Baroreflex and Vagal Mechanisms Modulating Left Ventricular Contractile Responses to Sympathomimetic Amines in Conscious Dogs

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SUMMARY The steady state effects of intravenous norepinephrine (NE), 0.2 μg/kg per min, isoproterenol, 0.02 μg/kg per min, and dopamine, 10 μg/kg per min, on measurements of arterial and left ventricular (LV) pressures, dP/dt, LV diameter, and velocity of shortening were compared before and after muscarinic blockade with atropine sulfate or methyl atropine bromide (0.1 mg/kg). In intact conscious dogs, NE increased mean arterial pressure by 24 ± 2 mm Hg and LV dP/dt by 1140 ± 90 mm Hg/sec, but did not change LV velocity significantly and decreased heart rate by 13 ± 3 beats/min.

After muscarinic blockade, NE caused significantly greater (P < 0.01) increases in mean arterial pressure of 49 ± 6 mm Hg, LV dP/dt of 3290 ± 240 mm Hg/sec, LV velocity of 24 ± 6 mm/sec, and heart rate of 7 ± 3 beats/min. A similar augmentation of the contractile response to infusions of isoproterenol and dopamine was observed following muscarinic blockade. These responses were dependent neither on arterial baroreceptors nor on an intact sympathetic nervous system. After vagotomy and arterial baroreceptor denervation (ABD), NE increased LV dP/dt by 2970 ± 170 mm Hg/sec and LV velocity by 20 ± 4 mm/sec, i.e., by amounts similar to those found after muscarinic blockade for intact dogs and dogs with ABD. However, in dogs with ABD and vagotomy, the contractile responses to NE were not augmented further by muscarinic blockade. Thus, the parasympathetic nervous system can exert a powerful inhibitory influence on the inotropic responses to infused sympathomimetic amines since, after muscarinic blockade, the inotropic responses to NE, isoproterenol, and dopamine increase 2-fold. The mechanism is independent of the arterial baroreceptor reflex and the sympathetic nervous system and appears to involve an inhibitory action of vagally released acetylcholine on the β-adrenergic inotropic response to sympathomimetic amines. Circ Res 44: 195-207, 1979

THE modulation of cardiac contractility and rate by the autonomic nervous system is of fundamental importance in the intact, conscious organism. This is particularly relevant to understanding the effects of exogenous sympathomimetic amines on the heart, since these agents not only exert direct inotropic and chronotropic actions through stimulation of adrenergic receptors, but elicit reflex buffering of these effects by the autonomic nervous system. Prior studies conducted on conscious and anesthetized animals as well as man have demonstrated an important effect for arterial baroreflexes as well as sympathetic and parasympathetic efferent mechanisms involved in this buffering (Kircheim, 1976).

Since general anesthesia is known to affect many aspects of circulatory control (Vatner and Braunwald, 1975), it was felt important to investigate these autonomic relationships in conscious dogs.

The primary goal of the present investigation was to examine the extent to which the autonomic nervous system, and in particular, the parasympathetic nervous system, buffered the direct positive inotropic and chronotropic responses to exogenous sympathomimetic amines in conscious dogs. To accomplish this, the effects of intravenous norepinephrine (NE), isoproterenol, and dopamine were examined before and after arterial baroreceptor denervation (ABD) and before and after sympathetic and parasympathetic blockades. After it had been observed that inotropic responses to sympathomimetic amines were substantially enhanced by muscarinic blockade but not by ABD, the mechanism of the augmentation was analyzed. This was accomplished by examining the extent to which muscarinic blockade increased inotropic responses to sympathomimetic amines with and without heart rate constant, and in the presence of ABD plus bilateral cervical vagotomy, as well as by examining responses to infusions of NE in the presence and absence of muscarinic blockade after administration of propranolol, reserpine, 6-OH dopamine, cocaine, and hexamethonium.
Methods

Forty-three mongrel dogs, weighing 17-32 kg, were anesthetized with intravenous (iv) sodium pentobarbital, 30 mg/kg. Through a left thoracotomy in the 5th intercostal space, stimulator electrodes were sutured to the right ventricle, a miniature pressure transducer (P22; Konigsburg Instruments) was implanted through a stab wound in the apex of the left ventricle, and ultrasonic diameter transducers were implanted on opposing anterior and posterior endocardial surfaces of the left ventricle. In three additional dogs, an electromagnetic flow transducer (Zepeda Instruments) was implanted around the ascending aorta, and Doppler flow probes were implanted on the left circumflex coronary artery. In all dogs, a heparin-filled Tygon (Norton Company) catheter was implanted in the thoracic aorta. In seven dogs, aortic baroreceptor denervation was performed at the time of implantation of transducers by stripping the aortic arch and great vessels. The carotid sinus nerves were sectioned in the neck 1-3 weeks later under sodium thiamyl anesthesia. The experiments were conducted in intact conscious dogs 3 weeks to 3 months postoperatively, but they were lying quietly. Ten-minute intravenous infusions of NE (0.02, 0.1, and 0.2 µg/kg per min), isoproterenol (0.02 µg/kg per min), and dopamine (10 µg/kg per min) were administered before and after muscarinic blockade with atropine sulfate or methylnaltropine bromide (0.1 mg/kg, iv). The drugs were given in random order to the conscious dogs on different days. The responses to NE (0.2 µg/kg per min), dopamine (10 µg/kg per min), and isoproterenol (0.02 µg/kg per min) were examined in dogs with ABD before and after muscarinic blockade. The response to NE (0.2 µg/kg per min) was also studied in intact dogs on separate days after (1) β-receptor blockade with propranolol (1.0 mg/kg); (2) chronic pretreatment with reserpine (0.25 mg/kg, im, daily for 3 days); (3) pretreatment with cocaine (10-30 mg/kg, iv); (4) pretreatment with 6-OH dopamine (50 mg/kg, im, over 7 days); or (5) pretreatment with hexamethonium (50 mg/kg, iv).

The adequacy of muscarinic blockade was shown by elimination of tachycardia and hypotension following acetylcholine (40 µg/kg, iv), that of β-receptor blockade by elimination of inotropic responses to isoproterenol (1 µg/kg, iv), that of reserpine by elimination of changes in heart rate, LV dP/dt, and arterial pressure following stellate ganglion stimulation in terminal experiments, and that of 6-OH dopamine and hexamethonium by elimination of reflex responses to nitroglycerin (40 µg/kg, iv).

After recovery from ABD but prior to experimentation, the adequacy of ABD was tested by examining reflex responses to bolus iv doses of nitroglycerin (40 µg/kg, iv). In intact dogs, this dose of nitroglycerin reduced mean arterial pressure by 25 mm Hg and increased heart rate by 83 beats/min and LV dP/dt by 40%. In the dogs with ABD, this dose of nitroglycerin reduced mean arterial pressure by 22 mm Hg and did not change heart rate or LV dP/dt.

To determine whether muscarinic blockade altered the fraction of cardiac output delivered to the left ventricle, cardiac output and left circumflex coronary blood flow were measured in three additional intact dogs before and after muscarinic blockade.

Data were recorded on a multichannel tape recorder and played back on a direct-writing oscillograph at paper speeds of 1, 25, and 100 mm/sec. A cardiograph, triggered by a signal from the
pressure pulse, provided instantaneous and continuous records of heart rate. Electronic resistance-capacitance filters with 2-second time constants were used to derive mean arterial blood pressure, and an 8-second time constant was used to derive mean blood flows. Continuous records of dP/dt and dD/dt were derived from the LV pressure and diameter signals, using Philbrick operational amplifiers connected as differentiators with frequency responses of 700 and 140 Hz, respectively. A triangular wave signal with a known slope (rate of change) was substituted for pressure to calibrate dP/dt directly. Average values ± standard errors of the mean (SEM) are reported. Control and response values were compared in the same dogs by using a paired t-test. Significant differences in the magnitude of changes induced by the sympathomimetic amines before and after muscarinic blockade and between the different groups of animals were assessed using two-way analysis of variance (Armitage, 1973).

**Results**

The steady state effects of 10-minute iv infusions of sympathomimetic amines were examined in conscious dogs before and after muscarinic receptor blockade with atropine sulfate or methylatropine bromide (0.1 mg/kg, iv). Since responses to sympathomimetic amines were nearly identical after either atropine sulfate or methylatropine bromide, the data obtained after use of each of these agents were pooled. Control values are available in the tables or figures. All changes discussed are statistically significant unless stated otherwise. Specific significance levels are noted in the tables.

### Table 1 Effects of Norepinephrine, 0.2 μg/kg per min, in Conscious Dogs with Sinus Rhythm when Intact, after ABD, and after ABD Plus Vagotomy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Δ</th>
<th>Muscarinic block</th>
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<tbody>
<tr>
<td><strong>Mean arterial pressure (mm Hg)</strong></td>
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</table>
| Intact (n = 14)          | 93.8 ± 2.9         | 23.6 ± 2.0† | 102 ± 2.7        | 48.6 ± 5.5† Absolute difference
| ABD (n = 7)              | 101 ± 7.7          | 35.0 ± 3.8† | 103 ± 7.9        | 50.3 ± 2.9† Absolute difference
| ABD and vagotomy (n = 7) | 114 ± 7.8          | 44.3 ± 8.2† | 111 ± 5.2        | 47.1 ± 10.4† Absolute difference
| **LV systolic pressure (mm Hg)** |                    |            |                  |            |
| Intact (n = 16)          | 123 ± 2.8          | 24.1 ± 2.1† | 120 ± 2.5        | 64.8 ± 6.0‡ Absolute difference
| ABD (n = 7)              | 123 ± 9.2          | 44.0 ± 3.5† | 121 ± 8.6        | 71.4 ± 7.3‡ Absolute difference
| ABD and vagotomy (n = 7) | 145 ± 6.3          | 63.3 ± 7.0† | 136 ± 4.4        | 65.0 ± 9.1† Absolute difference
| **LV dP/dt (mm Hg/sec)** |                    |            |                  |            |
| Intact (n = 16)          | 3790 ± 100         | 1140 ± 90† | 3570 ± 110       | 3290 ± 240‡ Absolute difference
| ABD (n = 7)              | 3970 ± 290         | 1460 ± 130† | 3780 ± 280       | 3000 ± 250‡ Absolute difference
| ABD and vagotomy (n = 7) | 3890 ± 330         | 2970 ± 179† | 3580 ± 270       | 3350 ± 440‡ Absolute difference
| **LV end-diastolic diameter (mm)** |                    |            |                  |            |
| Intact (n = 8)           | 36.97 ± 1.15       | 1.14 ± 0.18† | 32.71 ± 1.28     | 1.80 ± 0.37† Absolute difference
| ABD (n = 6)              | 41.44 ± 0.99       | 1.31 ± 0.39* | 38.06 ± 1.34     | 1.54 ± 0.41* Absolute difference
| ABD and vagotomy (n = 7) | 38.68 ± 1.34       | 0.73 ± 0.18† | 38.72 ± 1.26     | 1.07 ± 0.33* Absolute difference
| **LV stroke shortening (mm)** |                    |            |                  |            |
| Intact (n = 8)           | 9.80 ± 0.59        | 0.86 ± 0.28* | 6.56 ± 0.70      | 2.18 ± 0.46† Absolute difference
| ABD (n = 6)              | 7.82 ± 0.68        | 1.20 ± 0.23† | 5.54 ± 0.73      | 2.21 ± 0.14§ Absolute difference
| ABD and vagotomy (n = 7) | 5.78 ± 0.76        | 1.12 ± 0.32* | 5.85 ± 0.62      | 1.31 ± 0.27† Absolute difference
| **Velocity (mm/sec)**    |                    |            |                  |            |
| Intact (n = 8)           | 85.8 ± 5.1         | 1.5 ± 2.2  | 74.8 ± 4.8       | 24.0 ± 5.8‡ Absolute difference
| ABD (n = 6)              | 80.3 ± 4.1         | 8.0 ± 2.0* | 70.9 ± 5.1       | 24.4 ± 3.5‡ Absolute difference
| ABD and vagotomy (n = 7) | 53.7 ± 4.5         | 19.6 ± 3.7† | 53.8 ± 3.6       | 21.1 ± 2.7† Absolute difference
| **Heart rate (beats/min)** |                    |            |                  |            |
| Intact (n = 16)          | 89.4 ± 3.2         | -12.6 ± 2.6‡ | 177 ± 5.9        | 7.3 ± 2.9‡ Absolute difference
| ABD (n = 7)              | 110 ± 4.7          | 3.8 ± 2.3  | 177 ± 7.5        | -2.3 ± 5.0 Absolute difference
| ABD and vagotomy (n = 7) | 178 ± 5.3          | 5.6 ± 2.0* | 176 ± 4.3        | 5.3 ± 2.5 Absolute difference

* Significant change from control, P < 0.05.
† Significant change from control, P < 0.01.
‡ Response after muscarinic block significantly different from response without block, P < 0.05.
§ Response after muscarinic block significantly different from response without block, P < 0.01.
§§ ABD or ABD plus vagotomy response significantly different from intact response, P < 0.05.
†† ABD or ABD plus vagotomy response significantly different from intact response, P < 0.01.
NE, 0.2 μg/kg per min: Spontaneous Rhythm (Table 1)

**Intact**

NE increased mean arterial pressure (23.6 ± 2.0 mm Hg), LV systolic pressure, dP/dt (1140 ± 90 mm Hg/sec), stroke shortening (0.86 ± 0.28 mm) and end-diastolic diameter, decreased heart rate (12.6 ± 2.6 beats/min), and did not change LV shortening velocity significantly (Table 1). After muscarinic blockade, NE caused significantly greater increases in mean arterial pressure (48.6 ± 5.5 mm Hg), LV systolic pressure, dP/dt (3290 ± 240 mm Hg/sec), velocity (24.0 ± 5.8 mm/sec), and stroke shortening (2.18 ± 0.46 mm), while heart rate increased (7.3 ± 2.9 beats/min). NE increased LV end-diastolic diameter to the same extent as prior to muscarinic blockade. Muscarinic blockade also augmented inotropic responses to smaller doses of NE, i.e., 0.02 and 0.1 μg/kg per min, iv, for 10 minutes (Fig. 1).

**ABD (Fig. 2)**

NE increased mean arterial pressure (35.0 ± 3.8 mm Hg), LV systolic pressure, dP/dt (1460 ± 130 mm Hg/sec), shortening velocity (8.0 ± 2.0 mm/sec), stroke shortening, and end-diastolic diameter, but there was no significant change in heart rate. The increases in mean arterial pressure, LV systolic pressure, and velocity were significantly greater than responses in intact dogs. After muscarinic blockade, note the greater increases in mean arterial pressure, LV pressure, dP/dt, LV diameter, LV velocity, and heart rate before blockade (left panel) and after muscarinic blockade with atropine, 0.1 mg/kg (right panel). After muscarinic blockade, note the greater increases in mean arterial pressure, LV pressure, dP/dt, and velocity with NE.

**Figure 1** The steady state effects of 10-minute intravenous infusions of graded doses of norepinephrine (NE) on LV dP/dt in intact dogs are shown before (unfilled bars) and after muscarinic blockade (filled bars). Control values ± SE are shown at the base of the bars. With each dose, the increase in LV dP/dt was augmented following muscarinic blockade.

**Figure 2** The effects of NE, 0.2 μg/kg per min, are compared in the same dog after recovery from arterial baroreceptor denervation on mean arterial pressure, left ventricular (LV) pressure, dP/dt, LV diameter, LV velocity, and heart rate before blockade (left panel) and after muscarinic blockade with atropine, 0.1 mg/kg (right panel). After muscarinic blockade, note the greater increases in mean arterial pressure, LV pressure, dP/dt, and velocity with NE.
cardiac blockade, NE increased mean arterial pressure (50.3 ± 2.9 mm Hg), LV systolic pressure, dP/dt (3000 ± 250 mm Hg/sec), velocity (24.4 ± 3.5 mm/sec), and stroke shortening significantly more than observed in dogs with ABD prior to muscarinic blockade. After muscarinic blockade, none of the responses to NE was significantly different from those observed in intact dogs after muscarinic blockade.

ABD and Vagotomy

NE increased mean arterial pressure (44.3 ± 8.2 mm Hg), LV systolic pressure, dP/dt (2970 ± 170 mm Hg/sec), velocity (19.6 ± 3.7 mm/sec), stroke shortening, and heart rate (5.6 ± 2.0 beats/min). The NE induced increases in mean arterial pressure, LV systolic pressure, dP/dt, velocity, and heart rate were significantly greater than those observed in intact dogs. The NE-induced increases in dP/dt and velocity were significantly greater in dogs with ABD and vagotomy than in those with ABD alone. In contrast to observations in intact dogs and those with ABD, muscarinic blockade did not augment inotropic responses to NE in dogs with ABD and vagotomy (Fig. 3). Moreover, none of the responses to NE after muscarinic blockade was significantly different from those observed in intact dogs or dogs with ABD after muscarinic blockade.

NE, 0.2 μg/kg per min: Heart Rate Constant (Table 2)

Responses to NE with heart rate constant before and after muscarinic block in intact dogs, dogs with ABD, and dogs with ABD and vagotomy were essentially similar to responses of dogs with spontaneous rhythm. This was not surprising considering the relatively minor effects on heart rate induced by NE and also in view of the minor effects of alterations of heart rate on myocardial contractility in the conscious dog (Higgins et al., 1973b). The responses to NE for dogs with heart rate constant are shown in Table 2.

NE, 0.2 μg/kg per min, in Intact Dogs after Autonomic Blockade (Fig. 4)

Propranolol

To examine the role of β-adrenergic receptors in mediating the augmented inotropic response to NE after atropine, experiments were conducted in conscious dogs after β-adrenergic blockade with propranolol. NE infused in seven animals pretreated with propranolol (1 mg/kg, iv) did not increase LV dP/dt significantly. However, when NE was infused in the presence of combined β-adrenergic receptor and muscarinic blockade, there was a small but significant (P < 0.05) increase in LV dP/dt (420 ± 70 mm Hg/sec). These responses to NE were significantly smaller (P < 0.01) than observed in unblocked dogs.

Reserpine

To determine whether the augmented inotropic response to NE after atropine was dependent upon release of NE from sympathetic nerve endings, experiments were conducted in conscious animals after catecholamine depletion with reserpine. In four dogs chronically pretreated with reserpine, NE increased LV dP/dt (1550 ± 290 mm Hg/sec). With additional blockade, NE produced a significantly greater increase (P < 0.01) in LV dP/dt (8090 ± 1360 mm Hg/sec). The response to NE after muscarinic blockade was significantly greater (P < 0.01) than in dogs without reserpine pretreatment.

6-OH Dopamine

To determine whether the augmented inotropic response to NE after atropine was dependent upon intact sympathetic nerves, experiments were conducted in conscious animals after destruction of sympathetic nerves with 6-OH dopamine. In three dogs chronically pretreated with 6-OH dopamine, NE increased LV dP/dt (3650 ± 100 mm Hg/sec). After additional muscarinic blockade, NE produced
TABLE 2  Effects of Norepinephrine, 0.2 μg/kg per min, with Heart Rate Constant in Intact Conscious Dogs, after ABD, and after ABD Plus Vagotomy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Muscarinic block</th>
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<tr>
<td></td>
<td>No block</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Intact (n = 8)</td>
<td>107 ± 4.7</td>
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<tr>
<td>ABD (n = 7)</td>
<td>98.0 ± 5.7</td>
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<td>ABD and vagotomy (n = 7)</td>
<td>96.3 ± 6.5</td>
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</tr>
<tr>
<td>ABD</td>
<td>122 ± 5.6</td>
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<tr>
<td>ABD and vagotomy</td>
<td>118 ± 6.6</td>
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<tr>
<td>LV systolic pressure (mm Hg)</td>
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<td></td>
</tr>
<tr>
<td>Intact (n = 7)</td>
<td>122 ± 5.6</td>
<td></td>
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<tr>
<td>ABD (n = 7)</td>
<td>112 ± 4.5</td>
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<tr>
<td>ABD and vagotomy (n = 7)</td>
<td>118 ± 6.6</td>
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<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3020 ± 220</td>
<td>2130 ± 290†</td>
</tr>
<tr>
<td>Intact (n = 7)</td>
<td>2790 ± 220</td>
<td>2280 ± 190†</td>
</tr>
<tr>
<td>ABD (n = 7)</td>
<td>2370 ± 220</td>
<td>2280 ± 190†</td>
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<td>LV end-diastolic diameter (mm)</td>
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<td>ABD (n = 6)</td>
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<td>35.59 ± 1.92</td>
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<td>ABD and vagotomy (n = 5)</td>
<td>37.87 ± 1.45</td>
<td>38.53 ± 1.23</td>
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<td>LV stroke shortening (mm)</td>
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<tr>
<td>ABD (n = 6)</td>
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<td>ABD and vagotomy (n = 5)</td>
<td>4.14 ± 0.51</td>
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<tr>
<td>Heart rate (beats/min)</td>
<td>188 ± 7.2</td>
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<tr>
<td>Intact (n = 8)</td>
<td>210 ± 0</td>
<td>213 ± 1.8</td>
</tr>
<tr>
<td>ABD (n = 7)</td>
<td>213 ± 1.8</td>
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</tr>
<tr>
<td>ABD and vagotomy (n = 7)</td>
<td>213 ± 1.8</td>
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</table>

* Significant change from control, P < 0.05.
†† Significant change from control, P < 0.01.
† † † Response after muscarinic block significantly different from response without block, P < 0.05.
§ Response after muscarinic block significantly different from response without block, P < 0.01.
† ABD or ABD plus vagotomy response significantly different from intact response, P < 0.05.
†† ABD or ABD plus vagotomy response significantly different from intact response, P < 0.01.
** ABD and vagotomy response significantly different from ABD response, P < 0.05.
††† Response after muscarinic block significantly different from response without block, 0.05 < P < 0.01
a significantly greater increase (P < 0.01) in LV dP/dt (10,950 ± 170 mm Hg/sec). These responses to NE were significantly greater (P < 0.01) than in dogs without 6-OH dopamine pretreatment.

Cocaine

To determine whether the augmented inotropic response to NE after atropine was dependent upon altered neuronal uptake of NE, experiments were conducted in conscious dogs after neuronal uptake of NE was inhibited with cocaine. In three dogs pretreated with cocaine, NE increased LV dP/dt (4660 ± 130 mm Hg/sec). After additional muscarinic blockade, NE produced a significantly greater increase (P < 0.01) in LV dP/dt (11,000 ± 400 mm Hg/sec). The responses to NE after cocaine were significantly greater (P < 0.01) than in dogs without cocaine pretreatment.

Hexamethonium

To determine whether the augmented inotropic response to NE after atropine involved autonomic neural pathways, responses to NE before and after atropine were examined in conscious dogs after autonomic ganglionic blockade with hexamethonium. In six dogs pretreated with hexamethonium, NE increased LV dP/dt (2990 ± 370 mm Hg/sec). With additional muscarinic blockade, NE induced a similar increase in LV dP/dt (3440 ± 500 mm Hg/sec). The response of LV dP/dt to NE before muscarinic block was significantly greater (P < 0.01) than the response in dogs without hexametho-
EFFECT OF AUTONOMIC BLOCKADES ON RESPONSES TO INTRAVENOUS NOREPINEPHRINE. 0.2 µg/kg/min

**Figure 4** The steady state effects of 10-minute intravenous infusions of NE, 0.2 µg/kg per min, on left ventricular (LV) dP/dt are shown before (unfilled bars) and after muscarinic blockade (filled bars) in intact dogs without blockade and following pretreatment with propranolol, reserpine, 6-OH dopamine, cocaine, and hexamethonium. Control values ± SE are shown at the base of the bars. Hexamethonium blocked the augmentation of LV dP/dt to NE following muscarinic blockade which was still observed when NE was infused in dogs pretreated with propranolol, reserpine, 6-OH dopamine, and cocaine.

Dopamine, 10 µg/kg per min (Table 3)

**Intact Dogs**

Dopamine increased LV systolic pressure, dP/dt (1650 ± 170 mm Hg/sec), velocity (22.5 ± 3.5 mm/sec), end-diastolic diameter, and stroke shortening, but did not alter mean arterial pressure or heart rate significantly. After muscarinic blockade, dopamine induced significantly greater increases in mean arterial pressure (34.4 ± 9.9 mm Hg), LV systolic pressure, dP/dt (4790 ± 630 mm Hg/sec), and velocity (37.3 ± 4.9 mm/sec).

**ABD**

Dopamine increased mean arterial pressure (20.0 ± 5.9 mm Hg), LV systolic pressure, dP/dt (2080 ± 370 mm Hg/sec), stroke shortening, and heart rate, but did not change LV end-diastolic diameter significantly. The increases in mean arterial pressure and heart rate were significantly greater and the changes in LV end-diastolic diameter and stroke shortening were significantly less than observed in intact dogs, but increases in LV dP/dt and velocity were not significantly greater. After muscarinic blockade, dopamine increased mean arterial pressure (53.7 ± 6.3 mm Hg), LV systolic pressure, dP/dt (4440 ± 590 mm Hg/sec), and velocity (40.9 ± 5.0 mm/sec), significantly more than observed prior to muscarinic blockade. None of the responses to dopamine after muscarinic blockade in dogs with ABDwas significantly different from those observed after muscarinic blockade in intact dogs.

Isoproterenol, 0.02 µg/kg per min (Table 4)

**Intact Dogs**

Isoproterenol reduced mean arterial pressure (7.1 ± 1.5 mm Hg) and increased LV dP/dt (670 ± 90 mm Hg/sec), velocity (14.1 ± 1.7 mm/sec), and heart rate (34.7 ± 5.2 beats/min). LV systolic pressure, end-diastolic diameter, and stroke shortening did not change significantly. Following muscarinic blockade, isoproterenol induced significantly greater increases in LV dP/dt (1680 ± 280 mm Hg/sec) and velocity (29.0 ± 3.9 mm/sec) and induced a significantly smaller increase in heart rate (20.1 ± 3.7 beats/min).

**ABD**

Isoproterenol decreased mean arterial pressure (8.4 ± 1.3 mm Hg), LV systolic pressure, and end-diastolic diameter and increased LV dP/dt (600 ± 70 mm Hg/sec), velocity (13.4 ± 1.2 mm/sec), stroke shortening, and heart rate (26.7 ± 6.0 beats/min). None of these changes was significantly different from those seen in intact dogs. After muscarinic blockade, isoproterenol increased LV dP/dt (1470 ± 100 mm Hg/sec) and velocity (21.9 ± 2.3 mm/sec), significantly more than prior to musca-
Cardiac Function

In intact dogs, muscarinic blockade increased heart rate by 88 ± 6 beats/min, decreased LV end-diastolic diameter by 4.26 ± 0.65 mm, and stroke shortening by 3.24 ± 0.32 mm, but failed to change mean arterial pressure, LV systolic pressure, dP/dt or velocity. The effects of muscarinic blockade in dogs with ABD were similar (Table 1). In intact dogs with heart rate constant, muscarinic blockade exerted essentially no effect (Table 2).

Effects of Muscarinic Blockade on Basal Cardiac Function

Effects of Muscarinic Blockade on Percent of Cardiac Output Distributed to the Coronary Vascular Bed

In three dogs, cardiac output and left circumflex coronary flow were measured before and after muscarinic blockade. Prior to blockade, cardiac output was 3730 ± 670 ml/min and left circumflex coronary blood flow was 67.8 ± 1.7 ml/min. After muscarinic blockade, cardiac output was 4500 ± 600 ml/min and left circumflex coronary blood flow was 80.9 ± 1.6 ml/min. The percentages of cardiac output delivered to the left circumflex coronary bed before and after atropine were similar, the values being 1.94 ± 0.33% and 1.85 ± 0.21%, respectively.

Discussion

It is well established that atrial structures have substantial parasympathetic innervation and that, in the conscious dog or man, basal parasympathetic tone is relatively high, with the parasympathetic nervous system playing a major role in the baroreceptor control of heart rate (Vatner and Braunwald, 1975; Higgins et al., 1973a). It is clear also that a sparser population of parasympathetic fibers are present throughout the ventricles (Levy, 1977). Studies using direct vagal stimulation (De Geest et al., 1964, 1966; Daggett et al., 1967; Priola and Fulton, 1969; Harmon and Reeves, 1968; Pace and Keefe, 1970; Stanton and Vick, 1968) and indirectly eliciting vagal reflexes with powerful stimuli under controlled conditions in anesthetized animals (DeGeest et al., 1965a, 1966b; Levy et al., 1966a) have demonstrated a negative inotropic effect. Other studies have demonstrated a positive ino-

Table 3: Effects of Dopamine, 10 µg/kg per min, in Intact Conscious Dogs with Sinus Rhythm and after ABD

<table>
<thead>
<tr>
<th>Vascular Bed</th>
<th>Control</th>
<th>Δ</th>
<th>Muscarinic block</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean arterial Pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact (n = 11)</td>
<td>96.0 ± 4.0</td>
<td>21.2 ± 2.5</td>
<td>97.0 ± 2.4</td>
<td>34.4 ± 9.9†§</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>108 ± 8.6</td>
<td>20.0 ± 5.9*§</td>
<td>111 ± 4.1</td>
<td>53.7 ± 6.3†§</td>
</tr>
<tr>
<td>LV systolic pressure (mm Hg)</td>
<td>119 ± 2.0</td>
<td>17.8 ± 3.4†</td>
<td>120 ± 2.0</td>
<td>59.1 ± 8.9§</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>128 ± 10.1</td>
<td>29.2 ± 6.5†</td>
<td>125 ± 4.0</td>
<td>85.0 ± 6.5†§</td>
</tr>
<tr>
<td>LV dP/dt (mm Hg/sec)</td>
<td>3680 ± 200</td>
<td>1650 ± 170†</td>
<td>3480 ± 180</td>
<td>4790 ± 630§</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>3840 ± 188</td>
<td>2080 ± 370†</td>
<td>3530 ± 280</td>
<td>4440 ± 560§</td>
</tr>
<tr>
<td>LV end-Diastolic diameter (mm)</td>
<td>35.54 ± 1.28</td>
<td>1.37 ± 0.40*</td>
<td>32.02 ± 1.58</td>
<td>0.54 ± 0.62</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>38.30 ± 1.46</td>
<td>0.34 ± 0.18†§</td>
<td>35.46 ± 0.87</td>
<td>0.95 ± 0.57</td>
</tr>
<tr>
<td>LV stroke shortening (mm)</td>
<td>8.40 ± 1.71</td>
<td>2.06 ± 0.36†</td>
<td>7.35 ± 1.30</td>
<td>2.17 ± 0.39†</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>7.56 ± 0.72</td>
<td>0.94 ± 0.11†§</td>
<td>7.51 ± 0.46</td>
<td>2.18 ± 0.47†</td>
</tr>
<tr>
<td>Velocity (mm/sec)</td>
<td>82.8 ± 4.4</td>
<td>22.5 ± 3.5†</td>
<td>76.2 ± 3.9</td>
<td>37.3 ± 4.9‡</td>
</tr>
<tr>
<td>ABD (n = 5)</td>
<td>79.3 ± 6.7</td>
<td>24.6 ± 1.4†</td>
<td>72.7 ± 2.3</td>
<td>40.9 ± 5.0‡‡</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>95.3 ± 3.7</td>
<td>1.8 ± 3.0</td>
<td>167.5 ± 8.0</td>
<td>17.9 ± 4.3†</td>
</tr>
<tr>
<td>ABD (n = 6)</td>
<td>106 ± 7.0</td>
<td>13.0 ± 3.1†§</td>
<td>156 ± 3.8</td>
<td>18.5 ± 7.1†</td>
</tr>
</tbody>
</table>

* Significant change from control, P < 0.05
† Significant change from control, P < 0.01.
‡ Response after muscarinic block significantly different from response without block, P < 0.05.
§ Response after muscarinic block significantly different from response without block, P < 0.01.
; ABD response significantly different from intact response, P < 0.05.
¶ ABD response significantly different from intact response, P < 0.01.
++ Response after muscarinic block significantly different from response without block, 0.05 < P < 0.06.
tropic response during vagal stimulation of the atropinized heart (Priola and Fulton, 1969; Randall et al., 1967, 1968). It is also important to note that there is a functional interaction between adrenergic and cholinergic nerve terminals (Levy et al., 1966b; Lindmar et al., 1968; Loffelholz and Muscholl, 1969; Haeusler et al., 1968) for which there is morphological support (Levy, 1977). Levy and co-workers found that the negative chronotropic and inotropic responses from stimulation of the vagus nerves or administration of acetylcholine are greater in the presence of increasing sympathetic nervous system activity (Levy, 1971). Moreover, inhibition of the inotropic action of NE by acetylcholine has been observed in vitro (Lindmar et al., 1968; Loffelholz and Muscholl, 1969; Haeusler et al., 1968) for which there is morphological support (Levy, 1977). Levy and co-workers found that the negative chronotropic and inotropic responses from stimulation of the vagus nerves or administration of acetylcholine are greater in the presence of increasing sympathetic nervous system activity (Levy, 1971).

In the present investigation, considerable parasympathetic control of basal heart rate but not contractility was found, since muscarinic blockade increased heart rate by 88 ± 6 beats/min but failed to alter LV dP/dt or velocity. Muscarinic blockade also failed to alter LV dP/dt or velocity significantly in dogs with ABD or intact dogs with heart rate constant.

Although muscarinic blockade did not alter basal levels of contractility, it did modify the inotropic response to NE strikingly in the conscious animal. For instance, the responses of left ventricular dP/dt and velocity to NE more than doubled after administration of atropine. Augmented inotropic responses were observed for three different doses of NE. The dose of atropine used in this study is thought to block Type I cholinergic cardiac receptors (Buccino et al., 1966), intimately related to vagal nerve endings, which exert a negative inotropic effect and may be termed "muscarinic." Other muscarinic cholinergic receptors are present in smooth muscle and at both cortical and subcortical levels of the brain (Goodman and Gilman, eds., 1975). Because of atropine sulfate's known stimulatory effects in the central nervous system, methylatropine bromide, which does not cross the blood-brain barrier (Goodman and Gilman, eds., 1975), also was used as a muscarinic blocking agent. With methylatropine bromide, almost identical augmentation of the inotropic response to exogenous NE was seen, indicating that this response was not due to central nervous system stimulation.

To determine whether the enhanced inotropic response is specific for NE, which increases arterial pressure, the effects of dopamine, which causes little change in arterial pressure, or isoproterenol, which decreases arterial pressure, also were examined. It was observed that the direction of arterial pressure change was not critical, since a similar augmentation of the LV inotropic response follow-
In the dogs with ABD, inotropic responses to NE and dopamine were slightly but not significantly greater than in intact dogs, while inotropic responses to isoproterenol were slightly but not significantly less than in intact dogs. However, after muscarinic blockade, similar increases in the inotropic responses to all three sympathomimetic amines were observed in the dogs with ABD as in intact dogs. Thus, the mechanism of the augmented inotropic responses to NE, isoproterenol, or dopamine following muscarinic blockade cannot be ascribed to the arterial baroreceptor reflex.

There are several pieces of evidence indicating that different responses of cardiac frequency were not responsible for the augmented inotropic responses to sympathomimetic amines. First, although NE and dopamine elicited greater increases in heart rate after muscarinic blockade, isoproterenol did not; yet all three agents showed enhanced inotropic responses. Second, in dogs with ABD, heart rate responses to NE, dopamine, or isoproterenol were not greater after muscarinic blockade, although inotropic responses still doubled. Finally, with heart rate held constant by pacing in intact dogs, the augmented inotropic response to NE was still observed after muscarinic blockade. Thus, changes in heart rate could not account for the observed greater increases in contractility with each of the sympathomimetic amines following muscarinic blockade. This is consistent with prior work from this laboratory, in which it was observed that increasing cardiac rate elicited only minor increases in myocardial contractility (Higgins et al., 1973b).

Chronotropic responses to sympathomimetic amines were increased to a lesser extent by muscarinic blockade in intact dogs than were inotropic responses. In dogs with ABD, for which arterial baroreflex buffering was not a factor, inotropic responses to sympathomimetic amines were still enhanced by muscarinic blockade, although chronotropic responses were not affected significantly. The fact that the chronotropic response to sympathomimetic amines was not augmented substantially by muscarinic blockade is difficult to interpret, since baseline heart rate was substantially different before and after atropine. It is also possible that the chronotropic stimulation by iv infusions of NE was too small to be examined critically. For instance, even after vagotomy and ABD, when the direct effects of NE are manifest, NE increased heart rate only slightly. In contrast, the direct inotropic effects of NE were much more impressive (2970 ± 170 mm Hg/sec). Another major difference in the chronotropic and inotropic response was in the mechanism of autonomic buffering. As expected, the buffering of direct chronotropic effects of NE was dependent on arterial baroreflexes. This conclusion is based on the finding that, in dogs with ABD, responses of heart rate to NE were similar before and after vagotomy. Moreover, as has been observed previously (Vatner and Braunwald, 1975; Higgins et al., 1973a) and as also confirmed in this investigation, this effect is known to occur through an increase in parasympathetic restraint rather than withdrawal of sympathetic tone. In contrast, in dogs with ABD, inotropic responses to NE were only slightly greater than in intact dogs, indicating that buffering of inotropic responses to NE occurs to a lesser extent through arterial baroreflexes, although the buffering is also dependent upon the parasympathetic nervous system.

As noted above, augmented inotropic responses to sympathomimetic amines could not be attributed to a change in baseline myocardial contractile state before and after atropine, since the drug did not increase left ventricular dP/dt and velocity.

It was considered that if atropine markedly increased the fraction of cardiac output flowing to the coronary vascular bed, this might result in greater delivery of the drug to the heart after muscarinic blockade which could evoke an apparently greater inotropic response. However, it was observed that the fraction of cardiac output delivered to the left circumflex coronary artery was not different in the presence or absence of atropine, and thus such a mechanism could not explain the marked augmentation of the inotropic responses with infused sympathomimetic amines following muscarinic blockade.

To determine the role of sympathetic mechanisms in the enhanced inotropic response to exogenous catecholamines following muscarinic blockade, dogs were studied following pretreatment with reserpine (which depletes endogenous catecholamine stores), cocaine (which inhibits neuronal uptake of norepinephrine), and 6-OH dopamine, which destroys adrenergic nerve fibers (Jonsson et al., 1975).

Following infusion of NE in dogs pretreated with...
reserpine, cocaine, or 6-OH dopamine, the inotropic responses were greater than those observed in untreated dogs. This was attributable to "denervation sensitivity" to exogenous catecholamines in the presence of reserpine and 6-OH dopamine and to blockade of the NE reuptake mechanism following cocaine (Goodman and Gilman, eds., 1975). However, when NE was infused in these pretreated dogs with the addition of muscarinic blockade, the inotropic response was significantly augmented, indicating that it was not dependent on intact sympathetic nerves, endogenous catecholamine stores, or neuronal reuptake of norepinephrine.

To investigate further the role of the parasympathetic nervous system in modulating these responses, infusions of NE were repeated following bilateral cervical vagotomy in dogs with ABD. After vagotomy, the inotropic responses to NE were similar to those observed in intact dogs or dogs with ABD after muscarinic blockade. However, in the dogs with vagotomy, the augmentation of the inotropic response to NE following muscarinic blockade was no longer observed. This indicates that the mechanism of the enhanced inotropic response to NE by muscarinic blockade depends upon an intact parasympathetic nervous system.

It is also of interest that a similar elimination of this augmented response to NE following muscarinic blockade was seen following pretreatment with hexamethonium, which blocks parasympathetic as well as sympathetic ganglia. Since the experiments with reserpine, 6-OH dopamine, and cocaine indicated that sympathetic mechanisms were not important, it must have been the parasympathetic ganglionic blocking effect of hexamethonium that was responsible for eliminating the enhanced inotropic response to NE.

The results of these experiments suggest that sympathomimetic amine infusions increase vagal activity either centrally or peripherally, at least preganglionically, to release acetylcholine. The acetylcholine could exert an inhibitory effect resulting in a reduction of the inotropic effect of the sympathomimetic amine. Then, after muscarinic blockade, the inhibitory action of acetylcholine would be eliminated, thereby allowing full expression of the inotropic effects of the sympathomimetic amine. An alternative explanation is that acetylcholine exerted a direct negative inotropic effect in the absence of muscarinic blockade but that after blockade, it exerted a positive inotropic effect, thereby potentiating the action of the sympathomimetic amine. Several studies have shown a positive inotropic effect of acetylcholine in the presence of muscarinic blockade (Dempsey and Cooper, 1969; Hoffman et al., 1945; Middleton et al., 1956; Blumenthal et al., 1968; Endoh et al., 1970). However, this latter alternative, i.e., a stimulatory effect of acetylcholine in the presence of muscarinic blockade, most likely is not the mechanism, since responses to NE in dogs with vagotomy or hexamethonium, but not muscarinic blockade, were already as great as those observed after muscarinic blockade in intact dogs and dogs with ABD. If vagally released acetylcholine were exerting a significant positive inotropic effect after muscarinic blockade, then the responses to NE after vagotomy should have been less than those observed in intact dogs or dogs with ABD after muscarinic blockade.

Thus, the mechanism for the striking inotropic augmentation to exogenous sympathomimetic amines following muscarinic blockade probably is related to release of the inhibitory action of acetylcholine. This does not refer specifically to only the direct negative inotropic effects of acetylcholine (Blumenthal et al., 1968; Endoh et al., 1970; Levy and Zieske, 1969) since, after β-adrenergic blockade with propranolol, this action should still be present, but was found to be minor. Rather, it is the ability of acetylcholine to inhibit the inotropic action of catecholamines (Dempsey and Cooper, 1969; Meester and Hardman, 1967; Hollenberg et al., 1965; Ross, 1973) that is probably responsible for the phenomenon observed in the present investigation. With this in mind, it is noteworthy that previous investigators have provided clear evidence for muscarinic inhibition of NE release from sympathetic fibers to the heart (Lindmar et al., 1968; Loffelholz and Muscholl, 1969; Haeusler et al., 1968; Levy and Blattberg, 1976). Whereas this latter mechanism of inhibitory muscarinic receptors is conceptually similar, it involves sympathetic nerves and therefore cannot explain the results of the present investigation, since 6-OH dopamine, which destroys sympathetic nerves, did not block the augmented inotropic response to sympathomimetic amines following muscarinic blockade. Thus, it appears that the vagally released acetylcholine may be inhibiting the action of the sympathomimetic amines at the β-adrenergic receptor. In this connection, it is pertinent that acetylcholine has been found to increase cyclic guanosine 3',5'-monophosphate levels (George et al., 1970; Lee et al., 1972; Watanabe and Besch, 1975; Kuo et al., 1972; Keely et al., 1978) and antagonize the increases in cyclic adenosine 3',5'-monophosphate induced by sympathomimetic amines (Kuo et al., 1972; Keely et al., 1978; Glaviano et al., 1975; Watanabe et al., 1978). This latter effect, i.e., inhibition of the action of sympathomimetic amines on cyclic adenosine 3',5'-monophosphate production, would be consistent with the results of the present investigation. For example, if exogenous sympathomimetic amines activate the vagus to release acetylcholine, this would attenuate the β-receptor-induced increase in adenylyl cyclase. Following muscarinic blockade, however, there would be loss of this inhibitory effect on adenylyl cyclase production, and a substantial increase in inotropy could occur. After vagotomy or hexamethonium, acetylcholine would no longer be released from the vagus and one would expect to see full expression of the inotropic effect of exogenous sympathomim-
metanic amines in the presence or absence of muscarinic blockade, as was observed.

The afferent mechanism responsible for vagal activation by sympathomimetic amines was not elucidated. While clearly it is not mediated by arterial baroreceptor reflexes, stimulation of inhibitory cardiac receptors with vagal afferents could not be excluded. It is also possible that the sympathomimetic amines acted directly on the central nervous system or the vagus.

In conclusion, although there is little resting parasympathetic control of myocardial contractility in the conscious dog, the parasympathetic nervous system can exert a powerful inhibitory influence on the inotropic responses to sympathomimetic amines to the extent that the inotropic responses to infused sympathomimetic amines are doubled in the presence of muscarinic blockade. The mechanism is independent of the arterial baroreceptor reflex and the sympathetic nervous system and appears to involve an inhibitory action of vagally released acetylcholine on the β-adrenergic inotropic response to sympathomimetic amines.

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Interactions of Vasoactive Effects of Adenosine and Potassium Ion on Isolated Feline Coronary Artery Smooth Muscle

DUANE H. FOLEY, EZRA A. AMSTERDAM, AND DEAN T. MASON

SUMMARY This study evaluated the interactions of adenosine and alterations in K⁺ concentration [K⁺] on isolated coronary artery smooth muscle. Helical strips of cat coronary arteries, suspended in physiologic salt solution (37 °C, 95% O₂, and 5% CO₂) were used. In some experiments, isometric tension was induced by acetylcholine (ACh), while in others, spontaneously contracting strips were studied. In the first series of experiments, equilibration of artery strips in solutions of increasing [K⁺] (2.0-10.0 mM) resulted in progressively decreasing responses to adenosine. ACh-stimulated strips were less responsive to 0.1-10.0 µM adenosine than were strips developing spontaneous tone. In the second series of experiments, [K⁺] was elevated abruptly in small increments both in the absence and presence of a background level of adenosine. From an initial concentration of 3.0 mM, a 2.0 mM increment of [K⁺] induced a transient relaxation of 16.0 ± 2.7% in the absence of adenosine. However, following the addition of adenosine, which produced a 20.4 ± 3.0% relaxation, a 2.0 mM increment of [K⁺] induced an additional relaxation of 29.7 ± 4.6%, which was significantly greater than the relaxation in the absence of adenosine (P < 0.005). Simultaneous addition of potassium and adenosine produced significantly greater relaxation than either substance individually. The latter two findings support the concept that vasoactive agents may interact to relax arterial smooth muscle. These results may have implications with regard to local regulation of coronary blood flow. Circ Res 44: 207-215, 1979

THE close, direct relationship between myocardial metabolism and coronary blood flow has long been recognized (Anrep, 1926; Berne, 1964; Eckenhoff et al., 1947; Shipley and Gregg, 1945), but the mechanisms involved remain controversial (Rubio and Berne, 1975). Current evidence strongly supports a major role for the purine nucleoside adenosine in local regulation of coronary vascular resistance (Berne, 1963; Berne and Rubio, 1974; Rubio and Berne, 1975), but contributions by factors such as K⁺, H⁺, O₂, and CO₂ have not been excluded (Haddy, 1969). In this regard, it has been proposed that two or more vasoactive substances of metabolic origin may act in concert to alter coronary vascular resistance in association with reactive hyperemia, autoregulation, and altered myocardial metabolism (Haddy, 1969; Haddy and Scott, 1968).

It has been found that hypoxia potentiates vaso-dilation by potassium in vivo (Skinner and Powell,
Baroreflex and vagal mechanisms modulating left ventricular contractile responses to sympathomimetic amines in conscious dogs.

S F Vatner, J D Rutherford and H R Ochs

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