Adrenergic Influence in the Coronary Circulation of Conscious Dogs during Maximal Vasodilation with Adenosine

Gus J. Vlahakes, Robert W. Baer, Paul N. Uhlig, Edward D. Verrier, J. David Bristow, and Julien I.E. Hoffman
From the Cardiovascular Research Institute, and the Departments of Medicine, Pediatrics, and Surgery, University of California, San Francisco, California

SUMMARY. The coronary arteries receive rich adrenergic innervation. The present study examines the effects of changes in adrenergic activity on the coronary circulation without the complicating influence of autoregulation. Diastolic and mean circumflex coronary artery pressure-flow relations were generated in conscious dogs and were described by their slope and zero-flow, pressure-axis intercept during vasodilation produced by intracoronary adenosine, at a dose that abolished reactive hyperemia. \(\beta\)-Adrenergic blockade with propranolol (1 mg/kg, iv) decreased coronary flow at all pressures, increasing diastolic pressure-axis intercept from 20.5 (4.7) (mean and sd) to 24.7 (so 4.5) mm Hg, without a significant change in slope. \(\alpha\)-Adrenergic blockade with phentolamine (0.3 mg/kg, iv) increased flow at all pressures, with the greatest increases occurring at lower pressures. Thus, diastolic pressure-axis intercept decreased from 24.0 (SD 5.5) to 20.9 (SD 6.3) mm Hg, and calculated slope decreased slightly from 3.9 (so 1.3) to 3.5 (so 1.0) ml/min per mm Hg. \(\alpha\)-Adrenergic agonist stimulation with intracoronary phenylephrine (0.3 \(\mu\)g/kg per min) produced little change in pressure-flow relations; however, in the presence of \(\beta\)-adrenergic blockade, the same dose of phenylephrine decreased coronary flow at all pressures, thus increasing diastolic pressure-axis intercept from 24.4 (so 3.7) to 29.1 (so 3.6) mm Hg. \(\beta\)-Adrenergic agonist stimulation with isoproterenol (0.03 \(\mu\)g/kg per min, iv) produced small further increases in flow as compared with control, decreasing diastolic pressure-axis intercept from 26.0 (so 2.9) to 24.9 (so 2.8) mm Hg. These results suggest that significant resting \(\alpha\)- and \(\beta\)-adrenergic tone can be demonstrated in coronary circulation during maximal adenosine-induced vasodilation. Resting \(\beta\)-adrenergic tone is near maximal, and changes in adrenergic tone exert their influence on maximal flow primarily through changes in pressure-axis intercept, rather than through changes in the slope of the pressure-flow relationship. (Circ Res 51: 371-384, 1982)

THE coronary circulation is richly innervated (Woollard, 1926; Friedman et al., 1968). Histochemical fluorescence studies have suggested that this innervation includes many adrenergic fibers in close association with coronary arterioles and venules (Dahlstrom et al., 1965). Furthermore, both \(\alpha\) - and \(\beta\)-adrenergic receptor activities have been demonstrated in the coronary circulation (Klocke et al., 1965; Pitt et al., 1967; Ross and Jorgensen, 1970; McRaven et al., 1971; Baron et al., 1972; Malindzak et al., 1972; Johansson, 1973; Bayer et al., 1974; Cornish and Miller, 1975).

Sympathetic nerve stimulation (Granata et al., 1965; Feigl, 1967) has produced transient coronary vasoconstriction followed by increased coronary flow secondary to increased flow demand in response to nerve stimulation. Feigl (1967, 1975) demonstrated that this transient vasoconstrictor effect could be enhanced by \(\beta\)-adrenergic blockade with propranolol and could be inhibited by \(\alpha\)-adrenergic blockade with phenoxybenzamine. In subsequent studies (Mohrman and Feigl, 1978), some aspects of competition between \(\alpha\)-adrenergic coronary vasoconstriction and myocardial metabolism were evaluated. It has been suggested that coronary adrenergic vasoconstriction may be an important pathophysiological mechanism in humans (Mudge et al., 1976, 1979; Orlick et al., 1979). Despite all these studies, however, the role of adrenergic influences on coronary vascular tone remains unclear, as do the effects of adrenergic stimulation and blockade on maximal attainable flows at any given perfusion pressure.

Many of the previous studies with intact heart preparations have been complicated by coronary flow changes in response to alterations in flow demand produced by sympathetic nerve stimulation or \(\beta\)-adrenergic blockade. These studies suggest that when coronary vascular reserve and autoregulation are present, any changes in flow produced by sympathetic stimulation or adrenergic blockade, for example, may be modified by changes in autoregulatory tone. This may account for inability of previous investigators to demonstrate tonic adrenergic activity in the coronary circulation (Mueller et al., 1980; Chilian et al., 1981; Vatner and Hintze, 1981). The present study examines
changes in coronary flow produced by adrenergic blockade or pharmacological stimulation without the complicating influence of autoregulation.

With decreasing perfusion pressure, coronary flow during autoregulation stays relatively constant until coronary vascular reserve is exhausted. After that point, when the coronary circulation is in a state of maximal metabolic vasodilation, coronary flow decreases approximately linearly with decreasing perfusion pressure. The coronary pressure-flow relation obtained during maximal metabolic vasodilation represents the maximal flow that the coronary vasculature can conduct in response to increasing demand. Maximal vasodilation can also be produced pharmacologically and, again, results in a roughly linear relation between pressure and flow; pharmacological vasodilation serves to uncouple coronary flow from myocardial oxygen demand. As a result, the relationship of coronary flow to perfusion pressure can be studied without the complicating effects of autoregulation or of myocardial ischemia, at least until very low perfusion pressures are reached.

Previous investigators assessed vasoconstriction by measuring coronary pressures and flows at a single point and calculated coronary resistance assuming an opposing, downstream pressure equal to coronary sinus pressure or to LV end-diastolic pressure. Recent investigators, however, have demonstrated that with decreasing diastolic coronary perfusion pressure, coronary flow ceases at a pressure higher than coronary sinus pressure (Bellamy, 1978; Klocke et al., 1981); this phenomenon has been attributed to a vascular “waterfall” mechanism in the coronary circulation (Permutt and Riley, 1963; Klocke et al., 1981).

By measuring coronary pressures and flows at different pressures, one obtains pressure-flow relationships that are linear or nearly linear. These relationships can be described by the slope of the line and the zero flow intercept on the pressure axis ($P_{o}$). The physiological meaning of these two parameters is not settled. One popular explanation invokes a waterfall model (Permutt and Riley, 1963) in which the slope of the pressure-flow relationship is regarded as the conductance of the coronary vascular bed and $P_{o}$ is regarded as a “waterfall” pressure that is a function of tissue pressure and the tone of smooth muscle in distal coronary vessels. These interpretations, however, are disputed. In the present study, we use these parameters as convenient descriptors of the pressure-flow relationship without attributing specific physiological meaning to them.

The present study was designed to generate coronary artery pressure-flow relations during maximal adenosine-induced vasodilation and at constant heart rate in conscious dogs. The purpose was to demonstrate the presence and magnitude of tonic $\alpha$- and $\beta$-adrenergic activity in the coronary circulation without the complicating effects of autoregulation and to examine the effects of $\alpha$- and $\beta$-adrenergic agonist stimulation during maximal pharmacologic coronary vasodilation.

Methods

Male mongrel dogs weighing 27.7-34.5 kg (mean 31.3, so 1.8), serologically negative for microfilariae, were sedated with droperidol (1 mg/kg, im) and fentanyl (0.02 mg/kg, im) (Innovar-Vet, Pitman-Moore). Anesthesia was induced with sodium pentothal (10 mg/kg, iv) and was maintained by ventilation with a gas mixture of 65% nitrous oxide and 35% oxygen, containing 1% halothane. After satisfactory anesthesia was achieved, temporary muscle paralysis was produced with succinylcholine chloride (2 mg/kg, iv). A left 5th interspace thoracotomy was performed, by sterile technique, and the pericardium was opened parallel to the phrenic nerve. Catheters for pressure measurement were placed in the aortic arch via the left internal mammary artery and in the left ventricle via the apex; some dogs also had catheters placed in the coronary sinus. Heart rate was controlled by producing heart block with formalin injection of the atrioventricular node (Steiner and Kovalik, 1968) and ventricular pacing with an implanted rate-programmable pacemaker (Medtronic) and pacing electrodes placed on the anterior wall of the left ventricle near the septum. Catheters for drug infusion and pressure measurement were placed in the proximal and distal parts of the circumflex artery, respectively, using a modification of the Herd-Barger (1964) technique (Verrier et al., 1980). A 2.5 mm in diameter electromagnetic flow transducer (Howell Instruments) and a miniature hydraulic constrictor (Debly, 1971) were placed around the artery between the two catheters. Catheters, the occluder tubing, and the flow transducer cable were brought out through small pericardial incisions and exteriorized between the scapulae; the pericardium was closed. An intercostal nerve block for postoperative analgesia was placed at ribs 2-7 using 0.5% bupivicaine with epinephrine 1:200,000 (Marcaine; Breon Laboratories); a chest tube was inserted, the chest was closed, and air was evacuated. Each dog received procaine penicilllin (800,000 units, im) and streptomycin (1 g, im) (Combiotic; Pfizer) at the time of surgery and daily for 4 days. Catheters were aspirated and flushed daily with saline containing heparin (100 units/ml) and fibrinolysin (50 Merck units/ml) (Thrombolysin; Merck, Sharp, & Dohme); dogs were trained to stand quietly in a sling. Heart rate was set at 100-115 beats/min on the day of surgery and was decreased to 90 beats/min on the 2nd postoperative day and 70-80 beats/min on the 4th postoperative day. All studies were performed beginning the 7th postoperative day.

Dogs were studied in a dimly lit room while they stood quietly in a sling. Catheters were connected to strain gauges (P23dB, Statham), and the flow transducer was connected to a flowmeter (Narcomatic RT-500). Prior to implantation, we calibrated each flow transducer with the flowmeter by passing saline through the flow transducer over a range of known flow rates. Circumflex flow and distal pressure, and left ventricular, aortic, and coronary sinus pressures were recorded on a strip chart (Beckman Instruments) and on FM magnetic tape (Hewlett-Packard).

The five channels of data were digitized simultaneously by sampling at 5-msec intervals (Horowitz, 1980; Horowitz and Glantz, 1979). All subsequent data analysis was carried out on digitized data by digital computer (PDP 11/70, Digital Equipment Corporation); diastole was defined as the interval from the end of ventricular relaxation to the beginning of the systolic rise in ventricular pressure.

Coronary artery diastolic and mean pressure-flow relations were generated during complete vasodilation pro-
duced with intracoronary adenosine, infused through the proximal circumflex catheter. No further increase in flow was observed for adenosine doses above 1-3 μg/kg per min in most dogs; experiments were thus performed at an adenosine dose of 20 μg/kg per min to ensure complete adenosine-induced vasodilatation. With each experimental protocol and during each intervention, the adequacy of vasodilatation was repeatedly confirmed by noting the absence of reactive hyperemia after a 15-second circumflex occlusion and by the absence of a flow increase to a supplemental 2-mg bolus intracoronary dose of adenosine.

At the end of the study, dogs were killed. Necropsy examination confirmed that no dog had wound infection, pericardial or pleural effusion, or apparent myocardial infarction; coronary catheters were patent and there was no gross evidence of coronary embolization.

Data Analysis

Twelve to 14 brief, partial circumflex occlusions were performed to produce a wide range of distal pressures and flows; attempts were made to distribute points evenly along the pressure-flow relationship, including points at very low flows (see figures). The hydraulic occluder was used to reduce distal pressure to the desired point; during maximal vasodilatation, when flow was pressure-dependent, pressure and flow equilibrated within 2-3 beats. Constriction then was maintained long enough to record data for 5 seconds. Data then were analyzed over the first 4 consecutive recorded cardiac cycles. The occlusive zero of the flowmeter was checked before and after each pressure-flow relation was generated. Average diastolic coronary pressure and flow were determined for each cardiac cycle by digital integration of the diastolic interval of each data channel and division by the duration of diastole. Thus, the linear regression of average diastolic flow on average diastolic pressure (Zar, 1974) was calculated from 48-56 points and was extrapolated to the pressure axis. The zero-flow, pressure-axis intercept (Pf_o), the slope, and the correlation coefficient were used to describe each diastolic pressure-flow relationship. Similarly, mean coronary pressure-flow relations were generated for each cardiac cycle by determining mean pressure and mean flow across each cardiac cycle studied and calculating the regression of mean flow on mean pressure. Pf_o, slope, and regression coefficient were calculated for mean pressure-flow relations.

Mean aortic pressure, left ventricular (LV) end-diastolic pressure, the maximum rate of rise of left ventricular pressure (maximum (+) LV dP/dt), and mean coronary sinus pressure were determined for each cardiac cycle analyzed. For each pressure-flow relation generated, the mean of each of these values was calculated for all of the cardiac cycles studied.

All data are expressed as mean and SD. Statistical comparisons were performed by one-way analysis of variance with repeated measures (Winer, 1971) and the Newman-Keuls test for multiple comparisons (Zar, 1974), or two-way analysis of variance with replication (Zar, 1974), where appropriate. Correlation coefficients were also compared. However, since the distribution of correlation coefficients is non-Gaussian, these data were compared after transformation with Fisher's z-transformation (Snedecor and Cochran, 1980).

Experimental Protocols

Twelve dogs were successfully instrumented and studied; each dog was used in more than one experimental protocol, although within each protocol, no dog was used more than once. Before a dog was used for another protocol, at least 48 hours were allowed after adrenergic antagonists had been given, and at least 24 hours were allowed after protocols with adrenergic agonists, volume loading, or complete coronary occlusion.

Resting Adrenergic Tone

In nine dogs, coronary artery pressure-flow relations were generated before (Control) and after β-adrenergic blockade with propranolol (1 mg/kg, iv). Subsequently, α-adrenergic blockade was added by giving phenolamine (0.3 mg/kg, iv), and pressure-flow relations were again determined. At the conclusion of the protocol, the adequacy of β-adrenergic blockade was confirmed by noting the absence of response of maximum (+) LV dP/dt and the atrial rate to isoproterenol (0.3 μg/kg, iv); the adequacy of α-adrenergic blockade was tested by slowly infusing norepinephrine (0.3 μg/kg, iv) and noting the absence of an increase in aortic pressure.

In nine dogs, the foregoing sequence was reversed. Control coronary artery pressure-flow relations were generated; α-adrenergic blockade was produced with phenolamine (0.3 mg/kg, iv), and again pressure-flow relations were determined. Subsequent β-adrenergic blockade was produced with propranolol (1 mg/kg, iv) and a final set of pressure-flow relations was determined. At the conclusion of this protocol, the adequacy of β- and α-adrenergic blockade was confirmed as described.

In both protocols, data obtained with α- or β-adrenergic blockade alone were compared with control data, and data obtained after combined adrenergic blockade were compared with α- or β-adrenergic blockade alone using one-way analysis of variance with repeated measures and the Newman-Keuls test for multiple comparisons.

Effects of α-Adrenergic Agonist Stimulation

In seven dogs, control pressure-flow relations were determined and intracoronary infusion of phenylephrine (0.15 μg/kg per min) was begun. After a 5-minute equilibration period, pressure-flow relations were again determined; the phenylephrine dose then was increased to 0.3 μg/kg per min and after another 5-minute equilibration period, pressure-flow relations were again determined. In seven dogs, β-adrenergic blockade was first produced with propranolol (1 mg/kg, iv); control pressure-flow relations then were determined, and the protocol with phenylephrine infusion was carried out. Adequacy of β-adrenergic blockade was confirmed as described. Results obtained during phenylephrine infusion at each dose were compared to their respective control data by one-way analysis of variance with repeated measures and the Newman-Keuls test for multiple comparisons. The effect of β-adrenergic blockade on the changes in a given parameter produced by phenylephrine was tested by two-way analysis of variance with replication.

Effects of β-Adrenergic Agonist Stimulation

In seven dogs, coronary artery pressure-flow relations were determined before (control) and after intravenous administration of isoproterenol (0.03 μg/kg per min). Data obtained before and after isoproterenol were compared by one-way analysis of variance with repeated measures.

Effects of LAD Occlusion

To assess the possible contribution of collateral flow to circumflex coronary artery pressure-flow relations, four of
the 12 dogs studied were also instrumented with hydraulic occluders on the proximal left anterior descending (LAD) coronary artery. Control pressure-flow relations were generated. A second set of pressure-flow relations then was generated by first setting circumflex pressure to the desired level, then briefly completely occluding the LAD artery and recording data. This was repeated 12-14 times to generate a pressure-flow relation.

**Effect of Volume Loading**

In some dogs, β-adrenergic blockade with propranolol produced small, 1-3 mm Hg increases in LV end-diastolic pressure. To determine whether small increases in filling pressure influence pressure-flow relations in this model, data were obtained in three dogs before and after incremental administration of warm, fresh dog blood in amounts sufficient to produce 1-3 mm Hg increases in LV end-diastolic pressure (50-250 ml).

**Results**

All 12 dogs studied were healthy throughout the period of study, as evidenced by lack of fever, cough, or wound infection. Mean hematocrit was 40.5 (so 7.2)% and mean arterial blood gases were P02: 87.8 (so 8.7) mm Hg, Pco2: 32.1 (so 4.8) mm Hg, and pH: 7.38 (so 0.03). Intracoronary adenosine at the dose selected in this study consistently produced complete vasodilation as evidenced by the absence of reactive hyperemia following temporary coronary occlusion or by lack of flow increases to a supplemental, bolus intracoronary dose of adenosine. The regression of average diastolic flow increases to a supplemental, bolus intracoronary dose of adenosine. The regression of average diastolic flow increases to a supplemental, bolus intracoronary dose of adenosine.

Coronary pressure-flow relations were generated and described assuming a linear model. In six of the 12 dogs studied, there was slight curvature in the diastolic pressure-flow relation, particularly at low perfusion pressures, a phenomenon described by Klocke et al. (1981). In these dogs, all diastolic pressure-flow relations generated were also analyzed by fitting to a second-order curvilinear model (Snedecor and Cochran, 1980). For the six dogs that demonstrated slight curvilinearity, second-order curve fitting produced a small second-order term (0.01 to 0.06) and increased the correlation coefficient only from 0.96 (so 0.01) to 0.97 (so 0.02); this difference was not statistically significant. Curvilinearity can cause overestimation of Pr-o; however, this potential error was minimized by including data points at very low pressures and flows (Klocke et al., 1981).

Control diastolic Pr-o for all protocols varied from 12.9 to 31.3 mm Hg with a standard deviation of 5.3 mm Hg. Within each dog, however, when examined on different days, control diastolic Pr-o varied less, with a mean standard deviation for 12 dogs of 2.3 mm Hg. Similarly, control diastolic slopes ranged from 1.9 to 6.8 ml/min per mm Hg, with a standard deviation of 1.8 ml/min per mm Hg; there was less variation of diastolic slope in each dog on different days with a mean standard deviation of 0.4 ml/min per mm Hg. Since different groups of dogs were used for each protocol, the variations in control Pr-o and slope in different dogs resulted in variations in the mean values for control data.

**β-Adrenergic Blockade and Subsequent α-Adrenergic Blockade**

As summarized in Table 1, β-adrenergic blockade with propranolol during maximal adenosine-induced

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>β-Blockade</th>
<th>β-Blockade + α-blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic pressure-flow relations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr-o (mm Hg)</td>
<td>20.5 (4.7)</td>
<td>$24.7 (4.5)$</td>
<td>$20.5 (4.7)$</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>3.9 (1.8)</td>
<td>3.7 (1.7)</td>
<td>3.2 (1.5)</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.97 (0.03)</td>
<td>0.96 (0.06)</td>
<td>0.93 (0.04)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>37</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Mean pressure-flow relations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr-o (mm Hg)</td>
<td>21.9 (4.5)</td>
<td>$27.5 (6.4)$</td>
<td>$22.7 (5.7)$</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>3.0 (1.5)</td>
<td>2.8 (1.4)</td>
<td>2.3 (1.2)</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.97 (0.03)</td>
<td>0.93 (0.06)</td>
<td>0.94 (0.04)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>24</td>
<td>7</td>
<td>17</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>104.4 (14.2)</td>
<td>106.1 (15.4)</td>
<td>95.5 (10.7)</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>13.2 (3.0)</td>
<td>14.9 (2.6)</td>
<td>14.9 (2.7)</td>
</tr>
<tr>
<td>Maximum (+) LV dP/dt (mm Hg/sec)</td>
<td>3540 (890)</td>
<td>32670 (720)</td>
<td>2550 (660)</td>
</tr>
</tbody>
</table>

* = Mean coronary sinus pressure (mm Hg)

Mean (so); n = 9 (*n = 4); heart rate = 70 beats/min. One-way analysis of variance with repeated measures and the Newman-Keuls test: control vs. β-blockade ($\dagger P < 0.05$, $\ddagger P < 0.005$, $\S P < 0.001$); β-blockade vs. β-blockade + α-blockade ($\S P < 0.05$, $\S P < 0.025$). Abbreviation: LV = left ventricular.
vasodilation decreased coronary flow at all pressures, thus producing a right-shift in the pressure-flow relation, increasing diastolic $P_{\omega_0}$ by 20.5% above control, and maintaining constancy of slope; this increase in $P_{\omega_0}$ occurred despite the continued absence of a reactive hyperemia. Addition of $\alpha$-adrenergic blockade increased flow at all pressures, with the greatest increases occurring at lower pressures, thus producing a small but statistically significant decrease in calculated slope and decreasing $P_{\omega_0}$ back to control value. In this and subsequent tables, the average flows calculated at mean diastolic or mean full cycle coronary perfusion pressures of 30 mm Hg are given to exemplify the magnitudes of the differences in flows at low pressures with different adrenergic interventions. The changes in diastolic pressure-flow relations are illustrated by an example in Figure 1. Similar changes were noted for mean pressure-flow relations.

Of the nine preparations studied with $\beta$-adrenergic blockade, six had a small increase in LV end-diastolic pressure, two had no change, and one dog had a small decrease. These changes resulted in a small but statistically significant increase in mean LV end-diastolic pressure. There was no relation between the magnitude or direction of changes in end-diastolic pressure and the magnitude of the increases in $P_{\omega_0}$.

$\alpha$-Adrenergic blockade also produced a small, significant decrease (9.9%) in mean aortic pressure; with $\beta$-adrenergic blockade, maximum (+) LV $dP/dt$ decreased (32.6%). Four of the nine preparations studied also had coronary sinus catheters; there were no significant changes in mean coronary sinus pressure.

### a-Adrenergic Blockade and Subsequent $\beta$-Adrenergic Blockade

As shown in Table 2, $\alpha$-adrenergic blockade with phenolamine during maximal adenosine-induced vasodilation increased coronary flow at all pressures, thus decreasing diastolic $P_{\omega_0}$ by 12.9%. The greatest increases occurred at lower pressures, thus producing a 12.3% decrease in calculated diastolic slope which was statistically significant. Addition of $\beta$-adrenergic blockade decreased coronary flow at all pressures resulting in a parallel, right-shift in the pressure-flow relation toward the control line. The change in diastolic pressure-flow relations with $\alpha$- and subsequent $\beta$-adrenergic blockades are illustrated by an example in Figure 2. Similar changes were noted in mean pressure-flow relations.

$\alpha$-Adrenergic blockade produced a 14.4% decrease in mean aortic pressure and an increase (16.9%) in maximum (+) LV $dP/dt$; with subsequent $\beta$-adrenergic blockade, maximum (+) LV $dP/dt$ decreased 44.3%. In the four dogs that had coronary sinus catheters, there was no significant change in mean coronary sinus pressure.

### a-Adrenergic Agonist Stimulation without and with $\beta$-Adrenergic Blockade

In two groups of seven dogs, intracoronary phenylephrine was given at two doses without and with concurrent $\beta$-adrenergic blockade with propranolol; data are summarized in Table 3. Without $\beta$-adrenergic blockade, intracoronary phenylephrine at 0.15 µg/kg per min did not produce any change in coronary flow. At a higher dose, 0.3 µg/kg per min, there was a small increase in $P_{\omega_0}$ in four of the seven dogs studied; mean diastolic $P_{\omega_0}$ with this higher dose increased slightly (10.6%), but this increase was not statistically significant. In contrast, after $\beta$-adrenergic blockade, intracoronary phenylephrine at the two doses tested decreased coronary flow and produced significant increases in diastolic $P_{\omega_0}$, 13.1% and 19.3%, respectively. The effect of intracoronary phenylephrine on $P_{\omega_0}$ without $\beta$-adrenergic blockade was compared to the effect with $\beta$-blockade by two-way analysis of variance with replication; the effect of $\beta$-adrenergic
blockade on the changes in Pf-o produced by phenylephrine was significant at the \( P < 0.025 \) level. The changes in diastolic pressure-flow relations are illustrated by an example in Figure 3. Similar results were noted for mean pressure-flow relations.

In both groups of dogs, intracoronary phenylephrine at the doses used caused no significant changes in slope, correlation coefficient, mean aortic pressure, LV end-diastolic pressure, and maximum (+) LV dP/dt. In dogs that had coronary sinus catheters, there were no significant changes in mean coronary sinus pressure.

**β-Adrenergic Agonist Stimulation**

In seven dogs, coronary pressure-flow relations were generated during maximal adenosine-induced vasodilation before and after intravenous administration of isoproterenol; data are summarized in Table 4, and an example is shown in Figure 4. In all seven dogs studied, isoproterenol produced a small, consistent increase in coronary flow at all perfusion pressures, thus producing a small, parallel left-shift in the pressure-flow relation; the resulting 4.2% decrease in diastolic Pf-o was significant at the \( P < 0.05 \) level. Similar changes were noted for mean pressure-flow relations. There were no significant changes in slope or correlation coefficient. Isoproterenol also produced a significant 16.4% increase in maximum (+) LV dP/dt; there was a significant, 8.3% increase in LV end-diastolic pressure, possibly the result of isoproterenol-induced increases in venous return (Kaiser et al., 1964). There was a small, significant decrease in mean aortic pressure; in three dogs that had coronary sinus catheters, there was no significant change in mean coronary sinus pressure.

**Effects of LAD Occlusion and Volume Loading**

In all four dogs tested, LAD occlusion had no significant effect on Pf-o [diastolic: 19.2 (control) vs. 18.9 mm Hg] or the slope [diastolic: 5.0 (control) vs. 5.2 ml/min per mm Hg] of pressure-flow relations. Brief LAD occlusions during pressure-flow relations did not affect correlation coefficient, mean aortic pressure, LV end-diastolic pressure, maximum (+) LV dP/dt, or mean coronary sinus pressure.

In three dogs, incremental volume loading with small quantities of blood resulted in a mean increase in LV end-diastolic pressure of 2.7 mm Hg (\( P < 0.05 \)). In all three dogs tested, small increases in filling pressure did not affect Pf-o [diastolic: 26.3 (control) vs. 26.6 mm Hg] or the slope [diastolic: 3.2 (control) vs. 3.3 ml/min per mm Hg] of pressure-flow relations. There were no significant changes in correlation coefficient, mean aortic pressure, maximum (+) LV dP/dt, or mean coronary sinus pressure.

**Critique of the Methods**

The purpose of the present study is to examine changes produced by adrenergic agonists or antagonists in coronary flow during vasodilation produced by adenosine infusion, that is, when coronary flow has been uncoupled from myocardial metabolism. During maximal adenosine vasodilation, when flow is pressure-dependent and there is no autoregulatory plateau, changes in coronary flow may occur in response to changes in perfusion pressure or conductance. Hence, data based on flow determinations at a single point can be complicated by changes in perfusion pressure due to adrenergic interventions or due to spontaneous changes in aortic pressure that may...
Above are two graphs labeled A and B. Graph A shows the control pressure-flow relation, where diastolic flow increases with decreasing pressure. Following a-blockade, the flow decreases at all pressures, indicating a decrease in conductance. The slope of this relation is also decreased. In graph B, following a-blockade and after beta-blockade, the pressure-flow relation shifts to the right, indicating an increase in conductance and a decrease in the slope.

In the present study, adrenergic blockade decreased slope, although the apparent conductance decreased, there was never a functional consequence (decreased flow) in any dog. Therefore, in analyzing the data presented in this study, attention should be directed to increases or decreases in flow, rather than to specific changes in $P_{\text{f-o}}$ or slope.

The finding of a predominant effect of changes in adrenergic tone on $P_{\text{f-o}}$ does raise the question as to how this effect might be mediated. It is well established that $P_{\text{f-o}}$ is considerably higher than LV end-diastolic or coronary sinus pressures (Bellamy, 1978). The mechanism for this effect, however, remains controversial. The coronary vascular bed can be modeled as a series of collapsible tubes (Permutt and Riley, 1963) having active smooth muscle tone (Bellamy, 1978) that acts to promote collapse with decreasing pressure; this tendency to collapse is opposed by pressure in the lumen. Thus, at perfusion pressures above collapse pressure, flow is determined by the conductance properties of the coronary vasculature upstream from the collapse point. With decreasing perfusion pressure, flow ceases when the forces tending to collapse the vasculature (active tension plus extravascular compressive forces) exceed lumen pressure. This results in a model characterized by a vascular waterfall where smooth muscle tension influences the pressure at which collapse occurs ($P_{\text{f-o}}$). Bellamy (1978) clearly demonstrated that with metabolic vasodilation, there is a decrease in diastolic $P_{\text{f-o}}$, consistent with such a model. The findings of the present study are consistent with a waterfall hypothesis where adrenergically mediated changes in smooth muscle tone influence diastolic $P_{\text{f-o}}$; for example, increasing vasomotor tone with phenylephrine in the presence of $\beta$-coronary blockade increased diastolic $P_{\text{f-o}}$, and decreasing tone with $\alpha$-adrenergic blockade decreased diastolic $P_{\text{f-o}}$, both with the continued absence of reactive hyperemia.

In the beating heart, where the coronary vasculature is exposed to pulsatile pressure, capacitance of the extramural coronary arteries may give a falsely high value for $P_{\text{f-o}}$ because flow downstream to the flow transducer may continue as the artery discharges its contents even though flow is zero at the upstream flowmeter (Eng et al., 1982; Kirkeeide et al., 1981). Furthermore, Spaan et al. (1981) have suggested that, in systole, blood contained in intramural vessels is pumped both backward and forward so that systolic intramyocardial capacitance may play some part in regulating coronary flow. We believe that these capacitative effects did not affect our results or interpretations for two reasons. Although flows early in diastole may be influenced by capacitance, these effects are less, later in diastole (Klocke et al., 1981). Thus, using a slow heart rate should minimize the capacitative contribution to averaged diastolic data. More important is the fact that both mean diastolic and mean full cycle coronary pressure-flow relations yielded similar changes in slopes and $P_{\text{f-o}}$ with the different agents used in each protocol; averaging over the cardiac cycle effectively cancels effects due to fit.

**FIGURE 2.** An example of the effects of $\alpha$-adrenergic blockade and subsequent $\beta$-adrenergic blockade on diastolic flow during maximal vasodilation in one preparation. In panel A, the control pressure-flow relation is shown in open circles ($P_{\text{f-o}}$ 24.9 mm Hg; slope 5.5 ml/min per mm Hg; $r = 0.98$). Following $\alpha$-blockade (filled circles), note the increase in flow and left-shift of the pressure-flow relation ($P_{\text{f-o}}$ 20.7 mm Hg; slope 5.0 ml/min per mm Hg; $r = 0.98$). In panel B, the pressure-flow relation following $\alpha$-adrenergic blockade is reproduced (filled circles); note the decrease in flow and right-shift of the pressure-flow relation after addition of $\beta$-adrenergic blockade (open triangles) ($P_{\text{f-o}}$ 23.2 mm Hg; slope 5.2 ml/min per mm Hg; $r = 0.98$).
phasic charging and discharging of extramural or intramural coronary vascular capacitances.

We chose for three reasons to examine average diastolic pressure-flow relations even though they may be influenced by capacitative effects. In diastole, the large effects of systolic intramyocardial pressure are absent; the bulk of coronary blood flow occurs in diastole, particularly to the subendocardial muscle, and in some circumstances mean flow alone gives misleading information about the distribution of coronary blood flow if the proportions of systolic and diastolic coronary blood flow are altered (Hoffman and Buckberg, 1976). Thus, analyses of both average diastolic and mean full cycle flows and pressures are likely to be more useful than either one alone.

Intramyocardial compressive forces can influence coronary pressure-flow relations, particularly systolic pressure-flow relations in the beating heart (Downey and Kirk, 1975). Interventions that change contractility can therefore influence pressure-flow relations, particularly during systole (L'Abbate et al., 1978; Marzilli et al., 1979). In the present study, this possibility was minimized by examining pressure and flow during diastole; however, the influence of systolic compressive forces on diastolic pressure-flow relations is unknown, but must be considered. The findings of L'Abbate et al. (1978) and Marzilli et al. (1979) would predict that interventions that increase contractility would produce a right-shift in the pressure-flow relation, and, conversely, interventions that decrease contractility would produce a left-shift. In the present study, both isoproterenol and \( \alpha \)-adrenergic blockade decreased contractility but resulted in decreased flow at all pressures. \( \beta \)-Adrenergic blockade increased coronary flow at all pressures. Decreases in (+) LV dp/dt or in regional myocardial function in the circumflex distribution could also result from ischemia during the occlusions used to generate pressure-flow relations. To minimize this possibility, occlusions were kept as brief as possible, particularly at low flows. Furthermore, circumflex flow during autoregulation in this preparation with a heart rate of 70 beats/min was approximately 25 ml/min. Thus, as shown in Figures 1-4, most of the points used to generate each pressure-flow relation occurred at flows greater than 70 beats/min and were not likely to be within ischemic range. Even if the lines had not been carried down to near-zero flow, the flow changes observed in the upper parts of each line are consistent with the data obtained using all of the points. Thus, these findings support the hypothesis that the observed changes in \( P_{\text{E,0}} \) were not mediated through ischemia-induced changes in intramyocardial pressure.

Circumflex pressure-flow relations could also be influenced by collateral flow from the LAD coronary artery distribution. In the present study, this possibil-

### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Without ( \beta )-adrenergic blockade</th>
<th>With ( \beta )-adrenergic blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Phenylinephrine (0.15) µg/kg per min</td>
<td>Phenyl-e-ephine (0.30) µg/kg per min</td>
</tr>
<tr>
<td>Diastolic pressure-flow relations</td>
<td>18.0 (5.8)</td>
<td>18.7 (4.4)</td>
</tr>
<tr>
<td>( P_{\text{E,0}} ) (mm Hg)</td>
<td>2.7 (0.8)</td>
<td>2.7 (1.1)</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>0.94 (0.05)</td>
<td>0.93 (0.11)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>32</td>
<td>31</td>
</tr>
<tr>
<td>Mean pressure-flow relations</td>
<td>22.7 (6.3)</td>
<td>23.0 (6.4)</td>
</tr>
<tr>
<td>( P_{\text{E,0}} ) (mm Hg)</td>
<td>2.1 (0.5)</td>
<td>2.1 (0.6)</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>0.95 (0.05)</td>
<td>0.93 (0.08)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>109.2 (13.0)</td>
<td>108.0 (6.9)</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>14.0 (3.6)</td>
<td>13.3 (3.7)</td>
</tr>
<tr>
<td>Maximum (+) LV dp/dt (mm Hg/sec)</td>
<td>3700 (890)</td>
<td>3840 (880)</td>
</tr>
<tr>
<td>* Mean coronary sinus pressure (mm Hg)</td>
<td>4.5 (3.9)</td>
<td>3.7 (2.7)</td>
</tr>
</tbody>
</table>

Mean (SD); \( n = 7 \) (* \( n = 3 \)); heart rate = 70 beats/min. One-way analysis of variance with repeated measures and the Newman-Keuls test: control vs. phenylephrine (+ \( P < 0.01 \), ± \( P < 0.005 \)); two-way analysis of variance with replication, effect of intracoronary phenylephrine on \( P_{\text{E,0}} \) without beta blockade vs. effect with beta blockade (‡ \( P < 0.025 \)).
Figure 3. Examples of the effects of $\alpha$-adrenergic agonist stimulation on diastolic flow during maximal vasodilation. Panel A: diastolic coronary pressure-flow relations without $\beta$-adrenergic blockade in one preparation. The control pressure-flow relation is shown with open circles ($P_f = 12.6$ mm Hg; slope 3.6 ml/min per mm Hg; $r = 0.97$). During $\alpha$-adrenergic agonist stimulation with intracoronary phenylephrine (0.3 $\mu$g/kg per min), there was little change in the pressure-flow relation (filled circles) ($P_f = 12.0$ mm Hg; slope 3.6 ml/min per mm Hg; $r = 0.98$). Panel B: Diastolic coronary pressure-flow relations with concurrent $\beta$-adrenergic blockade in another preparation. The control pressure-flow relation is shown in open triangles ($P_f = 21.5$ mm Hg; slope 4.0 ml/min per mm Hg; $r = 0.98$). With $\alpha$-adrenergic agonist stimulation in the presence of $\beta$-adrenergic blockade, there is a right-shift in the pressure-flow relation (filled triangles) ($P_f = 24.1$ mm Hg; slope 3.9 ml/min per mm Hg; $r = 0.99$).

The $\beta$-adrenergic agonist stimulation during maximal vasodilation was tested by generating pressure-flow relations before and during LAD occlusions and demonstrating no change in $P_f = 0$ or slope; similar results were obtained by Verrier et al. (1980) in an anesthetized model. These results support the fact that, in the present study, it is unlikely that there was significant collateral contribution to circumflex pressure-flow relations.

Prolonged adenosine infusion may produce late decreases in coronary resistance. L'Abbate et al. (1981) have shown in acute studies that, when adenosine is infused continuously in doses 2 to 9 times those used in the present study, there is a further decrease in resistance by 30–60 minutes. In the present study, adenosine was infused in pilot studies for as long as 1 hour with stability of both $P_f = 0$ and slope. Furthermore, all experimental protocols were completed in less than 1 hour, with most protocols requiring less than 30 minutes, thus minimizing the possibility of late changes in pressure-flow relations from prolonged adenosine infusion.

Phentolamine was selected because it is a specific $\alpha$-adrenergic agonist and has an adequately short half-life to prevent cumulative systemic effects over the time required to complete each protocol. Its properties as an inotropic agent become apparent only at doses several orders of magnitude greater than those used in the present study (Verma and McNeill, 1976). Furthermore, in early pilot studies, phentolamine was infused in the presence of both $\alpha$- and $\beta$-adrenergic blockades and there was no effect on flow. Thus, it is likely that the observed effects are specific to its $\alpha$-adrenergic agonist properties.

Phentolamine can vasodilate by acting directly on vascular smooth muscle as well as by blocking $\alpha$-adrenergic or serotoninergic receptors. However, at the high doses used in our study it is likely that $\alpha$-adrenergic blockade was produced. This conclusion is supported by the lack of response to infused noradrenaline in these dogs after phentolamine had been given, as well as by the similarity of our results.

### Table 4

$\beta$-Adrenergic Agonist Stimulation during Maximal Vasodilation

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic pressure-flow relations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_f = 0$ (mm Hg)</td>
<td>26.0 (2.9)</td>
<td>$\pm$24.9 (2.8)</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>4.6 (1.3)</td>
<td>4.3 (0.8)</td>
</tr>
<tr>
<td>Correlation coefficient ($r$)</td>
<td>0.98 (0.01)</td>
<td>0.98 (0.01)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Mean pressure-flow relations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P_f = 0$ (mm Hg)</td>
<td>27.1 (2.5)</td>
<td>$\pm$26.0 (2.5)</td>
</tr>
<tr>
<td>Slope (ml/min per mm Hg)</td>
<td>3.7 (1.0)</td>
<td>3.6 (0.6)</td>
</tr>
<tr>
<td>Correlation coefficient ($r$)</td>
<td>0.98 (0.01)</td>
<td>0.98 (0.01)</td>
</tr>
<tr>
<td>Calculated maximal flow at 30 mm Hg (ml/min)</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>112.6 (8.0)</td>
<td>$\pm$103.1 (11.1)</td>
</tr>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>16.7 (4.9)</td>
<td>18.1 (5.1)</td>
</tr>
<tr>
<td>Maximum (+) LV dp/dt (mm Hg/sec)</td>
<td>3180 (210)</td>
<td>$\pm$3700 (380)</td>
</tr>
</tbody>
</table>

* Mean coronary sinus pressure (mm Hg)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic pressure (mm Hg)</td>
<td>16.7 (4.9)</td>
</tr>
<tr>
<td>Maximum (+) LV dp/dt (mm Hg/sec)</td>
<td>3180 (210)</td>
</tr>
</tbody>
</table>

Mean (SD); $n = 7$ (* $n = 3$); heart rate = 70 beats/min. One-way analysis of variance with repeated measures: control vs. isoproterenol ($P < 0.05$, $\pm P < 0.025$, $\parallel P < 0.01$).
to those obtained with a more specific α-adrenergic blocking agent, phenoxybenzamine (Feigl, 1967).

A more complex issue is whether the results obtained with propranolol were due to blockade of coronary vascular β-adrenergic receptors or secondary to its effects on myocardial contractility and metabolism. Studies in intact dogs with practolol, a selective β₁-adrenergic blocking agent, have shown that in low doses it blocks the myocardial contractile response but not coronary vasodilation to infused isoproterenol (Ross and Jorgensen, 1970; McRaven et al., 1971). Higher doses of practolol (Ross and Jorgensen, 1970) or propranolol (McRaven et al., 1971) abolish the coronary vasodilating effect of isoproterenol. These findings indicate that the coronary arteries have β₂-adrenergic receptors that can be stimulated to cause vasodilation that is not secondary to changes in myocardial contractility. On the other hand, studies of isolated coronary arteries of dogs, (Baron et al., 1972), pigs (Johansson, 1973) and kittens (Cornish and Miller, 1975) all indicate strongly that the coronary arteries have β₁-adrenergic receptors. Whether the differences are due to a preponderance of β₂-adrenergic receptors in the small intramural coronary arteries and arterioles or to complex interactions among vessels, nerves, and myocardium is not known.

We avoided problems of which type of vascular β-adrenergic receptor to block by using propranolol, a non-specific blocker of both β₁- and β₂-adrenergic receptors. However, since propranolol also affects myocardial function and oxygen demand, it is important to determine whether its effect was primarily on the vascular bed, or secondary to changes in myocardial metabolism. In favor of the primary vascular mechanism is the fact that during β-adrenergic blockade heart rate and arterial pressure were not changed. There was a fall in maximum (+) LV dP/dt, but this might not be an important factor for two reasons. Some recent studies by Thomas et al. (1981) concluded that both β₁ and non-specific β-adrenergic blocking agents exert their effect on myocardial oxygen consumption by changing heart rate and blood pressure rather than by a direct effect on myocardial metabolism. Second, as discussed above, changes in contractility could not explain the results obtained. Similar conclusions were reached by Nayler et al. (1967) who found that propranolol caused an increased coronary vascular resistance in a beating but non-working heart on cardiopulmonary bypass, and by Feigl (1975) who showed that the coronary vasoconstriction produced by propranolol could be abolished by α-adrenergic blockade which did not change myocardial oxygen consumption. Finally, in adenosine-vasodilated coronary vascular beds that were examined in these studies, coronary flow is not determined by myocardial metabolism. The conclusion therefore is that the coronary vascular effects seen in these studies were due entirely to blockade of coronary vascular β-adrenergic receptors.

The decrease in flow at a given pressure during β-adrenergic blockade occurred despite continued infusions of adenosine and the absence of a reactive hyperemic response to transient coronary occlusion. These findings may mean that coronary vessels are still maximally dilated after the adrenergic blockade so that the reduced flows must be due to mechanisms unrelated to geometric factors that determine vascular conductance. If this is so, then the similarity of slopes of the pressure-flow relations before and after β-adrenergic blockade may be interpreted literally as showing no change in conductance. On the other hand, absence of reactive hyperemic responses may also coexist with vessels that are indeed narrowed but in some way no longer responsive to the doses of...
adrenergic Influence in the Coronary Circulation

Discussion

In conscious dogs with constant heart rate, adrenergic antagonists or agonists can produce changes in coronary flow despite maximal adenosine-induced coronary vasodilation and the attendant absence of reactive hyperemia. β-Adrenergic blockade with propranolol decreased coronary flow at all pressures, resulting in a parallel right-shift in the pressure-flow relation and a 4.2 mm Hg increase in diastolic P\(_{\text{end}}\). Previous investigators have suggested that β-adrenergic tone may be an important determinant of the limit to which blood flow can increase with increasing demand (Cobb et al., 1969, 1973), whereas other investigators have failed to show any resting β-adrenergic tone when examined in hearts with intact autoregulation (Mueller et al., 1980; Chilian et al., 1981; Vatner and Hintze, 1981). The present study during adenosine infusion supports the hypothesis that β-adrenergic tone is present and provides direct evidence for its influence on maximal flow. This effect is demonstrated by changes primarily in P\(_{\text{end}}\) and not by changes in coronary vascular conductance.

β-adrenergic blockade also produced small increases in LV end-diastolic pressure. Ellis and Klocke (1980) have shown that increases in preload can increase P\(_{\text{end}}\). They demonstrated in anesthetized dogs that a 14 mm Hg mean increase in left atrial pressure was necessary to produce a 4 to 7 mm Hg mean increase in P\(_{\text{end}}\). To test the possibility that small increases in LV end-diastolic pressure following β-adrenergic blockade might have contributed to the increase in P\(_{\text{end}}\), three dogs were studied before and after volume loading to produce small increases in LV end-diastolic pressure similar to those seen with β-adrenergic blockade. There was no significant effect on P\(_{\text{end}}\) or slope. Furthermore, β-adrenergic blockade did not increase LV end-diastolic pressure in all dogs, although P\(_{\text{end}}\) did increase in all dogs; thus, it is unlikely that small changes in preload significantly influenced coronary flow in this study.

The decrease in maximal flow with β-adrenergic blockade was reversed by adding α-adrenergic blockade. This suggests that the flow decrease resulted from blocking β-adrenergically mediated vasodilation, hence unmasking tonic α-adrenergic vasoconstriction.

When α-adrenergic blockade is produced alone during maximal adenosine-induced vasodilation, flow increases, suggesting that tonic α-adrenergic constriction tone is present. The ability to decrease flow subsequently with β-adrenergic blockade suggests that α-adrenergic blockade unmasks β-adrenergic vasodilation, thus increasing maximal flow. α-Adrenergic blockade produced the greatest increases in flow at lower perfusion pressures, with smaller increases at higher perfusion pressures. The net effect of this difference was to decrease P\(_{\text{end}}\) and to produce a small decrease in calculated slope. However, in no dog did α-adrenergic blockade produce a decrease in flow at any perfusion pressure as compared with control.

Other investigators have examined the possible role of α-adrenergic vasoconstriction in the coronary circulation. Feigl (1967) and Granata et al. (1965) observed that sympathetic nerve stimulation produced a transient decrease in flow in the autoregulating coronary circulation. Feigl (1967) demonstrated that this transient decrease could be blocked by phenoxybenzamine, suggesting that it was mediated through α-adrenergic vasoconstriction. Schwartz and Stone (1977) concluded that α- and β-adrenergic activities were present in the coronary circulation during reactive hyperemia following brief coronary occlusions. They demonstrated that the repayment of the flow debt incurred during occlusion could be decreased by propranolol and increased by phentolamine; these results are consistent with the findings of the present study where adenosine-induced maximal flow was similarly altered by adrenergic blocking agents. Johannsen et al. (1982) also used maximal adenosine-induced vasodilation to study α-adrenergic influences on the coronary circulation. In anesthetized dogs, they blocked β-adrenergic receptors with propranolol and infused vasoactive agents (phenylephrine, norepinephrine, tyramine, angiotensin) and also stimulated the cardiac sympathetic nerves. They observed decreased flows at constant perfusion pressures, and concluded that coronary arteries maximally dilated with adenosine were responsive to the vasoconstrictor effects of these stimuli. Their findings in general are similar to ours. However, no previous study has demonstrated that adrenergic tone exerts a predominant effect through changes in P\(_{\text{end}}\).

It should be noted that a decrease in maximal flow produced by β-adrenergic blockade with propranolol does not negate the clinical usefulness of propranolol in patients with angina pectoris. In the clinical setting, lowered heart rate and myocardial oxygen demand might improve the myocardial oxygen supply-demand balance despite a reduced maximal flow at any given pressure. On the other hand, occasional reports of worsening angina after propranolol could imply that flow was decreased out of proportion to the fall in myocardial oxygen demand.

The changes in P\(_{\text{end}}\) were small compared with perfusion pressure, but the relative effects on maximal flow may be important, particularly at lower perfusion pressures. This can be illustrated by sample calculations using the mean values for diastolic P\(_{\text{end}}\) and slope before and after β- and α-adrenergic blockade shown in Tables 1 and 2. At a perfusion pressure of 50 mm Hg, β blockade produces a 19% decrease in maximal flow from a control value of 115 ml/min. At a perfusion pressure of 30 mm Hg, however, flow decreases 47% from control. Similarly, at a perfusion pressure of 50 mm Hg, α-adrenergic blockade produces a small, 1% increase in maximal diastolic flow.
above a control value of 101 ml/min; however, at a perfusion pressure of 30 mm Hg, a-blockade produces a 36% increase in flow. Thus, tonic adrenergic influence in the coronary circulation may become potentially important with a decreased coronary perfusion pressure, for example, during hypotension or distal to a coronary stenosis, when coronary vascular reserve is exhausted and autoregulation is absent. This is illustrated in Tables 1-4 by calculations of mean diastolic and mean maximal flows at 30 mm Hg perfusion pressure.

Coronary vascular reserve can also be exhausted by increasing flow demand. Feigl (1975), Mohrman and Feigl (1978), and Buffington and Feigl (1981) have suggested that adrenergic vasoconstriction is capable of competing with the metabolic factors that produce vasodilation in response to changes in demand. In the present study, changes in P_{eq} occurred despite the continued absence of reactive hyperemia. If the mechanism that produces reactive hyperemia in response to coronary occlusion is similar to that which increases flow in response to increasing metabolic demand, then the findings of the present study suggest that adrenergic influence might therefore alter the extent to which flow can increase in response to increasing demand, and further suggests that adrenergically mediated changes in P_{eq} cannot be countered by metabolic factors.

Finding an influence of α- and β-adrenergic stimulation or blockade on flow in a coronary vascular bed that is maximally dilated by adenosine infusion does not indicate how the autoregulated coronary vascular bed would react. However, it is appropriate to point out that ischemia in a region does not usually occur until coronary vascular reserve is exhausted, and thus implies maximal vasodilation in that region. Although adenosine-induced and ischemia-induced coronary vasodilation may not be identical, in a few dogs we failed to see reactive hyperemia after we had occluded the coronary artery for 30 seconds; this would certainly be enough time for other metabolites to act on the coronary vessels if they were capable of further dilation. Therefore adrenergic effects that might promote or limit coronary vascular reserve are important and can legitimately be studied during maximal adenosine-induced vasodilation on the assumption that this indeed resembles metabolically induced maximal vasodilation.

The effects of both blocking agents demonstrate that both tonic α- and β-adrenergic tone are present in the coronary circulation, and that they can exert influences on maximal coronary flow despite adenosine-induced vasodilation. Combined α- and β-adrenergic blockade tended to return the pressure-flow relations toward control. This suggests that in the control state the effects of tonic α- and β-adrenergic activity approximately balance each other.

In the present study, further pharmacological β-adrenergic stimulation with isoproterenol at a dose of 0.03 μg/kg per min produced only a modest further increase in coronary flow. In two dogs in the present study, the isoproterenol dose was also increased to 0.075 μg/kg per min without a further increase in flow. These results suggest that tonic β-adrenergic vasodilating activity in this model is already nearly maximal, as evidenced by the small effect produced by adding further β-adrenergic stimulation.

Tonic β-adrenergic vasodilating tone may be important for maintaining coronary vascular reserve when demand increases (Cobb et al., 1969, 1973; Murray and Vatner, 1979). β-Adrenergic tone may also be important in modifying the deleterious effects of increases in coronary α-adrenergic activity. Intracoronary phenylephrine failed to produce changes in maximal flow unless β-adrenergic blockade was present. Phenylephrine was continuously infused into the circumflex coronary artery distribution at the fixed rates selected in this study. However, the concentration of phenylephrine reaching the coronary vasculature was a function of the coronary flow rate; therefore, interventions that affect flow rate can result in changes in the delivered concentration of this agonist. Thus, the brief, partial coronary occlusions used to generate pressure-flow relations likely resulted in transient, brief increases in delivered phenylephrine concentration. Despite this, intracoronary phenylephrine at the doses selected in this study did not result in significant decreases in maximal coronary flow unless β-adrenergic blockade was present; this suggests that tonic β-adrenergic activity might protect the coronary circulation from decreases in maximal flow produced by circulating catecholamines or increased sympathetic nerve activity.

Conclusions

Our conclusions are as follows: (1) Adrenergic activity can produce changes in coronary flow despite maximal adenosine vasodilation and the absence of reactive hyperemia. (2) Significant α- and β-adrenergic tone can be demonstrated in the coronary circulation of conscious dogs after the effects of metabolic autoregulation are removed by intracoronary adenosine infusion. (3) Resting β-adrenergic tone is near-maximal, as evidenced by only a small increase in flow at any given pressure in the maximally dilated coronary bed produced by β-adrenergic agonist stimulation. (4) Resting β-adrenergic tone may protect the coronary circulation from decreases in maximal flow produced by increased sympathetic nerve activity or circulating catecholamines. (5) Changes in maximal coronary flow produced by adrenergic activity are mediated primarily through changes in P_{eq} rather than through changes in coronary vascular conductance if current interpretations of the pressure-flow ratios are correct.

We thank Judith Jester for her excellent technical assistance and support, Les Williams for his expertise in electronics, Susan Axelrod and Kathy Storer for assistance in preparing this manuscript, and Dr. Edward Certz for supplying the pacemaker. Propranolol (Inderal) was generously supplied by Ayerst Laboratories, and...
fibrinolysin (Thrombolysin) was generously supplied by Merck, Sharp, & Dohme Research Laboratories.

Presented, in part, at the 54th Annual Scientific Sessions of the American Heart Association, Dallas, Texas, November 1981.

Supported by a grant from the U.S. Public Health Service, Program Project Grant HL4056 from the National Heart, Lung, and Blood Institute.

Dr. Vlahakes was supported by the American Heart Association, California Affiliate, Research Fellowship No. 80-N25A, with funds contributed by the Central Mission Trails Chapter. His present address is: Department of Surgery, Massachusetts General Hospital, Boston, Massachusetts 02114.

Dr. Bristow’s present address is: Division of Cardiology, Oregon Health Sciences University, Portland, Oregon 97201.

Address for reprints: Julien I.E. Hoffman, M.D., University of California, San Francisco, California 94143.

Received June 22, 1981; accepted for publication June 10, 1982.

References


Downey JM, Kirk ES (1975) Inhibition of coronary blood flow by a vascular waterfall mechanism. Circ Res 36: 753–760


Horowitz SL (1980) An integrated, interactive, user-oriented biomedical data acquisition, processing, and display system.

Ph.D. Dissertation, University of California, Berkeley


INDEX TERMS: Neural control • α-Adrenergic tone • β-Adrenergic tone • Propranolol • Phentolamine
Adrenergic influence in the coronary circulation of conscious dogs during maximal vasodilation with adenosine.
G J Vlahakes, R W Baer, P N Uhlig, E D Verrier, J D Bristow and J I Hoffmann

Circ Res. 1982;51:371-384
doi: 10.1161/01.RES.51.3.371

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/51/3/371.citation