Coronary Vascular Responses to Stimulation of Chemoreceptors and Baroreceptors

EVIDENCE FOR REFLEX ACTIVATION OF VAGAL CHOLINERGIC INNERVATION

By James G. Hackett, Francois M. Abboud, Allyn L. Mark, Phillip G. Schmid, and Donald D. Heistad

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ABSTRACT

Coronary vascular responses to stimulation of chemoreceptors were studied in anesthetized, artificially ventilated dogs. The circumflex coronary artery was perfused at constant flow so that changes in perfusion pressure reflected changes in coronary resistance. Practolol, a myocardioselective beta-receptor antagonist, and pacing were used to minimize indirect effects of myocardial responses on coronary resistance. Carotid and aortic injections of nicotine produced decreases in coronary perfusion pressure averaging −21 mm Hg and −22 mm Hg, respectively. Decreases with carotid and aortic injections of cyanide averaged −8 mm Hg and −17 mm Hg, respectively. These coronary dilator responses were abolished by bilateral vagotomy or atropine. Changes in perfusion pressure with carotid injections of nicotine averaged +3 mm Hg after vagotomy and +2 mm Hg after administration of atropine. The coronary dilator responses to carotid chemoreceptor stimulation were accompanied by increases in coronary sinus Po2 in five studies and no change in two studies. Carotid sinus nerve stimulation caused abrupt and sustained coronary vasodilatation. After vagotomy or administration of atropine, the response to carotid sinus nerve stimulation was no longer abrupt but occurred gradually, suggesting that a component of the reflex response was blocked. These studies indicate that stimulation of chemoreceptors activates a vagal cholinergic vasodilator pathway to coronary vessels in the dog. Activation of this pathway appears also to contribute to reflex coronary responses to stimulation of baroreceptors.

KEY WORDS practolol atropine nicotine cyanide phentolamine carotid sinus nerve stimulation coronary perfusion carotid body denervation coronary sinus Po2 mongrel dogs

Recent studies on reflex responses to stimulation of chemoreceptors (1–4) indicate that responses in different vascular beds are dissimilar. For example, Calvelo et al. (4) demonstrated that stimulation of chemoreceptors causes vasoconstriction in skeletal muscle and vasodilatation in the paw of the dog.

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These differential responses represent reflex activation of different autonomic sympathetic pathways to skeletal muscle and skin (4). The lack of information concerning effects of stimulation of chemoreceptors on coronary vascular resistance prompted this study.

Coronary vascular responses to stimulation of carotid and aortic chemoreceptors with nicotine and cyanide were studied in anesthetized, ventilated dogs. These responses were compared to those observed during electrical stimulation of the carotid sinus nerve. Observations made after autonomic blockade permitted identification of neural pathways involved in these reflex responses.

Methods

Male mongrel dogs weighing 18–25 kg were anesthetized with a mixture of alpha-chloralose (50 mg/kg, iv) and urethane (500 mg/kg, iv). Decamethonium bromide (0.3 mg/kg, iv) was administered, and the dogs were ventilated at a constant rate (15/min) with a tidal volume of approximately 17 ml/kg. Expiratory pressure of about 2 cm H₂O was maintained with a water trap to prevent atelectasis.

The heart was approached through a left thoracotomy in the fifth intercostal space. The left circumflex coronary artery was dissected free from surrounding tissue near its origin (Fig. 1). A short (2-inch) no. 6 over-needle catheter was placed into the left ventricle through the apex. A no. 6F cardiac catheter was placed into the aortic root via a femoral artery. The tip was positioned approximately 3 cm above the aortic valve by advancing the catheter tip into the left ventricle and then withdrawing it into the aortic root while monitoring pressure. These two catheters were connected to Statham P23Gb transducers to measure left ventricular pressure and systemic arterial blood pressure.

The dogs were then heparinized (5 mg/kg, iv), and blood was withdrawn from a brachial artery and passed through a peristaltic pump (Harvard model 1215). The left circumflex coronary artery was ligated, partially transected, cannulated with dispatch (15–45 seconds), and perfused with arterial blood at constant flow. With flow maintained constant, changes in coronary perfusion pressure reflected changes in coronary vascular resistance. At the start of each experiment flow was adjusted so that perfusion pressure equaled or slightly exceeded systemic arterial blood pressure. Flow, which ranged from 40 ml/min to 62 ml/min, was maintained constant. Perfusion pressure fell abruptly to 10–20 mm Hg when the perfusion pump was stopped, and there was essentially no back flow of blood from the distal end of the partially transected coronary vessel at the time of cannulation, suggesting that there was little or no collateral flow. A delay coil was inserted into the perfusion tubing upstream from the peristaltic pump to eliminate the direct effects of circulating vasoactive agents on the perfused coronary bed during reflex responses. In this preparation significant changes in coronary vascular resistance have been observed during electrical stimulation of left cardiac sympathetic nerves (5). In four experiments, the gracilis muscle was perfused simultaneously in the same manner at 10–14 ml/min to compare coronary responses to those occurring in skeletal muscle.

Left ventricular pressure, the first derivative of left ventricular pressure (left ventricular dP/dt), systemic arterial blood pressure, coronary perfusion pressure, and heart rate were recorded simultaneously on a Beckman type R Dynograph recorder.

Stimulation of Chemoreceptors.—An over-needle catheter (Portex 1/8 X 17 gauge) was placed in the left common carotid artery. Nicotine bitartrate (20 μg base) or sodium cyanide (100 μg base) dissolved in saline was injected through
this catheter to stimulate left carotid chemoreceptors. The catheter was loaded with 0.3 ml of solution and then flushed into the artery with 1.5 ml of saline. Injections of nicotine (4 µg/kg) and cyanide (50 µg/kg) were made also into the aortic root via the aortic root catheter to stimulate both aortic and carotid chemoreceptors. The catheter was loaded with 0.8-1.2 ml of solution and then flushed into the aorta with 4.5 ml of saline. Injection of these volumes of saline alone into the carotid artery or aortic root had no effect.

The changes in coronary resistance in response to stimulation of chemoreceptors reflect not only the direct effect of the reflex on coronary vessels but also the indirect "metabolic" effects produced by changes in heart rate and contractility. To avoid or to minimize changes in rate or contractility during the intervention, the heart was paced and a myocardioselective beta-receptor antagonist was given. The hearts were paced throughout each experiment with electrodes attached near the base of the left ventricle. Rectangular pacing pulses (5.0 v, 2 msec) were generated by a stimulator (American Electronic Laboratories model 104A) at a rate higher than the sinus rate (150-200/min). Practolol (AY-21,011), a beta-receptor antagonist which in small doses (1.0 mg/kg, iv) blocks myocardial but not vascular beta receptors (5-7), was administered at the beginning of each experiment. This dose of practolol effectively blocks increases in myocardial contractility caused by intracoronary injections of isoproterenol (0.25 µg) or norepinephrine (0.5 µg) and by electrical stimulation of left cardiac sympathetic nerves (10 v, 10 Hz, 4 msec) (5). Previous studies on effects of graded doses (1 mg/kg and 2 mg/kg) of practolol on coronary dilator responses to isoproterenol indicated that these doses of practolol do not block coronary vascular beta receptors (8).

### TABLE 1

<table>
<thead>
<tr>
<th></th>
<th>Left carotid</th>
<th>Aortic root</th>
<th>Intracoronary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nic, 20 µg (n = 10)</td>
<td>Chn, 100 µg (n = 8)</td>
<td>Nic, 4 µg/kg (n = 7)</td>
<td>Chn, 5 µg/kg (n = 7)</td>
</tr>
<tr>
<td>Resting CPP (mm Hg)</td>
<td>125 ± 7.6</td>
<td>133 ± 12.3</td>
<td>127 ± 5.5</td>
</tr>
<tr>
<td>ΔCPP (mm Hg)</td>
<td>-21 ± 3.7</td>
<td>-8 ± 3.2</td>
<td>-22 ± 2.8</td>
</tr>
<tr>
<td>Resting SAP (mm Hg)</td>
<td>103 ± 3.4</td>
<td>106 ± 3.5</td>
<td>104 ± 4.3</td>
</tr>
<tr>
<td>ΔSAP (mm Hg)</td>
<td>+15 ± 3.0</td>
<td>+8 ± 3.5</td>
<td>+27 ± 2.4</td>
</tr>
<tr>
<td>Resting LV dp/dt (mm Hg/sec)</td>
<td>2930 ± 317</td>
<td>3100 ± 365</td>
<td>2910 ± 366</td>
</tr>
<tr>
<td>ΔLV dp/dt (%)</td>
<td>+14 ± 3.7</td>
<td>+8 ± 3.3</td>
<td>+22 ± 4.0</td>
</tr>
</tbody>
</table>

*Entries represent means ± SE. N is the number of dogs tested. All experiments were done after treatment with practolol and during pacing. Nicotine (Nic) or cyanide (Chn) was injected into the left carotid artery or into the aortic root. Injections of nitroglycerin (Ng) and acetylcholine (ACh) were given into the perfused coronary artery to test the stability of the vasodilator responses with time and the effectiveness of cholinergic blockade with atropine, respectively. CPP = coronary perfusion pressure, SAP = systemic arterial pressure, and LV = left ventricular.*

*Values after atropine administration that are significantly different (P < 0.05) from corresponding values before atropine administration as determined by the t-test for paired data.

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1Practolol (AY-21,011) was generously supplied by Ayerst Laboratories, New York.
REFLEX CORONARY RESPONSES

In seven experiments, the PO2 of coronary sinus blood was monitored with an in-line flow-through PO2 electrode during stimulation of carotid chemoreceptors, intracoronary injections of nitroglycerin, and changes in pacing rate. Coronary sinus blood was obtained by inserting a balloon catheter into the coronary sinus through a right thoracotomy and atriotomy and then inflating the balloon to occlude the coronary sinus downstream from the tip of the catheter draining the sinus. Blood flow through the PO2 electrode did not change during the interventions (flow was either measured or held constant by a peristaltic pump). The electrode was calibrated at the start of each experiment with gas mixtures containing 0% and 3% oxygen.

Stimulation of Carotid Sinus Nerve.—The possibility that activation of baroreceptors may have contributed to the responses seen during stimulation of chemoreceptors with nicotine or cyanide had to be considered. Some investigators have suggested that nicotine or cyanide may chemically excite the carotid baroreceptors (9), although recent evidence tends to negate this possibility (10). The rise in arterial pressure during stimulation of chemoreceptors also may activate baroreceptor reflexes which would modify the coronary response. The left carotid sinus nerve was dissected free close to its emergence from the bulb of the sinus, and a bipolar electrode was affixed at a site before the junction of the nerve with the carotid body. The carotid sinus nerve was stimulated supramaximally (5 v, 60 Hz, 3 msec), and the stimulus was maintained during injection of nicotine into the ipsilateral left common carotid artery. With the baroreceptor nerves already maximally stimulated, the response to nicotine must represent activation of chemoreceptor and not baroreceptor afferents.

Bilateral Vagotomy, Atropine, and Phentolamine.—The effects of stimulation of carotid chemoreceptors and baroreceptors were studied before and after bilateral cervical vagotomy in some experiments and before and after atropine (0.5 mg/kg, iv) was administered in others. Since in this part of the study we were interested in identifying the efferent pathways, we obtained responses to carotid but not to aortic injections of nicotine, because vagotomy interrupts afferent pathways from the aortic bodies.

In two experiments, after atropine had been administered, coronary responses to carotid sinus nerve stimulation were tested before and after alpha-receptor blockade produced by intracoronary administration of phentolamine (0.5 mg). In three other experiments, phentolamine was given before atropine was administered.

Carotid Body Denervation.—In three experiments, carotid body denervation was achieved by stripping the adventitia off the occipital artery, thereby disrupting the innervation of the carotid body. Responses to intracarotid injections of nicotine were tested before and after denervation.

Administration of Agonists.—Since the reflex coronary responses were dilator responses, nitroglycerin (6 μg) was injected intermittently into the coronary perfusion tubing as an internal control to test the stability of the preparation and the specificity of blockade whenever antagonists were used. Isoproterenol (0.25 μg) was given to test blockade of myocardial beta receptors by practolol. Changes in left ventricular dP/dt were used to indicate the effectiveness of blockade. Intracoronary injections of acetylcholine chloride (4 μg) were used to test the blockade by atropine.

Statistical comparisons were made using the t-test for paired data, and P values < 0.05 were considered significant.

Results

RESPONSES TO STIMULATION OF CHEMORECEPTORS

After practolol had been given and during pacing, systemic arterial blood pressure and
The dilator response to nicotine (Nic.) was associated with a slight increase in coronary sinus $P_{O_2}$. Changes in heart rate produced by altering the pacing rate were associated with opposite changes in perfusion pressure (PP) and coronary sinus $P_{O_2}$. The delay in the changes in coronary sinus $P_{O_2}$ reflects the transit time in the catheter. SAP = systemic arterial pressure, Nitro. = nitroglycerin.

### TABLE 2

Effects of Chemoreceptor Activation and Increases in Heart Rate on Coronary Sinus $P_{O_2}$ and Coronary Perfusion Pressure

<table>
<thead>
<tr>
<th>Intervention</th>
<th>$\Delta$CPP (mm Hg)</th>
<th>$\Delta$CS$P_{O_2}$ (mm Hg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid chemoreceptor activation (nicotine 10-40 $\mu$g)</td>
<td>$-18 \pm 3.2$</td>
<td>$+1.1 \pm 0.4$</td>
<td>7</td>
</tr>
<tr>
<td>Increases in pacing rate by average of $+35 \pm 5$ beats/min$^*$</td>
<td>$-5 \pm 1.4$</td>
<td>$-3.8 \pm 1.1$</td>
<td>6</td>
</tr>
<tr>
<td>Nitroglycerin (6 $\mu$g intracoronary)</td>
<td>$-33 \pm 5.2$</td>
<td>$+0.3 \pm 0.3$</td>
<td>6</td>
</tr>
</tbody>
</table>

Entries are means $\pm$ SE. n is the number of dogs tested. Responses were obtained after administration of practolol (1 mg/kg, iv) and during pacing. $\Delta$CPP = change in coronary perfusion pressure, $\Delta$CS$P_{O_2}$ = change in the coronary sinus partial pressure of oxygen.

$^*$The coronary dilator response to an increase in metabolic demand induced by pacing of the heart at a rapid rate was minimal compared to that caused by activation of chemoreceptors. The increased metabolic demand during rapid pacing was manifested by a significant reduction in coronary sinus $P_{O_2}$ during activation of chemoreceptors.

Left ventricular $dP/dt$ rose significantly following injections of nicotine or cyanide into the carotid artery or the aortic root (Table 1). There was a simultaneous abrupt fall in coronary perfusion pressure (Fig. 2 and Table 1). The same stimuli caused simultaneous vasoconstriction in the perfused gracilis muscle (Fig. 2). The reflex constrictor response in the gracilis muscle averaged $+49 \pm 7$ (SE) mm Hg before administration of atropine and $+39 \pm 7$ mm Hg after administration of atropine.

In seven experiments, coronary sinus $P_{O_2}$ was monitored during the coronary dilatation produced by carotid chemoreceptor activation after administration of practolol and during pacing. The coronary dilator response was accompanied by an increase in coronary sinus $P_{O_2}$. 

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Po₂ in five of the studies and no change in two (Fig. 3 and Table 2). In contrast the slight dilator response caused by increases in pacing and heart rates was associated with decreases in Po₂ (Fig. 3 and Table 2). The dilatation with nitroglycerin was accompanied by slight

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**FIGURE 4**

Segments of record from one experiment showing responses to electrical stimulation of the left carotid sinus nerve before (left) and after (right) bilateral vagotomy. PP = perfusion pressure, CSNS = carotid sinus nerve stimulation.

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**FIGURE 5**

Coronary dilator responses to carotid sinus nerve stimulation (CSNS) at 5 v, 60 Hz, and 3 msec before and after bilateral vagotomy (BLV) and before and after atropine. Asterisks indicate that responses before atropine or vagotomy were significantly different from responses after atropine or vagotomy. Entries represent mean values ± se for five dogs.
Coronary dilator responses to stimulation of left carotid (LC) chemoreceptors with nicotine (NIC) during supramaximal electrical stimulation of the left carotid sinus nerve (CSNS). After bilateral vagotomy the coronary response to carotid sinus nerve stimulation was less abrupt and the response to nicotine was abolished. PP = perfusion pressure.

Increases in coronary sinus Po2 in three experiments, a slight decrease in one, and no change in two.

**Effect of Atropine and Bilateral Vagotomy on the Coronary Vasodilator Response to Stimulation of Chemoreceptors**

After administration of atropine the coronary vasodilator response to stimulation of chemoreceptors was blocked; however, the increases in arterial blood pressure and left ventricular dP/dt persisted (Table 1). The coronary vasodilator response to acetylcholine also was abolished, but the response to nitroglycerin was not altered significantly. Reflex vasoconstriction in the perfused gracilis muscle was maintained after administration of atropine (Fig. 2).

Bilateral vagotomy or denervation of the carotid body abolished the coronary vasodilator responses to carotid injections of nicotine (Table 3). Responses to the internal control, nitroglycerin, were reduced after vagotomy and carotid body denervation, but significant dilator responses were still observed at a time when dilator responses to nicotine were abolished.

**Coronary Vascular Responses to Stimulation of Carotid Baroreceptors**

Maximal stimulation of the carotid sinus nerve resulted in an abrupt fall in coronary perfusion pressure similar to that seen after stimulation of chemoreceptors; the dilatation was sustained until the stimulus was terminated (Figs. 4-6). Systemic arterial blood pressure decreased gradually 5-10 seconds after onset of carotid sinus nerve stimulation (Fig. 4). The maximal fall in arterial blood pressure averaged $-14 \pm 1.2$ mm Hg in ten dogs. Left

### Table 4

<table>
<thead>
<tr>
<th>Exp.</th>
<th>CSNS before atropine (mm Hg)</th>
<th>CSNS after atropine (mm Hg)</th>
<th>CSNS after phenolamine (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Resting CPP (mm Hg)</td>
<td>160</td>
<td>132</td>
</tr>
<tr>
<td></td>
<td>ΔCPP (mm Hg)</td>
<td>−22</td>
<td>−3</td>
</tr>
<tr>
<td></td>
<td>Resting SAP (mm Hg)</td>
<td>110</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>ΔSAP (mm Hg)</td>
<td>−15</td>
<td>−13</td>
</tr>
<tr>
<td></td>
<td>Resting LV dP/dt (mm Hg/sec)</td>
<td>9600</td>
<td>2200</td>
</tr>
<tr>
<td></td>
<td>ΔLV dP/dt (%)</td>
<td>−20</td>
<td>−10</td>
</tr>
<tr>
<td>2</td>
<td>Resting CPP (mm Hg)</td>
<td>160</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>ΔCPP (mm Hg)</td>
<td>−14</td>
<td>−18</td>
</tr>
<tr>
<td></td>
<td>Resting SAP (mm Hg)</td>
<td>115</td>
<td>105</td>
</tr>
<tr>
<td></td>
<td>ΔSAP (mm Hg)</td>
<td>−11</td>
<td>−13</td>
</tr>
<tr>
<td></td>
<td>Resting LV dP/dt (mm Hg/sec)</td>
<td>2800</td>
<td>3400</td>
</tr>
<tr>
<td></td>
<td>ΔLV dP/dt (%)</td>
<td>−5</td>
<td>−12</td>
</tr>
</tbody>
</table>

See footnote to Table 1 for abbreviations. Responses were measured 10 seconds and 30 seconds after onset of a 30-second period of carotid sinus nerve stimulation (CSNS).
ventricular dP/dt also decreased gradually with the onset of stimulation (−10 ± 1.8%). After bilateral vagotomy in five of these dogs (Fig. 5A) and after administration of atropine in the other five (Fig. 5B), the initial abrupt phase of the dilator response occurring during the first 10 seconds of carotid sinus nerve stimulation was almost abolished and the dilatation occurred more gradually, reaching a maximum toward the end of the 30-second period of stimulation.

In two experiments, the gradual coronary dilatation which persisted in response to carotid sinus nerve stimulation after administration of atropine was blocked by phentolamine (Table 4, see values after 30 seconds of stimulation). In two other experiments in which phentolamine was administered before atropine, a coronary dilator response to carotid sinus nerve stimulation was observed after phentolamine administration and subsequently abolished by administration of atropine.

**Discussion**

The results of these experiments indicate that the reflex response of the coronary vessels to stimulation of chemoreceptors is vasodilation. This vasodilation does not represent an indirect metabolic effect caused by changes in rate or contractility resulting from activation of aortic chemoreceptors (11) or an effect on heart rate or contractility resulting from changes in the response of chemoreceptors to stimulation of chemoreceptors in the peripheral circulation. This vasodilation is caused by activation of cholinergic fibers leading to the local release of acetylcholine, which causes a coronary vasodilator response (12). After vagotomy, the coronary response to carotid sinus nerve stimulation persisted but occurred more gradually. On the other hand, the response to stimulation of chemoreceptors was abolished (Fig. 6 and Table 5).

**TABLE 5**

Response to Activation of Carotid Chemoreceptors during Carotid Sinus Nerve Stimulation

<table>
<thead>
<tr>
<th></th>
<th>∆CPP (mm Hg)</th>
<th></th>
<th>∆SAP (mm Hg)</th>
<th></th>
<th>∆dP/dt (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 sec Plattus</td>
<td>+ Nic</td>
<td>10 sec Plattus</td>
<td>+ Nic</td>
<td>10 sec Plattus</td>
</tr>
<tr>
<td>Before Bilateral Vagotomy</td>
<td>(108 ± 9.8)</td>
<td>−18 ± 4.2</td>
<td>(89 ± 9.5)</td>
<td>−4 ± 4.6</td>
<td>(1640 ± 89)</td>
</tr>
<tr>
<td>After Bilateral Vagotomy</td>
<td>(101 ± 9.9)</td>
<td>−5 ± 1.9*</td>
<td>(88 ± 7.8)</td>
<td>−6 ± 3.8*</td>
<td>(1820 ± 78)</td>
</tr>
</tbody>
</table>

Resting values are shown in parentheses. See Table 1 for abbreviations. The data were taken after 10 seconds of carotid sinus nerve stimulation and during the plateau of the response approximately 40 seconds after onset of carotid sinus nerve stimulation. While continuing stimulation, at approximately 45 seconds, nicotine was injected into the left carotid artery. The data for nicotine and stimulation were taken during the peak response within 10 seconds of the injection and represent changes from control levels before stimulation. After the response to nicotine and while carotid sinus nerve stimulation continued, the values returned to plateau levels. With vagotomy and after administration of atropine, the initial abrupt phase of the dilator response occurring during the first 10 seconds of carotid sinus nerve stimulation was almost abolished and the dilatation occurred more gradually, reaching a maximum toward the end of the 30-second period of stimulation.
caused by changes in myocardial compression of the coronary vascular bed. By pacing the ventricles at a constant rate and by administering practolol, the chronotropic and inotropic responses to stimulation of chemoreceptors were abolished or minimized. The increase in left ventricular \(dP/dt\) and in arterial blood pressure seen after injections of nicotine and cyanide could not have contributed significantly to the coronary dilatation because the dilatation was blocked by atropine and by bilateral vagotomy despite persistence of the increases in arterial blood pressure and left ventricular \(dP/dt\) (Tables 1 and 3). The coronary dilator responses cannot be explained by negative inotropic effects of vagal stimulation (12), since these effects should produce coronary vasoconstriction by decreasing metabolic demands. In addition, the coronary vasodilator response to chemoreceptor activation was accompanied by an increase (five experiments) or no change (two experiments) in coronary sinus \(P_{O_2}\) in contrast to decreases in coronary sinus \(P_{O_2}\) which accompanied the slight dilator response to increases in heart rate and presumably myocardial oxygen consumption (Table 2). These observations indicate that the dilatation results from a direct neurogenic effect on coronary vessels.

Intravenous administration of atropine was effective in blocking the coronary dilator response but did not inhibit the reflex vasoconstriction in the gracilis muscle, suggesting that atropine modified the coronary responses through an effect on the efferent component of the reflex rather than an effect on the afferent component or a nonspecific central depression of the reflex response. The preservation of a response of coronary vessels to nitroglycerin after atropine indicates that the coronary vessels had maintained their capacity to dilate.

The afferent limb of this reflex response must be via fibers originating from the carotid body since denervation of the body abolished the response (Table 3). Any contribution of a central action of nicotine or cyanide to the reflex was probably negligible.

The efferent pathway mediating this response must be through vagal cholinergic fibers. The work of Berne et al. (13) and more recently the work of Feigl (14) demonstrated the presence of vagal cholinergic vasodilator fibers to coronary vessels by direct electrical stimulation of the distal ends of the cut vagi. The present experiments indicate that this parasympathetic cholinergic innervation of the coronary vessels can be activated reflexly during stimulation of chemoreceptors. It is doubtful that either activation of sympathetic cholinergic innervation or withdrawal of sympathetic constrictor tone contributes to this coronary vasodilator response for two reasons. Observations reported earlier by Feigl (15) did not support the presence of cholinergic sympathetic innervation in coronary vessels. Furthermore, the response was abolished after vagotomy despite the presence of intact sympathetic innervation.

Differential reflex activation of the components of the autonomic system is evident in these and in previous studies (4). Stimulation of chemoreceptors has been shown to activate sympathetic adrenergic constrictor fibers to the gracilis muscle and simultaneously to activate sympathetic noncholinergic vasodilator fibers in the paw (4). The myocardial response includes an initial bradycardia which is predominantly vagal and, with activation of aortic chemoreceptors, an increase in contractility which is of sympathetic adrenergic origin (11). The present studies indicate that the direct coronary response represents activation of vagal cholinergic innervation which, along with the indirect dilator response, would tend to increase flow to meet the metabolic demands of the positive inotropic response.

Simultaneous activation of baroreceptors with nicotine or cyanide could not have caused the coronary response for two reasons. First, during maximal stimulation of the baroreceptor nerves, the coronary vascular response to stimulation of chemoreceptors was not altered (Fig. 6), and, second, the baroreceptor response was not abolished by atropine or by bilateral vagotomy.
One other point deserves mentioning. The work of Vatner et al. (16) has shown that carotid sinus nerve stimulation causes a withdrawal of sympathetic constrictor tone and coronary vasodilatation in conscious dogs. We also attributed the response to carotid sinus nerve stimulation after atropine administration or bilateral vagotomy in our studies to withdrawal of sympathetic tone, because it was abolished by administration of phentolamine (Table 4). Our experiments indicate that there is, in addition, a significant vagal cholinergic component to this baroreceptor reflex (Fig. 5). Vatner et al. did not recognize this effect. They indicated that after withdrawal of sympathetic constrictor tone produced by administering phenoxybenzamine carotid sinus nerve stimulation did not lower coronary resistance. In their experiments coronary resistance remained constant in the face of a fall in arterial blood pressure and an insignificant change in heart rate. One might have expected a passive increase in coronary resistance to occur during the fall in arterial blood pressure, and the absence of such an increase may be due to a latent cholinergic dilator effect counteracting the passive increase in resistance.

We wish to suggest on the basis of current experimental work that (1) stimulation of chemoreceptors activates reflexly a vagal cholinergic vasodilator pathway to the coronary vessels and that (2) carotid sinus nerve stimulation causes coronary vasodilatation reflexly by withdrawal of sympathetic constrictor tone and by activation of a vagal cholinergic vasodilator pathway which causes an abrupt initial transient dilatation.

References

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