Effects of Norepinephrine on Coronary Circulation and Left Ventricular Dynamics in the Conscious Dog

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ABSTRACT

The effects of norepinephrine (0.1 and 1.0 μg/kg, iv) on coronary blood flow and resistance, left ventricular pressure and diameter, dP/dt, (dP/dt)/P, and the velocity (V<sub>iso</sub>) of myocardial fiber shortening were studied in conscious dogs. When the heart rate was held constant, norepinephrine caused an initial reduction in coronary vascular resistance which was associated with increases in mean arterial blood pressure, systolic left ventricular pressure, end-diastolic diameter, dP/dt, (dP/dt)/P, and V<sub>iso</sub>. After this brief coronary vasodilator response, a sustained increase occurred in mean coronary vascular resistance (+0.55 ± 0.07 mm Hg/ml min<sup>-1</sup>), and increases persisted in mean arterial blood pressure (+67 ± 7 mm Hg), left ventricular systolic pressure (+74 ± 6 mm Hg), left ventricular end-diastolic pressure (+4 ± 1 mm Hg), left ventricular internal diameter (+1.3 ± 0.3 mm), peak dP/dt (+1660 mm Hg/sec), (dP/dt)/P (+15 ± 2 sec<sup>-1</sup>), and V<sub>iso</sub> (+11 ± 2 mm/sec); coronary sinus Po<sub>2</sub> decreased. Beta-receptor blockade prevented the inotropic effects of norepinephrine, attenuated the early coronary vasodilator effects, and increased the late vasoconstrictor effects. Alpha-receptor blockade abolished the late coronary vasoconstrictor effects of norepinephrine; only dilatation occurred. In contrast to the effects of norepinephrine in conscious dogs without autonomic blockade, norepinephrine (1.0 μg/kg, iv) failed to produce late coronary vasoconstriction in anesthetized, open-chest dogs; only dilatation occurred. Thus, in the normal, conscious dog, norepinephrine exerts an important coronary vasoconstrictor effect which is sufficiently intense to counteract completely the simultaneous tendency toward metabolic vasodilatation.

KEY WORDS catecholamines alpha receptors beta receptors coronary vasoconstriction myocardial contractility left ventricular diameter

Norepinephrine exerts a direct constricting effect on coronary vessels mediated by activation of alpha receptors (1-6) and a direct dilating effect mediated by activation of beta receptors (4-9). It is widely held that these direct effects are overshadowed in the beating heart by the metabolic coronary vasodilatation induced by norepinephrine's powerful stimulation of myocardial oxygen consumption, which results from increases in ventricular pressure and contractility (1-6, 8). However, this concept is based largely on studies in anesthetized animal preparations (1, 2, 4-8); norepinephrine's action could be altered by the effects of the anesthetic agent and the open chest. Other cardioactive agents have substantially different actions in conscious and anesthetized animals (10-14), and the effects of norepinephrine on the left ventricle and the coronary vessels in normal, unanesthetized animals could differ from those observed in anesthetized, open-chest preparations. In a previous study in conscious dogs (3), only coronary vasodilatation was observed when norepinephrine was administered; however, that study only reported peak responses. Therefore, responses occurring later, when inotropic stimulation has subsided and alpha-adrenergic effects are not overshadowed to such a great extent by increases in ventricular pressure and contractility, should also be studied. Accordingly, in this investigation, we administered norepinephrine to healthy, conscious dogs instrumented for direct, continuous measurement of left circumflex coronary blood flow, left ventricular and systemic arterial pressures, left ventricular diameter, dP/dt, and the velocity of myocardial...
fiber shortening. The goal of the present study was to clarify noradrenalin's normal action by comparing its effects when it was administered (1) intravenously in a bolus or an infusion, (2) before and after administration of selective alpha- and beta-receptor blocking agents, and (3) before and after induction of hypoxia. Results following administration of noradrenalin to intact, conscious animals were also compared with those following administration to anesthetized animals with an open chest.

Methods

Twelve mongrel dogs (24–34 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv) and a thoracotomy was performed in the fifth left intercostal space. Miniature Konigsberg P22 pressure gauges were implanted within the left ventricle through a stab wound in the apex (10 dogs). Opposing ultrasonic diameter transducers were sutured to the epicardium of the anterior and posterior walls of the left ventricle (6 dogs) or implanted on opposing endocardial surfaces of the left ventricle (4 dogs), and Doppler ultrasonic transducers (10 dogs) or Statham SP2000 electromagnetic transducers (2 dogs) were placed around the left circumflex coronary artery. Stimulating electrodes were sutured to the left ventricle (10 dogs), and heparin-filled Tygon catheters were chronically implanted in the posterior descending artery (12 dogs). During a subsequent operation, 4 dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv) and a right thoracotomy was performed; heparin-filled Tygon catheters were implanted in the coronary sinus. Five additional dogs were anesthetized with sodium pentobarbital (30 mg/kg, iv) and studied with their chests open immediately after placement of Statham SP200 electromagnetic flow transducers on the left circumflex coronary artery, Konigsberg P22 miniature pressure gauges in the left ventricle, and catheters in the aorta.

The miniature pressure gauges were calibrated in vivo against a calibrated Statham P23Db strain-gauge manometer. At autopsy the position of the ventricular gauges within the ventricular cavity was confirmed. Arterial blood pressure was sampled with the previously implanted heparin-filled Tygon catheter and measured with a Statham P23Db strain-gauge manometer. Left circumflex coronary blood flow was measured with an ultrasonic Doppler flowmeter in eight dogs. This system, which has been described in detail previously, has a reliable zero reference (15, 16). In the present experiments, the electrical zero blood flow was determined repeatedly and was confirmed by calibration terminally. The relationship between velocity, as measured by the Doppler flowmeter, and volume flow is linear as long as the cross-sectional area of the blood vessel within the transducer remains constant. This linear relationship between velocity and volume flow has been demonstrated repeatedly and confirmed by time collections of blood flow (16). At the time of autopsy, the vessels were firmly attached to the flow transducers by a fibrous scar which minimized changes in the cross-sectional area of the vessel within the flow transducers. In two conscious dogs and five anesthetized open-chest dogs, a Statham SP2000 electromagnetic flowmeter was used to measure coronary blood flow. In these experiments, zero blood flow was determined by inflating a previously implanted, hydraulic occlusive cuff.

An improved ultrasonic transit time dimension gauge was used to measure left ventricular diameter (17); its principle of operation is similar to that of other ultrasonic gauges described previously (18, 19). It measured the transit time of acoustic impulses traveling at the sonic velocity of approximately 1.5 × 10^8 mm/sec between the 5- or 3-MHz piezoelectric crystals that were sutured at opposing sites to the left ventricular epicardium or endocardium. This gauge was calibrated by substituting signals of a known time duration from a calibrated pulse generator. A voltage proportional to transit time was recorded and was confirmed by calibration terminally. Thus, a measure of the external or internal diameter of the left ventricle was continuously recorded. At a constant temperature, the drift of the instrument was less than 0.15 mm/hour, and its frequency response was flat to 60 Hz.

The experiments were conducted 3 weeks to 2 months after surgery when the dogs had recovered from the operation and were vigorous and healthy. While the unsedated dogs were resting quietly, control records of left ventricular pressure and diameter, the time rate of change of diameter (dD/dt), i.e., the velocity of myocardial shortening, the rate of change of pressure, (dp/dt) the circumflex coronary blood flow, arterial blood pressure, and heart rate were obtained. These variables were continuously recorded during all interventions. In 12 conscious dogs, noradrenalin (0.1 and 1.0 μg/kg) was administered intravenously as a bolus via a peripheral vein; it was administered as an infusion at the rate of 0.5 μg/kg min^-1 in 5 dogs and 0.2 μg/kg min^-1 in 3 dogs by a Harvard model 940 drug infusion pump.

All dogs were studied while their heart rate was controlled by electrical stimulation of the ventricles at a frequency slightly higher than the spontaneous rhythm. Heart rate was again controlled while eight dogs were studied on a separate day after beta-receptor blockade with propranolol (1.0–2.0 mg/kg, iv) and six dogs were studied after alpha-receptor blockade with phentolamine (0.2–1.0 mg/kg, iv). The adequacy of beta-receptor blockade was tested with isoproterenol (1 μg/kg, iv). Alpha-receptor blockade was assessed with noradrenalin (1.0 μg/kg, iv); 0.1 μg/kg of noradrenalin was the smallest dose that consistently caused perceptible changes in systemic and coronary dynamics, and 1.0 μg/kg was the largest dose that the conscious dogs could consistently tolerate without adverse side effects. Noradrenalin (1.0 μg/kg, iv) was administered to five conscious dogs made hypoxic by breathing 10% O2 through a face mask. In these experiments as well as those in anesthetized open-chest dogs and those in which the O2 content of coronary sinus blood was tested, 4

1 Construction details available upon request to the authors.

2 Construction details available upon request to the authors.

3 Generously supplied by Ayerst Co.

4 Generously supplied by Ciba Co.
arterial $P_O_2$ was measured with a Copenhagen radiometer (model PHM-72) blood-gas analyzer.

Data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph at a paper speed of 100 mm/sec. A cardiostimulator triggered by the signal from the pressure pulse provided instantaneous, continuous records of heart rate. Electronic resistance-capacitance filters with 2-second time constants were used to derive mean arterial blood pressure and mean and late circumflex coronary blood flow. Mean and late diastolic coronary vascular resistances were calculated as the quotients of the mean and the late diastolic arterial blood pressures and coronary blood flows, respectively. Continuous records of $dP/dt$ and $dD/dt$ were derived from the left ventricular pressure and diameter signals by using Philbrick operational amplifiers connected as differentiators having frequency responses of 60 or 30 Hz, respectively. A triangular wave signal with a known slope (rate of change) was substituted for pressure and diameter signals to calibrate the $dP/dt$ and $dD/dt$ channels directly.

The effects of norepinephrine on myocardial force-velocity relationships were assessed by determining the velocity of shortening and the intraventricular pressure at an identical ventricular diameter (isovalve length point), i.e., $V_{ls}$; this technique has been described previously (11, 13, 14, 20–22). All isovalve length points were obtained during the first one-third of ejection. In addition, the effects of norepinephrine on peak $dP/dt$ and the quotient of $dP/dt$ and developed pressure (left ventricular isovolumic pressure minus end-diastolic pressure), i.e., $(dP/dt)/P$, were examined. The same level of pressure that occurred during isometric contraction, before and after each intervention, was used for the calculation, and $dP/dt$ and developed pressure were determined at that level of pressure. This technique for evaluating the myocardial contractile state has also been described previously (11, 13, 14, 21–23).

**Results**

Norepinephrine administered intravenously as a bolus produced two distinct phases of action. First, the peak increase in coronary blood flow and the maximal reduction in coronary resistance occurred 20–30 seconds after injection. This point, designated A in Figure 1 and in the following discussion, was used to describe the early effect. Later, a sustained rise in coronary resistance above control levels occurred while pressures and contractility remained elevated (Fig. 2). This point, designated B in Figure 1 and in the following discussion, was recorded 60 seconds after injection. The results with the larger dose of norepinephrine (1.0 $\mu$g/kg) will be discussed in detail, but the results with the smaller dose (0.1 $\mu$g/kg) are simply presented in Table 1 and illustrated in Figures 1, 3, and 4. The paired $t$-test was used to compare the results at points A and B with the control results and to compare the changes from control at points A and B in the different states for the same dog. The group $t$-test was used to compare the changes in the anesthetized open-chest dogs. Significance was determined at the 0.05 level (24).

**NORMAL CONSCIOUS DOGS: BOLUS INJECTION**

**Pressures.**—Norepinephrine (1.0 $\mu$g/kg) increased mean arterial blood pressure from 97 ± 3 (SE) mm Hg to 172 ± 7 mm Hg at point A; pressure remained elevated at 165 ± 6 mm Hg at point B (Table 2). Late diastolic pressure increased by similar amounts (Fig. 3). Left ventricular peak systolic and isovolume systolic pressures increased similarly; the latter rose from a control value of 121 ± 2 mm Hg to 193 ± 7 mm Hg at point A and remained elevated at 195 ± 6 mm Hg at point B. Left ventricular end-diastolic pressure increased from a control of 6 ± 1 mm Hg to 10 ± 1 mm Hg at point A and remained elevated at 10 ± 1 mm Hg at point B.

**Diameters.**—Norepinephrine (1.0 $\mu$g/kg) increased left ventricular end-diastolic external and internal diameters by 1.3 ± 0.3 (SE) mm and 1.2 ± 0.1 mm, respectively, at point A from control values of 61.7 ± 1.1 mm and 35.6 ± 0.9 mm, respectively (Table 1). End-diastolic diameters remained at the same level at point B (Fig. 4). Left ventricular end-systolic diameters increased by small amounts (Table 1).

**Contractility.**—Norepinephrine (1.0 $\mu$g/kg) increased peak $dP/dt$ from 3350 ± 210 (SE) mm
Hg/sec to 9620 ± 350 mm Hg/sec at point A (Table 1); this variable remained elevated above the control level and was 5010 ± 290 mm Hg/sec at point B. (dP/dt)/P increased from 38 ± 2 sec⁻¹ to 66 ± 2 sec⁻¹ at point A and remained elevated above the control level at a value of 53 ± 2 sec⁻¹ at point B. Left ventricular isovelocity velocity increased from 241 ± 8 mm/sec to 276 ± 6 mm/sec at point A and remained elevated above the control level at a value of 272 ± 5 mm/sec at point B.

**Coronary Dynamics.**—Norepinephrine (1.0 µg/kg) dilated the coronary vascular bed at point A. At this point, mean coronary blood flow rose from a control of 48 ± 3 (SE) ml/min to a maximal level of 112 ± 5 ml/min; late diastolic flow rose similarly (Table 2). Mean coronary vascular resistance fell from 2.05 ± 0.11 mm Hg/ml min⁻¹ to 1.56 ± 0.10 mm Hg/ml min⁻¹; late diastolic coronary resistance decreased similarly (Fig. 3). However, mean and late diastolic coronary blood flows began to return to the control level, but left ventricular pressures, dimensions, and contractility remained elevated and a sustained increase in mean and late diastolic resistance ensued (Figs. 1, 4). At point B, mean and late diastolic coronary blood flows were only 16 ± 2 ml/min and 18 ± 3 ml/min above the control level, whereas calculated mean and late diastolic coronary resistances had increased by 0.55 ± 0.07 mm Hg/ml min⁻¹ and 0.50 ± 0.05 mm Hg/ml min⁻¹, respectively, above the control levels. The effect of the smaller dose of norepinephrine (0.1 µg/kg) was slightly different in that coronary blood flow was not significantly elevated at point B (Table 2); in fact, in several experiments it actually fell below the control level at point B despite elevated pressures and contractility. After falling below the control level at point A, mean and late diastolic coronary resistances rose by 0.29 ± 0.05 mm Hg/ml min⁻¹ and 0.28 ± 0.06 mm Hg/ml min⁻¹, respectively, above the control levels at point B.

Thus, when norepinephrine was administered intravenously as a bolus in the conscious dog, a brief early period of coronary dilatation occurred and was followed by a sustained period of coronary vasoconstriction despite elevated left ventricular pressures, dimensions, and contractility.

**Arterial and Coronary Sinus Oxygen.**—During the period of coronary vasoconstriction that occurred after the injection of norepinephrine (1.0 µg/kg), i.e., at point B, arterial Po₂ remained at control levels of 84 ± 3 (SE) mm Hg, but in four conscious dogs coronary sinus Po₂ fell from 16 ± 1 mm Hg to 13 ± 1 mm Hg (P < 0.01).

**Conscious Dogs with Adrenergic Blockades**

**Beta-Receptor Blockade.**—Following the administration of propranolol (1.0-2.0 mg/kg, iv) and
TABLE 1

Left Ventricular Effects of Norepinephrine in Normal Conscious Dogs

<table>
<thead>
<tr>
<th>NE dose (µg/kg)</th>
<th>Control</th>
<th>A</th>
<th>Δ</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>External diameter (mm)</td>
<td>0.1</td>
<td>61.7 ± 1.1/55.2 ± 1.0</td>
<td>62.7 ± 1.2/55.9 ± 1.1</td>
<td>1.0 ± 0.3*0.7 ± 0.2</td>
</tr>
<tr>
<td>(end-diastolic/end-systolic)</td>
<td>1.0</td>
<td>61.7 ± 1.1/55.2 ± 1.0</td>
<td>63.0 ± 0.9/56.9 ± 1.1</td>
<td>1.1 ± 0.3*0.7 ± 0.2</td>
</tr>
<tr>
<td>Internal diameter (mm)</td>
<td>0.1</td>
<td>35.6 ± 0.9/39.1 ± 1.1</td>
<td>36.8 ± 1.0/39.9 ± 1.1</td>
<td>1.2 ± 0.3*0.8 ± 0.2</td>
</tr>
<tr>
<td>(end-diastolic/end-systolic)</td>
<td>1.0</td>
<td>35.6 ± 0.9/39.1 ± 1.1</td>
<td>36.8 ± 0.9/39.6 ± 1.0</td>
<td>1.2 ± 0.1*0.5 ± 0.1</td>
</tr>
<tr>
<td>Velocity (mm/sec)</td>
<td>0.1</td>
<td>65 ± 5/61 ± 4</td>
<td>70 ± 6/65 ± 5</td>
<td>5 ± 1*0.4 ± 1</td>
</tr>
<tr>
<td>(Peak/Vo.)</td>
<td>1.0</td>
<td>65 ± 5/61 ± 4</td>
<td>82 ± 7/76 ± 6</td>
<td>17 ± 1*0.5 ± 3</td>
</tr>
<tr>
<td>Pressure (mm Hg)</td>
<td>0.1</td>
<td>125 ± 3/121 ± 2 ± 1</td>
<td>151 ± 5/145 ± 5 ± 1</td>
<td>36 ± 7/33 ± 3*0 ± 1</td>
</tr>
<tr>
<td>(Peak/ISIlength/EDP)</td>
<td>1.0</td>
<td>125 ± 3/121 ± 2 ± 1</td>
<td>212 ± 9/193 ± 7 ± 1</td>
<td>87 ± 5/72 ± 7*7 ± 4</td>
</tr>
<tr>
<td>Peak dP/dt (mm Hg/sec)</td>
<td>0.1</td>
<td>3350 ± 210</td>
<td>4720 ± 370</td>
<td>1370 ± 110*</td>
</tr>
<tr>
<td>(dP/dt)/P (sec⁻¹)</td>
<td>1.0</td>
<td>3350 ± 210</td>
<td>4720 ± 370</td>
<td>6270 ± 310*</td>
</tr>
</tbody>
</table>

All values are means ± 88. NE = norepinephrine; see text for definition of A and B.
* Changes significant, P < 0.01.
† Change significant, P < 0.05.

The responses in the coronary vascular bed after administration of isoprenaline (0.5-1.0 mg/kg, iv) increased left diastolic coronary blood flow and arterial blood pressure and decreased coronary vascular resistances (0.19 ± 0.10 Hg/ml/min, respectively; at point B, they remained depressed by 0.18 ± 0.08 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.36 ± 0.10 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.25 ± 0.06 Hg/ml/min, respectively).

The responses in the coronary vascular bed after administration of propranolol (0.1-0.5 mg/kg, iv) increased systolic pressure and mean arterial pressure and reduced coronary vascular resistances (0.06 ± 0.06 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.22 ± 0.04 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.25 ± 0.06 Hg/ml/min, respectively).

The responses in the coronary vascular bed after administration of phentolamine (0.5-1.0 mg/kg, iv) increased systolic pressure and mean arterial pressure and reduced coronary vascular resistances (0.04 ± 0.04 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.22 ± 0.06 Hg/ml/min, respectively). The responses in the coronary vascular bed were significantly different from those observed in the control group (0.25 ± 0.06 Hg/ml/min, respectively).
Coronary Dynamic Effects of Norepinephrine

### TABLE 2

<table>
<thead>
<tr>
<th>State</th>
<th>NE dose (µg/kg)</th>
<th>Control</th>
<th>A</th>
<th>Δ</th>
<th>B</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious, unblocked</td>
<td>0.1</td>
<td>10</td>
<td>99 ± 3/83 ± 6</td>
<td>122 ± 4/105 ± 3</td>
<td>23 ± 3*/22 ± 3*</td>
<td>116 ± 3/101 ± 3</td>
</tr>
<tr>
<td>Conscious, unblocked</td>
<td>1.0</td>
<td>12</td>
<td>97 ± 3/81 ± 5</td>
<td>172 ± 7/150 ± 6</td>
<td>75 ± 6*/69 ± 6*</td>
<td>165 ± 6/144 ± 5</td>
</tr>
<tr>
<td>Conscious, beta-receptor blockade</td>
<td>1.0</td>
<td>5</td>
<td>103 ± 3/86 ± 3</td>
<td>170 ± 6/145 ± 7</td>
<td>67 ± 4*/59 ± 6*</td>
<td>164 ± 6/139 ± 5</td>
</tr>
<tr>
<td>Conscious, alpha-receptor blockade</td>
<td>1.0</td>
<td>6</td>
<td>90 ± 3/72 ± 3</td>
<td>99 ± 4/81 ± 3</td>
<td>9 ± 1†/9 ± 1†</td>
<td>96 ± 3/78 ± 3</td>
</tr>
<tr>
<td>Anesthetized, open-chest</td>
<td>1.0</td>
<td>5</td>
<td>109 ± 10/90 ± 9</td>
<td>160 ± 16/142 ± 13</td>
<td>51 ± 9*/52 ± 9*</td>
<td>148 ± 18/131 ± 15</td>
</tr>
</tbody>
</table>

**Arterial Pressure (mm Hg) (Mean/Late Diastolic)**

<table>
<thead>
<tr>
<th>State</th>
<th>NE dose (µg/kg)</th>
<th>Control</th>
<th>A</th>
<th>Δ</th>
<th>B</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious, unblocked</td>
<td>0.1</td>
<td>10</td>
<td>50 ± 3/56 ± 3</td>
<td>68 ± 4/78 ± 5</td>
<td>18 ± 2*/22 ± 3*</td>
<td>51 ± 3/57 ± 3</td>
</tr>
<tr>
<td>Conscious, unblocked</td>
<td>1.0</td>
<td>12</td>
<td>48 ± 3/54 ± 3</td>
<td>112 ± 5/123 ± 5</td>
<td>64 ± 3*/69 ± 3*</td>
<td>64 ± 3/72 ± 3</td>
</tr>
<tr>
<td>Conscious, beta-receptor blockade</td>
<td>1.0</td>
<td>5</td>
<td>45 ± 4/51 ± 5</td>
<td>80 ± 5/90 ± 5</td>
<td>35 ± 3*/40 ± 3†</td>
<td>52 ± 4/59 ± 5</td>
</tr>
<tr>
<td>Conscious, alpha-receptor blockade</td>
<td>1.0</td>
<td>6</td>
<td>52 ± 4/56 ± 4</td>
<td>70 ± 5/75 ± 5</td>
<td>18 ± 3*/19 ± 3†</td>
<td>65 ± 4/70 ± 4</td>
</tr>
<tr>
<td>Anesthetized, open-chest</td>
<td>1.0</td>
<td>5</td>
<td>51 ± 4/56 ± 4</td>
<td>125 ± 18/134 ± 20</td>
<td>74 ± 19*/78 ± 21*</td>
<td>71 ± 6/79 ± 7</td>
</tr>
</tbody>
</table>

**Coronary Flow (ml/min) (Mean/Late Diastolic)**

<table>
<thead>
<tr>
<th>State</th>
<th>NE dose (µg/kg)</th>
<th>Control</th>
<th>A</th>
<th>Δ</th>
<th>B</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conscious, unblocked</td>
<td>0.1</td>
<td>10</td>
<td>2.0 ± 0.13/1.52 ± 0.09</td>
<td>1.83 ± 0.10/1.40 ± 0.09</td>
<td>-0.20 ± 0.05*/-0.12 ± 0.02*</td>
<td>2.32 ± 0.04/1.80 ± 0.09</td>
</tr>
<tr>
<td>Conscious, unblocked</td>
<td>1.0</td>
<td>12</td>
<td>2.05 ± 0.11/1.54 ± 0.08</td>
<td>1.56 ± 0.10/1.24 ± 0.09</td>
<td>-0.49 ± 0.07*/0.30 ± 0.06*</td>
<td>2.60 ± 0.14/2.04 ± 0.10</td>
</tr>
<tr>
<td>Conscious, beta-receptor blockade</td>
<td>1.0</td>
<td>8</td>
<td>2.31 ± 0.20/1.75 ± 0.14</td>
<td>2.09 ± 0.17/1.61 ± 0.15</td>
<td>0.22 ± 0.06*/-0.12 ± 0.04††</td>
<td>3.12 ± 0.25/2.35 ± 0.22</td>
</tr>
<tr>
<td>Conscious, alpha-receptor blockade</td>
<td>1.0</td>
<td>6</td>
<td>1.80 ± 0.16/1.32 ± 0.12</td>
<td>1.44 ± 0.09/1.09 ± 0.07</td>
<td>-0.36 ± 0.09*/0.23 ± 0.07*</td>
<td>1.51 ± 0.09/1.14 ± 0.08</td>
</tr>
<tr>
<td>Anesthetized, open-chest</td>
<td>1.0</td>
<td>5</td>
<td>2.17 ± 0.58/1.60 ± 0.44</td>
<td>1.33 ± 0.11/0.95 ± 0.33</td>
<td>-0.84 ± 0.30*/-0.65 ± 0.22*</td>
<td>2.10 ± 0.26/1.54 ± 0.21</td>
</tr>
</tbody>
</table>

**Coronary Resistance (mm Hg/ml min⁻¹) (Mean/Late Diastolic)**

All values are means ± SE. NE = norepinephrine; see text for definition of A and B.

* Change from control significant, *P* < 0.01.
† Change significantly different from conscious dogs without blockade (1.0 µg/kg), *P* < 0.01.
‡ Change from control significant, *P* < 0.05.
§ Change significantly different from conscious dogs without blockade (1.0 µg/kg), *P* < 0.05.
Average changes ± SE in response to norepinephrine, 1.0 µg/kg (left) and 0.1 µg/kg (right), in ten conscious dogs for mean and late diastolic values of arterial pressure, coronary flow, and coronary resistance.

ways. (1) The rise in arterial blood pressure was significantly less at both points A and B. (2) The rise in coronary blood flow was less at point A but not at point B. (3) The early coronary vasodilation was similar, but the late coronary vasoconstriction did not occur and was actually reversed (Table 2). Thus, alpha-receptor blockade attenuated the pressor action of norepinephrine and prevented the striking later increase in coronary resistance.

After partial alpha-receptor blockade with phentolamine (0.2 mg/kg, iv), norepinephrine (1.0 µg/kg, iv) was administered to three dogs with heart rate maintained constant at 126 beats/min. In these dogs mean arterial blood pressure rose from 107 mm Hg to 146 mm Hg at point A and remained above the control level at 114 mm Hg at the late response. Mean coronary blood flow rose from 42 ml/min to 108 ml/min (point A) and remained above the control level at 55 ml/min at the late response. Mean coronary resistance fell in all three dogs from an average of 2.54 mm Hg/ml min⁻¹ to 1.34 mm Hg/ml min⁻¹ at point A and remained depressed at an average of 2.09 mm Hg/ml min⁻¹ at point B (Fig. 5). Thus, the late increase in coronary resistance was not observed after partial alpha-receptor blockade. During this blockade, norepinephrine stimulated alpha receptors sufficiently to elevate arterial blood pressure; however, coronary alpha receptors were blocked sufficiently to reverse the late coronary vasoconstrictor response to a vasodilator response.

CONSCIOUS DOGS WITH HYPOXIA

After hypoxia had been induced in five dogs by breathing 10% O₂, norepinephrine (1.0 µg/kg, iv) was administered as a bolus. Arterial Po₂ fell from

Typical response to intravenously administered norepinephrine (NE), 1.0 µg/kg, after partial alpha-receptor blockade with phentolamine, 0.2 mg/kg, iv, with the heart rate held constant. Responses for mean arterial blood pressure, phasic and mean left circumflex coronary flow, and computed mean coronary resistance are shown. Norepinephrine still caused pressure to increase, but coronary vasconstriction was no longer observed in contrast to the normal response illustrated in Figure 1.
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With heart rate held constant by pacing at 132 ± 6 beats/min, norepinephrine increased mean arterial blood pressure from a control of 109 ± 5 mm Hg to 141 ± 6 mm Hg at point A and to 135 ± 6 mm Hg at point B; (dP/dt)/P rose from a control of 43 ± 3 sec⁻¹ to 75 ± 5 sec⁻¹ at point A and remained elevated at 59 ± 4 sec⁻¹ at point B. Mean coronary blood flow rose from a control of 72 ± 10 ml/min to 142 ± 10 ml/min at point A and remained elevated at 78 ± 6 ml/min at point B. Mean coronary resistance fell from 1.55 ± 0.10 mm Hg/ml min⁻¹ to 1.00 ± 0.08 mm Hg/ml min⁻¹ at point A and then increased above the control level to 1.74 ± 0.09 mm Hg/ml min⁻¹ at point B. Thus, the early period of coronary vasodilatation and the later period of coronary vasoconstriction were observed in hypoxic dogs as well as in normal, conscious, eupneic dogs.

NORMAL CONSCIOUS DOGS NOREPINEPHRINE INFUSION

Infusion of norepinephrine (0.5 μg/kg min⁻¹) to five dogs whose heart rates were held constant caused a transient coronary vasodilatation (Fig. 6) followed by steady-state increases in arterial blood pressures that were associated with smaller increases in coronary blood flow. Accordingly, coronary vascular resistance rose (Fig. 6). Mean arterial blood pressure increased from 99 ± 4 (SE) mm Hg to 154 ± 5 mm Hg, mean coronary blood flow rose from 44 ± 3 ml/min to 61 ± 5 ml/min, and calculated mean coronary resistance increased from 2.28 ± 0.12 mm Hg/ml min⁻¹ to 2.59 ± 0.19 mm Hg/ml min⁻¹ (P < 0.05). Similar changes occurred in late diastolic arterial pressure, coronary blood flow, and coronary vascular resistance.

Infusion of norepinephrine (0.2 μg/kg min⁻¹) to three conscious dogs whose heart rates were held constant did not affect mean arterial blood pressure (98 mm Hg) but did reduce mean and late diastolic coronary blood flows from averages of 39 ml/min and 42 ml/min to 34 ml/min and 35 ml/min, respectively. Mean and late diastolic coronary resistances rose in all three dogs from averages of 2.53 mm Hg/ml min⁻¹ and 1.99 mm Hg/ml min⁻¹ to 2.89 mm Hg/ml min⁻¹ and 2.37 mm Hg/ml min⁻¹, respectively. Thus, norepinephrine infusion constricted the coronary vessels; however, at lower doses of norepinephrine coronary constriction was observed without a concomitant elevation in arterial blood pressure (Fig. 7).

**FIGURE 6**
Typical response to infusion of norepinephrine (NE), 0.5 μg/kg min⁻¹, for phasic and mean arterial pressure, phasic and mean coronary flow velocity, calculated mean coronary resistance, and heart rate. With the heart rate held constant, norepinephrine produced a brief initial decrease in coronary resistance and then a sustained increase during the steady state. The capability of the coronary vessels to dilate markedly is shown by the response to an injection of 1 mg of nitroglycerin (NTG).
Response to infusion of norepinephrine (NE) 0.2 μg/kg min⁻¹, for mean arterial blood pressure, phasic and mean coronary flow, and computed mean coronary resistance. Left: With the heart rate (HR) held constant, norepinephrine produced a reduction in coronary flow without a rise in arterial blood pressure, i.e., coronary vasoconstriction took place. Right: After administration of phentolamine, 1 mg/kg, iv, norepinephrine infusion, 0.5 μg/kg min⁻¹, caused only coronary dilatation with a substantial increase in coronary flow.

Infusion of norepinephrine (0.5 μg/kg min⁻¹) after administration of phentolamine (1 mg/kg, iv) caused only coronary dilatation. Although mean arterial blood pressure fell slightly from 99 mm Hg to 94 mm Hg, mean and late diastolic coronary blood flows rose from 46 ml/min and 51 ml/min to 61 ml/min and 66 ml/min, respectively, and mean and late diastolic coronary resistances fell from 2.15 mm Hg/ml min⁻¹ and 1.69 mm Hg/ml min⁻¹ to 1.56 mm Hg/ml min⁻¹ and 1.25 mm Hg/ml min⁻¹, respectively.

ANESTHETIZED, OPEN-CHEST DOGS

With heart rate held constant at 186 ± 8 beats/min, norepinephrine (1.0 μg/kg, iv) increased mean arterial blood pressure by 51 ± 9 (SE) mm Hg from a control value of 109 ± 10 mm Hg at point A; the pressure remained 39 ± 10 mm Hg above control levels at point B (Table 2). Late diastolic arterial blood pressure and left ventricular systolic pressure increased similarly. Arterial PO₂ remained at the control level, 82 ± 3 mm Hg. Peak dP/dt increased by 7130 ± 670 mm Hg/sec at point A from a control of 2080 ± 210 mm Hg/sec and remained elevated at point B. (dP/dt)/P increased by 39 ± 5 sec⁻¹ from a control of 21 ± 4 sec⁻¹ at point A and remained elevated at point B. Mean left circumflex coronary blood flow increased by 74 ± 19 ml/min from a control of 51 ± 4 ml/min at point A and remained elevated by 20 ± 4 ml/min above control at point B. These increases in coronary blood flow were slightly, although not significantly, greater than those observed in the conscious dog. Calculated mean coronary resistance decreased by 0.84 ± 0.30 mm Hg/ml min⁻¹ from a control of 2.17 ± 0.58 mm Hg/ml min⁻¹ at point A. In contrast to the experiments in the normal, conscious dogs, calculated mean coronary resistance did not rise at point B but returned to 2.10 ± 0.26 mm Hg/ml min⁻¹, a level very close to control (Table 2).

In two anesthetized dogs treated with propranolol, norepinephrine caused only coronary vasoconstriction; at point B coronary resistance rose by 0.79 mm Hg/ml min⁻¹ and 0.61 mm Hg/ml min⁻¹ from controls of 2.39 mm Hg/ml min⁻¹ and 2.24 mm Hg/ml min⁻¹, respectively.

Thus, general anesthesia and the open-chest state modified the normal response to norepinephrine in that the later prominent elevation of coronary resistance was not observed.

Discussion

The coronary vascular bed, like other vascular beds, responds to both direct alpha-receptor (constrictor) and direct beta-receptor (dilator) stimulation (1-9). It is generally agreed, however, that these direct effects are minor in comparison with the predominant metabolic effects induced by the stimulation of myocardial oxygen needs that results from norepinephrine’s concomitant powerful pressor and inotropic actions (1-8). Accordingly, when norepinephrine is administered to the beating heart, the major effect is thought to be the coronary vasodilatation (1-8) which follows a transient vasoconstriction. Alpha-adrenergic vasoconstriction has been observed only in the nonbeating heart (1) or only after the beta-adrenergic effect has been prevented in the beating heart (2-8). However, two recent studies in man have found no change in coronary resistance with the infusion of norepinephrine (25, 26); this finding suggests that norepinephrine’s alpha-adrenergic vasoconstricting action might offset its secondary metabolic vasodilating effects.

In the present study conducted in healthy, conscious dogs, the results were substantially different and actually opposite in direction from those noted in earlier investigations conducted in experimental animals (1-8). When norepinephrine was administered intravenously as a bolus, two effects were observed. First, a transient period of coronary vasodilatation occurred. This vasodilatation was
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associated with peak increases in left ventricular systolic pressure and contractility and probably resulted mainly from increases in myocardial oxygen consumption and to a lesser extent from activation of coronary vascular beta receptors. Then a period of sustained coronary vasoconstriction ensued. This coronary vasoconstrictor effect could not have resulted from a reduction in the myocardial oxygen requirements below the control levels, since heart rate was maintained constant. The major hemodynamic determinants of myocardial O2 consumption (i.e., left ventricular pressures, end-diastolic diameter, and myocardial contractility) were elevated, and the coronary arteriovenous Po2 difference was widened above control levels. When norepinephrine was administered as an infusion, coronary vasoconstriction occurred during the steady state; this finding further supports the importance of this action. Since a similar coronary vasoconstrictor component was observed whether the Doppler or the electromagnetic flowmeter was used and whether mean or late diastolic resistance was calculated, our results could not be attributed to possible errors due to reverse flow during systole consequent to increased myocardial compression of the coronary vessels.

Autoregulation has been observed in the coronary vascular bed (27, 28); the tendency for coronary blood flow to return toward the control level and for coronary vasoconstriction to occur during the late response to norepinephrine could, in part, be explained on the basis of autoregulation. However, this explanation is incomplete for the following reasons. When norepinephrine was administered as a bolus or an infusion in the presence of phentolamine, an alpha-receptor blocking agent, the period of coronary vasoconstriction was not observed and only a sustained vasodilatation resulted, presumably owing to beta2-adrenergic increases in myocardial contractility and stimulation of beta2 coronary vascular receptors (4-7). In some of the experiments in which the smaller bolus dose of norepinephrine (0.1 μg/kg) was administered, coronary blood flow actually decreased below the control level during the later period of coronary vasoconstriction. Similarly, when the smaller dose of norepinephrine was administered as an infusion, coronary blood flow fell while arterial blood pressure remained at control levels. A reduction in coronary blood flow in association with an elevation in arterial blood pressure certainly cannot be explained on the basis of autoregulation. Furthermore, in the anesthetized, open-chest dogs and in the conscious dogs with partial alpha-receptor blockade (Fig. 5), the late increase in coronary resistance did not occur when arterial blood pressure rose. If autoregulation had been entirely responsible for the increase in coronary vascular resistance in the conscious dogs without blockade, this increase should also have occurred in the anesthetized dogs and in the conscious dogs with partial alpha-receptor blockade in which the coronary vessels dilated despite arterial blood pressure elevation. Finally, after beta-receptor blockade, the increases in coronary resistance produced by norepinephrine were greater than those produced without such treatment. These findings further support the concept that active alpha-adrenergic vasoconstriction was primarily responsible for the increase in resistance, but they do not completely rule out the contribution of an autoregulatory response.

Both the previous studies in which only dilatation occurred in response to norepinephrine (1-8) and those in which alpha-receptor activity in the coronary vascular bed appeared to be trivial (4, 5) were conducted primarily in anesthetized, open-chest preparations (1, 2, 4, 8); the presence of general anesthesia and the open chest might explain the differing results. When norepinephrine was administered to five anesthetized, open-chest dogs in the present study, the later period of coronary vasoconstriction was not observed, i.e., our results resembled those previously reported. A number of explanations might be invoked to explain this difference in responses. (1) The coronary vascular bed was relatively constriicted in the anesthetized state even prior to the administration of norepinephrine. (2) The anesthetized dogs were hypoxic and constriction might not be observed in hypoxia. (3) The anesthetic agent masked the constrictor action of norepinephrine on the coronary vessels and perhaps acted directly as a vascular depressant (29). (4) The relative increases in myocardial oxygen requirements induced by norepinephrine were much greater in the anesthetized dogs than in the conscious dogs. Since control values for coronary resistance in both the conscious and the anesthetized dogs were not significantly different (Table 2), the first possibility appears to be excluded. Second, alterations in arterial Po2 could not explain the differences between the results in the conscious and anesthetized dogs. In the anesthetized dogs ventilation was well maintained as evidenced by arterial Po2 values. Moreover, the conscious
dogs were studied in the hypoxic state. Even after the coronary vascular bed was dilated by hypoxia, norepinephrine still produced the later phase of vasodilation. Thus, the difference between the results in the conscious and the anesthetized dogs was probably due to the differing experimental preparations. The presence of a general anesthetic agent (1) affects higher central nervous system control of the cardiovascular system to an unknown extent, (2) alters reflex control of the circulation (30), (3) substantially depresses the myocardial contractile state (11), and (4) exerts a direct dilating effect on the resistance vessels (29). Moreover, inotropic agents such as cardiac glycosides (11) and norepinephrine exert a relatively greater inotropic effect on the myocardium depressed by general anesthesia and, accordingly, can be expected to cause a relatively greater augmentation in myocardial oxygen consumption and secondarily, coronary vasodilation. These considerations could explain the finding that the effects of norepinephrine in conscious and anesthetized dogs differ strikingly. The difference between our results and those of Pitt et al. (3), who reported that coronary dilatation occurred with the administration of norepinephrine, cannot be resolved on the same basis, since their study was conducted in conscious dogs. However, in that investigation the response to norepinephrine was reported only at one instant (20-30 seconds after intravenous administration of norepinephrine), a point which corresponded to the early peak effects of norepinephrine in the present study (point A) where coronary vasodilatation was also observed.

Thus, in normal, healthy, conscious dogs, norepinephrine causes a significant alpha-adrenergic constrictor response despite increases in left ventricular pressures, end-diastolic diameter, and myocardial contractility. Failure to demonstrate this action in open-chest, anesthetized dogs in both this and previous studies (1, 2, 4-8) underscores the importance of elucidating cardiovascular pharmacological responses in normal, healthy, conscious animals in which the anesthetic agent and recent surgery have not produced myocardial depression (11), altered vasoactivity of the peripheral vessels, or both.

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References

18. Rushmer, R.F., Franklin, D., and Ellis, R.M.: Left ven-
NOREPINEPHRINE-INDUCED CORONARY VASOCONSTRICTION

Effects of Norepinephrine on Coronary Circulation and Left Ventricular Dynamics in the Conscious Dog

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