.31 ± 0.20</td>
<td>2.23 ± 0.20</td>
</tr>
<tr>
<td>Myocardial oxygen extraction (%)</td>
<td>81.1 ± 1.2</td>
<td>80.2 ± 1.1</td>
</tr>
<tr>
<td>Myocardial lactate extraction (%)</td>
<td>55.5 ± 1.6</td>
<td>56.4 ± 1.4</td>
</tr>
<tr>
<td>Myocardial oxygen consumption (ml/min per 100 g)</td>
<td>9.5 ± 1.1</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>Hemoglobin concentration (g/dl)</td>
<td>14.9 ± 0.3</td>
<td>15.3 ± 0.3</td>
</tr>
</tbody>
</table>

Average values from 13 animals ± SEM. P values were calculated by analysis of variance.
The response of a single animal is plotted vs. oxygen consumption in Figure 4. Data obtained before and after phenoxybenzamine are shown along with the curves fitted for the purpose of interpolation. Figure 6 shows the average values obtained for all 13 dogs. Coronary resistance was significantly lower following phenoxybenzamine at oxygen consumption values between 8 and 18 ml O2/min per 100 g. Vasodilation caused by the removal of the α constrictor influence resulted in lower oxygen extraction and higher coronary sinus blood oxygen tension following phenoxybenzamine. The number of paired comparisons and probabilities that the results were due to chance alone are also shown. Paired comparison of lactate extraction data before and after phenoxybenzamine found no significant differences.

**Discussion**

This experiment was designed to simulate increased sympathetic activity in patients with moderately severe coronary artery lesions who are asymptomatic at rest. The experimental maneuver was to increase myocardial oxygen consumption by intracoronary norepinephrine infusion in the presence of partial occlusion of the left main coronary artery while holding aortic pressure constant (±5 mm Hg) by decreasing peripheral resistance with an arteriovenous shunt. Aortic blood pressure was held constant so that similar conditions before and after a receptor blockade could be compared. The results indicate that an α receptor-mediated coronary vasoconstrictor effect increased myocardial oxygen extraction even in the presence of a coronary artery stenosis. However, this vasoconstrictor effect was not sufficient to result in net myocardial lactate production.

The stenosis used in these experiments was created by advancing a spherical stainless steel ball into the inflow port of the flow transducer. The cross-sectional area of the port was reduced by approximately 70%. The restriction to flow thus produced was characterized by determining the stenosis pressure gradient as a function of flow (Fig. 2). The slope of this relationship (stenosis resistance) was fairly constant at low flows but increased at high flows, a finding in keeping with more complete studies of stenosis hemodynamics (Young and Tsai, 1973; Gould, 1978). Elevated resistance at high flows can be attributed to energy losses due to expansion, separation, and friction associated with turbulent flow. Resting flows on the order of 60 ml/min per 100 g produced a stenosis gradient of 6–10

---

**Figure 6** Summary of the effects of a receptor blockade on the response variables vs. myocardial oxygen consumption during intracoronary norepinephrine infu-
mm Hg. During sympathetic activation, coronary flows generally doubled or tripled causing increases in the stenosis pressure gradient to 30-50 mm Hg. The stenosis used in these experiments reduced peak flows elicited by a 10-second complete occlusion. Peak reactive hyperemia flow was approximately four times the resting flow in the absence of stenosis. The stenosis limited the peak reactive hyperemic flow to approximately two times the resting flow (Fig. 3).

Although the stenosis was physically a part of a cannula, the hemodynamic effects probably are similar to a stenosis of the left main coronary artery. Flow and pressure into vessels supplying the majority of the left ventricular free wall and septum were affected. This model had both advantages and disadvantages when compared to segmental coronary stenosis. Homogeneous conditions of pressure and flow to most of the left ventricle permitted measurement of myocardial oxygen consumption; this is not possible with segmental stenosis because coronary sinus effluent is a mixture of blood from the normal and stenosed coronary vascular beds.

The primary disadvantage of the left mainstem coronary artery stenosis used in the present experiment was the loss of total left ventricular contractile force which occurred at high oxygen consumption values. In isolated segmental stenosis, normal myocardium probably compensates for the function lost in the ischemic area (Moir, 1972). The functional deterioration was manifest by signs of acute left ventricular failure, which was rapidly progressive and precluded steady state hemodynamic and biochemical measurements. Pilot experiments in which the situation was allowed to progress demonstrated irreversible hypotension, ventricular arrhythmias, and death. In the experiments involved in the present report, norepinephrine infusion was stopped and the stenosis removed as soon as failure was identified by a detectable increase in pulmonary artery wedge pressure or a fall in aortic blood pressure. Thus, while incipient left ventricular failure was the physiological limitation in all experiments, no data about the role of adrenergic vasoconstriction in the development of failure were obtained. The data do demonstrate that adrenergic vasoconstriction operates in the presence of coronary stenosis and persists up to the point of acute ventricular failure.

The present study provides no information about the transmural distribution of coronary flow. Myocardial hypoxia is most likely at high levels of sympathetic stimulation and will probably occur first in the more vulnerable subendocardium. It is possible that the vasoconstriction observed under these conditions occurred primarily in subepicardial vessels which were not maximally dilated.

Lactate extraction was positive, signifying net uptake, at low oxygen consumptions, but decreased and occasionally became negative, signifying net production, at high oxygen consumptions. No difference in lactate extraction before and after receptor blockade was observed. Myocardial lactate extraction was used as a measure of the adequacy of myocardial oxygen delivery. The heart normally uses lactate as a substrate for aerobic metabolism. The percentage extracted from arterial blood has been found to be between 26 and 46% in other studies (Opie et al., 1973; Case et al., 1969; Shea et al., 1962; Krasnow et al., 1962; Griggs and Chen, 1974). Production of lactate by the myocardium is a commonly accepted indicator of the anaerobic metabolism which accompanies tissue hypoxia (Brachfeld, 1976), but interpretation of lactate data is complicated (Apstein, 1979).

Decreases in lactate extraction with increasing levels of norepinephrine, in the present study, might represent a balance between regions of the myocardium that received adequate oxygen and those where anaerobic metabolism occurred because metabolism exceeded oxygen availability. Griggs et al. (1966) have shown that lactate uptake may persist despite net lactate production when coronary flow is lowered to the point of left ventricular failure, indicating that aerobic and anaerobic metabolism can occur simultaneously in different regions of the contracting myocardium.

The results of the present investigation may be relevant to recent clinical observations in patients with coronary artery disease. Adrenergic vasoconstriction has been implicated as a contributing factor in the production of angina (Mudge et al., 1976, 1979), coronary spasm (Hillis and Braunwald, 1978), and myocardial infarction (Maseri et al., 1978). Mudge et al. (1979) have demonstrated an increase in coronary vascular resistance in patients with coronary artery disease subjected to the cold pressor test, a known sympathetic stimulus. Coronary blood flow in these patients failed to increase despite increases in arterial pressure during the cold pressor test. In contrast, coronary blood flow increased and calculated vascular resistance decreased during atrial pacing in the same patients.

In conclusion, the present study demonstrates receptor-mediated coronary vasoconstriction in the presence of coronary stenosis. This vasoconstriction increases coronary vascular resistance, limits oxygen delivery to the myocardium, and increases myocardial oxygen extraction during norepinephrine infusion. The vasoconstriction is present up to the point of cardiac failure but is not powerful enough to cause net myocardial lactate production. The vasoconstriction demonstrated at high levels of sympathetic stimulation may occur primarily in the subepicardium, which is less vulnerable to the effects of coronary stenosis.

Acknowledgments

We thank Feltner Smith and Stephanie Lathrop for skillful technical assistance during these experiments.
ADRENERGIC CORONARY VASOCONSTRICTION AND STENOSIS/Buffington & Feigl

References

Apstein CS, Gravino F, Hood WB (1979) Limitations of lactate production as an index of myocardial ischemia. Circulation 60: 877-887


Feigl EO (1975) Control of myocardial oxygen tension by sympathetic coronary vasoconstriction in the dog. Circ Res 37: 88-95


Moir TW (1972) Coronary vascular adjustments to acute myocardial ischemia. Arch Intern Med 129: 799-807


Young DF, Tai FY (1973) Flow characteristics in models of arterial stenosis: I. Unsteady flow. J Biomech 6: 547-559
Adrenergic coronary vasoconstriction in the presence of coronary stenosis in the dog.
C W Buffington and E O Feigl

doi: 10.1161/01.RES.48.3.416

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1981 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/48/3/416