Comparison of the Reflexes Elicited from Combined or Separate Stimulation of the Aortic and Carotid Chemoreceptors on Myocardial Contractility, Cardiac Output and Systemic Resistance

By Shlomo Stern and Elliot Rapoport

ABSTRACT

Changes in left ventricular performance, stroke volume, and peripheral vascular resistance were studied in dogs after combined and separate stimulation of the aortic and carotid chemoreceptors. Selective stimulation of the aortic chemoreceptors produced an immediate increase in myocardial contractility as judged by the force developed by a strain gauge arch sewn into the left ventricular myocardium and by changes in the first derivative of the left ventricular pressure. Similar results were seen when heart rate changes were prevented by prior administration of atropine, when changes in outflow impedance were prevented by previous blockade of the alpha-adrenergic receptors, and when there was combined chemoreceptor stimulation. Beta-adrenergic blockade prevented the increase in myocardial contractility observed after chemoreceptor stimulation. With selective carotid chemoreceptor stimulation there was no significant change in contractility. Aortic chemoreceptor stimulation increased the heart rate and peripheral vascular resistance, while stroke volume decreased; carotid chemoreceptor stimulation slowed the heart rate and increased the stroke volume, but not change peripheral vascular resistance.

ADDITIONAL KEY WORDS: ventricular performance, chemoreflexes, hemodynamics, adrenergic receptor blockade, sympathetic fibers, anesthetized dogs

Recent reports on the effect of chemoreceptor stimulation on myocardial performance seemingly differ. Using anoxia as the stimulus to the carotid chemoreceptors, several investigators (1-3) described a negative inotropic effect. Using combined anoxic stimulation of the carotid and aortic chemoreceptors, other workers (4) described a positive inotropic effect. These opposing findings led us to re-evaluate the effects of chemoreceptor stimulation on the performance of the left ventricle. Data indicate that the hemodynamic responses to stimulation of the aortic and carotid chemoreceptors differ (5, 6); therefore, we were careful to separate the effects arising from each of these receptors. We were also able to separate any changes in myocardial contractility induced by direct sympathetic stimulation from those induced by reflex peripheral vasoconstriction and resultant increase in outflow impedance (7, 8) by using drugs to produce separate and combined blockade of the alpha- and beta-adrenergic receptors. We also studied the immediate changes in stroke volume following chemoreceptor stimulation, since measurements of cardiac output in pre-
previous studies (9, 10) have been steady-state observations made some minutes after applying a stimulus to the chemoreceptors.

Methods
We used mongrel dogs weighing 15 to 25 kg and induced anesthesia by 25 mg/kg pentobarbital iv. The corneal reflex served as a guide for the maintenance of anesthesia. We opened the thorax at the left fourth intercostal space and maintained respiration through a cuffed endotracheal tube with a Harvard constant-volume respirator. Aortic pressure was measured by a catheter introduced through the left femoral artery with its tip placed in the upper part of the descending aorta. Left ventricular pressure was measured either by puncturing the ventricle with a 14-gauge Rochester needle connected to a Statham P23D transducer or by an intracardiac micromanometer (Telco) introduced through the left brachial artery; this pressure was differentiated by an R-C circuit in order to obtain the first derivative. Calibration (millimeters mercury per second) was accomplished by introducing into the differentiator a voltage from a waveform generator as a sawtooth signal of known frequency, equivalent to a known value of millimeters mercury pressure on the strain gauge amplifier. A strain gauge arch was sewn into the myocardium of the left ventricle and then the underlying myocardium was stretched approximately 50% of its initial diastolic length by moving the feet of the arch apart. An electromagnetic flowmeter probe (16 mm diameter; Type Q, Statham) was slipped around the ascending aorta without closing the slot, thereby leaving the tissues and structures between the ascending aorta and pulmonary artery intact. The probe was connected to a Statham electromagnetic flowmeter (Model M-4000); the unit was calibrated in vitro with known flows. The velocity signal was either electrically integrated or calculated by planimetry to obtain flow values. An electrocardiogram was continuously monitored. An Electronics for Medicine Model PR7 or DR8 was used for recording.

The response to nicotine stimulation usually began 1.5 to 3.0 sec after the injection and the changes during the first 15 sec of the reaction are the subject of this study. This 15-sec interval was divided into three 5-sec periods. We measured the heart rate, the mean pressure in the aorta, the pressure in the left ventricle during systole and diastole, the first derivative of the left ventricular pressure pulse (\(dp/dt\)), the contractile force of the myocardium as obtained from the arch of the strain gauge, the stroke volume, the peak velocity of aortic blood flow, and the systemic vascular resistance. This resistance was calculated by dividing the mean aortic pressure by the over-all flow during each 5-sec period. The deflection from the arch of the strain gauge during the control period was taken as 100% and subsequent values were expressed as a percentage of this control condition; all other measurements were expressed as absolute values. The variables obtained during each 5-sec period were compared to the values obtained during a 5-sec control period just before the injection. Thus each experiment had its own control period. The measurements were made for each beat and then averaged for each 5-sec period, thus eliminating variations due to respiration or other factors. The results obtained were statistically evaluated for the significance of the changes from control values and the significance of the changes between each of the three 5-sec experimental periods. Figure 1 illustrates the type of recordings we obtained.

We used nicotine bitartrate to stimulate the chemoreceptors. The drug was injected through a catheter introduced by way of the right brachial artery into the ascending aorta near the aortic valve to stimulate the aortic chemoreceptors or both the aortic and carotid chemoreceptors (5 to 10 \(\mu g/kg\) diluted in 1.0 to 1.5 ml saline), through another catheter placed in the brachiocephalic artery by way of the right femoral artery to stimulate the carotid chemoreceptors (2 \(\mu g/kg\)), or through the catheter placed in the upper part of the descending aorta (5 to 10 \(\mu g/kg\)). A description of the separate procedures follows.

Results
AORTIC CHEMORECEPTOR STIMULATION (GROUP 1)
We used two methods to study the effects of selective aortic chemoreceptor stimulation. In 4 dogs we used the method described by Comroe and Mortimer (11), and inserted plastic coils 140 cm long into both common carotid arteries. Drugs injected at the base of the ascending aorta reach the aortic chemoreceptors immediately, but arrive at the carotid bodies 15 to 70 sec later. In 3 other dogs the nicotine was injected into the ascending aorta after the carotid bodies had been surgically denervated. Sixteen injections were performed in 7 dogs.

Selective stimulation of the aortic chemoreceptors by each method evoked identical responses. An increase in the force of myocardial contraction sensed by the strain gauge arch and in maximum left ventricular \(dp/dt\) was observed during each of the three 5-sec experimental periods after injection. Left ven-
FIGURE 1

Effect of selective aortic chemoreceptor stimulation (Group 1). Symbols used in this and in Figure 2: ARCH = signal from strain gauge arch sewn into left ventricle; dp/dt = the first derivative of left ventricular pressure; AOm = aortic mean pressure; LV = left ventricular pressure; V = velocity of flow in ascending aorta; Q = flow in ascending aorta, obtained by integration of velocity signal.
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**TABLE 1**

<table>
<thead>
<tr>
<th>Group 1—Selective Aortic Chemoreceptor Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate preinjection period</td>
</tr>
<tr>
<td>5 sec</td>
</tr>
<tr>
<td>Heart rate (beats/5 sec)</td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Left ventricle dp/dt (mm Hg/sec)</td>
</tr>
<tr>
<td>Aorta, mean pressure (mm Hg)</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
</tr>
<tr>
<td>Left ventricle stroke volume (ml)</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
</tr>
</tbody>
</table>

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**TABLE 2**

<table>
<thead>
<tr>
<th>Group 2—Combined Aortic and Carotid Chemoreceptor Stimulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate preinjection period</td>
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<tr>
<td>5 sec</td>
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<tr>
<td>Heart rate (beats/5 sec)</td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Left ventricle dp/dt (mm Hg/sec)</td>
</tr>
<tr>
<td>Aorta, mean pressure (mm Hg)</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
</tr>
<tr>
<td>Left ventricle stroke volume (ml)</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
</tr>
</tbody>
</table>

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TABLE 3

Group 3—Combined Aortic and Carotid Chemoreceptor Stimulation Following Pretreatment with Atropine

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Immediate preinjection period (5 sec)</th>
<th>Postinjection changes (% of control)</th>
<th>0-5 sec</th>
<th>5-10 sec</th>
<th>10-15 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/5 sec)</td>
<td>13.3 ± .6</td>
<td>+6.3</td>
<td>+.2</td>
<td>-.2</td>
<td></td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
<td>100 ± 0</td>
<td>+17.3</td>
<td>+17.4</td>
<td>+16.3</td>
<td></td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
<td>131 ± 2.8</td>
<td>+16.0</td>
<td>+27.7</td>
<td>+23.9</td>
<td></td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
<td>6 ± 3.6</td>
<td>+18.8</td>
<td>+9.5</td>
<td>+9.5</td>
<td></td>
</tr>
<tr>
<td>Left ventricle dp/dt (mm Hg/sec)</td>
<td>1010 ± 69.3</td>
<td>+22.9</td>
<td>+37.6</td>
<td>+39.6</td>
<td></td>
</tr>
<tr>
<td>Aorta mean pressure (mm Hg)</td>
<td>104 ± 3.3</td>
<td>+20.1</td>
<td>+33.0</td>
<td>+25.6</td>
<td></td>
</tr>
<tr>
<td>Peak velocity (cm/sec)</td>
<td>95 ± 4.8</td>
<td>-1.4</td>
<td>+9.6</td>
<td>+7.7</td>
<td></td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
<td>153 ± 0.7</td>
<td>+2.5</td>
<td>+10.5</td>
<td>+8.0</td>
<td></td>
</tr>
<tr>
<td>Left ventricle stroke volume (ml)</td>
<td>11.7 ± .6</td>
<td>-3.4</td>
<td>+10.2</td>
<td>+12.8</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>698 ± 24.5</td>
<td>+17.1</td>
<td>+19.6</td>
<td>+12.7</td>
<td></td>
</tr>
</tbody>
</table>

tricular systolic and aortic mean pressures increased. Systemic vascular resistance rose significantly during the first 5-sec period; stroke volume decreased but, with the concomitant increase in heart rate, the over-all flow changed only slightly. The trend was similar during the second and third 5-sec experimental period (Table 1, Fig. 1).

AORTIC AND CAROTID CHEMORECEPTOR STIMULATION (GROUP 2)

Nicotine injected into the base of the ascending aorta reached the aortic and the carotid chemoreceptors at almost the same time. Sixteen injections were performed in 7 dogs.

The changes were much the same as those in group 1, except for the effects on heart rate and stroke volume. During the first 5-sec period, a significant bradycardia was observed. With the slow heart rate, the stroke volume increased so that the over-all flow did not differ significantly from the control flow. The stroke volume remained elevated during all three 5-sec periods. The systemic vascular resistance also rose significantly during all three periods (Table 2).

COMBINED STIMULATION WITHOUT BRADYCARDIA (GROUP 3)

We injected 0.4 mg/kg atropine iv into the 7 dogs in group 2, waited 20 min, and injected nicotine into the base of the ascending aorta. Eleven injections were made.

The results during the first 5 sec after injection became similar to those obtained in group 1 after stimulation of the aortic chemoreceptors alone (Table 3).

CAROTID BODY STIMULATION (GROUP 4)

We used two methods to study the effects of selective carotid body stimulation. In the 4 dogs in which carotid coils had been inserted, we injected nicotine into the distal end of the coil. In 7 other dogs without coils, nicotine was injected into the brachiocephalic artery. Twelve injections were made.

There were small and statistically insignificant effects on myocardial contractility as judged by changes in the signal from the...
arch of the strain gauge and in dp/dt during the first 10 sec of response. The only significant effect was a decrease in heart rate and the consequent increase in stroke volume. There were no significant changes in left ventricular or arterial pressure, total flow, or systemic vascular resistance (Table 4).

**AORTIC CHEMORECEPTOR STIMULATION AFTER ALPHA-ADRENERGIC BLOCK (GROUP 5)**

We infused Dibenzyline, 5 mg/kg iv, over a period of 20 min into dogs having either carotid-delay coils or denervated carotid bodies. Ten to 30 minutes after the infusion, we injected 5 to 10 μg/kg of nicotine into the ascending aorta. Thirteen injections were made in these 7 dogs.

The prior blockade of the alpha-adrenergic receptors by Dibenzyline prevented the increase in systemic vascular resistance during the first 5 sec after selective aortic chemoreceptor stimulation, although a significant increase was seen in the later periods. The increase in left ventricular systolic and aortic mean pressures during this first 5 sec of response was small and significantly less than seen prior to alpha blockade (see Table 1). Nevertheless, there was still a significant increase in maximum dp/dt and the force developed underneath the arch of the strain gauge (Table 5, Fig. 2) and a significant increase in the peak velocity of ascending aorta flow during the first 10 sec, although there was no change in stroke volume during this period.

**AORTIC CHEMORECEPTOR STIMULATION AFTER BETA-ADRENERGIC BLOCK (GROUP 6)**

We infused 0.5 mg/kg iv propranolol in dogs either with carotid coils or with carotid body denervation. Five minutes after the propranolol, we stimulated the aortic chemoreceptors by injecting nicotine into the ascending aorta. Eight injections were made in 5 dogs.

The previous blockade of the beta-adrenergic receptors completely abolished the increase in myocardial contractility following aortic chemoreceptor stimulation observed with group 1. However, there was still a significant rise in the left ventricular systolic and
### TABLE 4

**Group 4—Selective Carotid Chemoreceptor Stimulation**

<table>
<thead>
<tr>
<th>Immediate preinjection period</th>
<th>Postinjection changes (% of control)</th>
<th>5 sec</th>
<th>0-5 sec</th>
<th>5-10 sec</th>
<th>10-15 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td>13.3± 0.5</td>
<td>-10.3</td>
<td>-5.5</td>
<td>-3.9</td>
</tr>
<tr>
<td>(beats/5 sec)</td>
<td></td>
<td>0.01 &lt; P &lt; 0.05</td>
<td>0.025 &lt; P &lt; 0.05</td>
<td>0.01 &lt; P &lt; 0.025</td>
<td></td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
<td></td>
<td>100± 0</td>
<td>-1.2</td>
<td>-0.5</td>
<td>-7.5</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
<td></td>
<td>126± 3.6</td>
<td>0.2 &lt; P &lt; 0.4</td>
<td>P &gt; 0.5</td>
<td>P &gt; 0.5</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
<td></td>
<td>2± 0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aorta mean pressure (mm Hg)</td>
<td></td>
<td>1126± 113</td>
<td>+5.5</td>
<td>+4.7</td>
<td>+3.9</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
<td></td>
<td>89± 4.8</td>
<td>-3.3</td>
<td>+2.8</td>
<td>+2.8</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
<td></td>
<td>104± 2.4</td>
<td>+2.7</td>
<td>+1.8</td>
<td>+2.4</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td>162± 7.5</td>
<td>-4.4</td>
<td>-4</td>
<td>+1.45</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
<td></td>
<td>122± 6.2</td>
<td>+6.9</td>
<td>+5.5</td>
<td>+7.7</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
<td></td>
<td>557± 41</td>
<td>+2.5</td>
<td>+1.4</td>
<td>+1.0</td>
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</table>

**Immediate preinjection period Postinjection changes (% of control) 5 sec 0-5 sec 5-10 sec 10-15 sec**

<table>
<thead>
<tr>
<th>Immediate preinjection period</th>
<th>Postinjection changes (% of control)</th>
<th>5 sec</th>
<th>0-5 sec</th>
<th>5-10 sec</th>
<th>10-15 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td>15.4± 0.5</td>
<td>+3.1</td>
<td>+5.2</td>
<td>+5.5</td>
</tr>
<tr>
<td>(beats/5 sec)</td>
<td></td>
<td>0.1 &lt; P &lt; 0.2</td>
<td>0.05 &lt; P &lt; 0.1</td>
<td>0.025 &lt; P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
<td></td>
<td>100± 0</td>
<td>+6.5</td>
<td>+8.2</td>
<td>+8.5</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
<td></td>
<td>95± 6.2</td>
<td>+5.4</td>
<td>+7.7</td>
<td>+6.7</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
<td></td>
<td>3± 0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aorta mean pressure (mm Hg)</td>
<td></td>
<td>1594± 153</td>
<td>+14</td>
<td>+25.5</td>
<td>+26.4</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
<td></td>
<td>66± 3.8</td>
<td>+2.9</td>
<td>+8.2</td>
<td>+1.3</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
<td></td>
<td>122± 6.5</td>
<td>+0.8</td>
<td>+15.5</td>
<td>+15.0</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td>178± 9.5</td>
<td>+2.9</td>
<td>-3.6</td>
<td>-8.3</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
<td></td>
<td>11.5± 4.1</td>
<td>+1</td>
<td>-7.7</td>
<td>-12.3</td>
</tr>
</tbody>
</table>

### TABLE 5

**Group 5—Selective Aortic Chemoreceptor Stimulation Following Pretreatment with Dibenzyline**

<table>
<thead>
<tr>
<th>Immediate preinjection period</th>
<th>Postinjection changes (% of control)</th>
<th>5 sec</th>
<th>0-5 sec</th>
<th>5-10 sec</th>
<th>10-15 sec</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td>15.4± 0.5</td>
<td>+3.1</td>
<td>+5.2</td>
<td>+5.5</td>
</tr>
<tr>
<td>(beats/5 sec)</td>
<td></td>
<td>0.1 &lt; P &lt; 0.2</td>
<td>0.05 &lt; P &lt; 0.1</td>
<td>0.025 &lt; P &lt; 0.05</td>
<td></td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
<td></td>
<td>100± 0</td>
<td>+6.5</td>
<td>+8.2</td>
<td>+8.5</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
<td></td>
<td>95± 6.2</td>
<td>+5.4</td>
<td>+7.7</td>
<td>+6.7</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
<td></td>
<td>3± 0.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Aorta mean pressure (mm Hg)</td>
<td></td>
<td>1594± 153</td>
<td>+14</td>
<td>+25.5</td>
<td>+26.4</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
<td></td>
<td>66± 3.8</td>
<td>+2.9</td>
<td>+8.2</td>
<td>+1.3</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
<td></td>
<td>122± 6.5</td>
<td>+0.8</td>
<td>+15.5</td>
<td>+15.0</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td></td>
<td>178± 9.5</td>
<td>+2.9</td>
<td>-3.6</td>
<td>-8.3</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
<td></td>
<td>11.5± 4.1</td>
<td>+1</td>
<td>-7.7</td>
<td>-12.3</td>
</tr>
</tbody>
</table>

**Immediate preinjection period Postinjection changes (% of control) 5 sec 0-5 sec 5-10 sec 10-15 sec**

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TABLE 6
Group 6—Selective Aortic Chemoreceptor Stimulation Following Pretreatment with Propranolol

<table>
<thead>
<tr>
<th>Variable</th>
<th>Immediate preinjection period</th>
<th>Postinjection changes (% of control)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-5 sec</td>
<td>5-10 sec</td>
</tr>
<tr>
<td>Heart rate (beats/5 sec)</td>
<td>11.4 ± .3  (P &gt; .50)</td>
<td>-2.3  (.40 &lt; P &lt; .50)</td>
</tr>
<tr>
<td>Left ventricle strain gauge arch (%)</td>
<td>100 ± 0  (P &gt; .50)</td>
<td>+1.0  (P &gt; .50)</td>
</tr>
<tr>
<td>Left ventricle systolic pressure (mm Hg)</td>
<td>124 ± 8.4  (P &gt; .50)</td>
<td>+10.1  (P &gt; .50)</td>
</tr>
<tr>
<td>Left ventricle diastolic pressure (mm Hg)</td>
<td>2 ± .4  (.001 &lt; P &lt; .005)</td>
<td>+1.4  (.01 &lt; P &lt; .025)</td>
</tr>
<tr>
<td>Left ventricle dp/dt (mm Hg/sec)</td>
<td>667 ± 82  (.20 &lt; P &lt; .40)</td>
<td>+7.1  (.10 &lt; P &lt; .20)</td>
</tr>
<tr>
<td>Aorta mean pressure (mm Hg)</td>
<td>96 ± 6.5  (.001 &lt; P &lt; .005)</td>
<td>+14.6  (.005 &lt; P &lt; .01)</td>
</tr>
<tr>
<td>Peak velocity, ascending aorta flow (cm/sec)</td>
<td>80 ± 6.0  (.025 &lt; P &lt; .05)</td>
<td>+3.1  (.20 &lt; P &lt; .40)</td>
</tr>
<tr>
<td>Ascending aorta flow (ml/5 sec)</td>
<td>122 ± 6.7  (.05 &lt; P &lt; .10)</td>
<td>-2.4  (P &gt; .50)</td>
</tr>
<tr>
<td>Left ventricle stroke volume (ml)</td>
<td>10.9 ± .6  (.01 &lt; P &lt; .025)</td>
<td>-3.9  (P &gt; .50)</td>
</tr>
<tr>
<td>Systemic vascular resistance (mm Hg/ml per 5 sec)</td>
<td>830 ± 74  (.01 &lt; P &lt; .025)</td>
<td>+20.3  (.05 &lt; P &lt; .10)</td>
</tr>
</tbody>
</table>

aortic mean pressure secondary to the increase in systemic vascular resistance (Table 6).

CONTROL GROUPS

We carried out the following studies as controls:

To study the effects of nicotine reaching the adrenals, without stimulating either aortic or carotid chemoreceptors, we injected 5 to 10 μg/kg of nicotine into the ascending aorta just below the origin of the subclavian artery on 8 occasions in 6 dogs (control group A).

We also studied the effect of nicotine injected into the ascending aorta after section of the afferent nerve fibers from the aortic body (12). Bilateral midcervical vagotomy was performed in 3 of the dogs in group 5 that also had alpha-adrenergic blockade. Six injections of nicotine were performed in these 3 dogs (control group B).

In a third group of 6 dogs, we studied the effect of nicotine following combined blockade of both the alpha- and the beta-adrenergic receptors. Dibenzyline, 5 mg/kg iv, was infused as described above and then propranolol, 0.5 mg/kg iv, was injected. Eight injections of nicotine into the ascending aorta were made in this group (control group C). No significant changes from preinjection values were seen in any of the control groups during either the first, second, or third 5-sec period after injection.

In Table 7 we analyze the differences in the responses of the measured variables in each group compared to the corresponding response observed in the group with selective aortic body stimulation (group 1). Combined stimulation produced a significantly different percent change from control in heart rate, peak velocity of aortic flow and stroke volume in the first 5 sec compared to selective aortic stimulation; the improvement in myocardial contractility, the rise in systemic vascular resistance, and the increase in left ventricular systolic and aortic mean pressures were comparable to those obtained in group 1. The immediate, 0- to 5-sec response in the group pretreated with atropine was in every respect qualitatively similar to the response in

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Differences of the Mean for Percent Change from Control of Each Variable in Group 1 Animals (Selective Aortic Chemoreceptor Stimulation) and Corresponding Measurement in the Other Groups

<table>
<thead>
<tr>
<th></th>
<th>Group 2</th>
<th>Group 3</th>
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<tr>
<td></td>
<td>0-5 sec</td>
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<tr>
<td>Heart rate</td>
<td>22.1</td>
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<tr>
<td></td>
<td>(P &lt; .001)</td>
<td>(P &lt; .05)</td>
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<td>Left ventricle strain</td>
<td>4.7</td>
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<tr>
<td>gauge arch</td>
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<td>(.10 &lt; P &lt; .20)</td>
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<tr>
<td>Left ventricle systo-</td>
<td>0.2</td>
<td>1.1</td>
</tr>
<tr>
<td>lic pressure</td>
<td>(P &gt; .50)</td>
<td>(P &gt; .50)</td>
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<tr>
<td>Left ventricle diastolic</td>
<td>7.8</td>
<td>21.8</td>
</tr>
<tr>
<td>pressure</td>
<td>(P &gt; .50)</td>
<td>(.20 &lt; P &lt; .40)</td>
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<tr>
<td>Left ventricle dp/dt</td>
<td>7.5</td>
<td>7.1</td>
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<tr>
<td></td>
<td>(.20 &lt; P &lt; .40)</td>
<td>(P &gt; .50)</td>
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<tr>
<td>Aorta mean pressure</td>
<td>1.8</td>
<td>10.9</td>
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<tr>
<td></td>
<td>(P &gt; .50)</td>
<td>(.10 &lt; P &lt; .20)</td>
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<tr>
<td>Peak velocity, ascend</td>
<td>10.2</td>
<td>11.2</td>
</tr>
<tr>
<td>ing aorta flow</td>
<td>(P = .025)</td>
<td>(.10 &lt; P &lt; .20)</td>
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<tr>
<td>Ascending aorta flow</td>
<td>3.4</td>
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<tr>
<td></td>
<td>(.40 &lt; P &lt; .50)</td>
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<tr>
<td>Stroke volume</td>
<td>17.3</td>
<td>14.4</td>
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<tr>
<td></td>
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<td>(P &lt; .05)</td>
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<tr>
<td>Systemic vascular resi-</td>
<td>7.8</td>
<td>0.3</td>
</tr>
<tr>
<td>stance</td>
<td>(.20 &lt; P &lt; .40)</td>
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group 1; however, the percent rise from control of aortic mean pressure was significantly greater in group 3. Nearly all responses to selective carotid chemoreceptor stimulation (group 4) differed from the response in group 1. When the alpha-adrenergic receptors were blocked by Dibenzyline, the rise in left ventricular systolic and aortic mean pressures was less than the response in group 1; however, the percent increase in the force of myocardial contraction and in peak dp/dt did not show a significant difference. Beta-adrenergic blockade prevented the increase in myocardial force and in peak dp/dt observed in group 1, despite the fact that the rise in left ventricular systolic and aortic mean pressures was comparable in the two groups. A significant rise in left ventricular end-diastolic pressure was seen in this group in response to the increased outflow impedance, which was not seen with group 1.

We have similarly analyzed the differences between the responses evoked by combined aortic and carotid chemoreceptor stimulation (group 2) and those obtained in the other groups as well as the differences evoked by selective carotid chemoreceptor stimulation (group 4) and the responses obtained in the other groups. Tables comparing these responses are available from the authors.

**Discussion**

Our data demonstrate that selective stimulation of the aortic body chemoreceptors with nicotine in artificially breathing dogs (group 1) evokes an immediate improvement in myocardial contractility, a rise in systemic arterial pressure, an increase in peripheral vascular resistance, and tachycardia. When stimulation of these receptors was immediately followed by carotid chemoreceptor stimulation (group 2), the over-all response was still an enhancement of ventricular performance and a rise in peripheral vascular resistance, although a decrease in heart rate and increase in stroke volume was now observed. When the bradycardia was prevented by pretreatment with atropine (group 3), the changes were again similar to those obtained by stimulating the aortic chemoreceptors only.

The evidence of immediate enhancement of ventricular performance following stimulation of the aortic chemoreceptors was provided primarily by analysis of two factors: the maximal slope of the isometric contrac-
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<table>
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<th>0-5 sec</th>
<th>5-10 sec</th>
<th>0-5 sec</th>
<th>5-10 sec</th>
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elation phase of the left ventricular pressure pulse (peak dp/dt) (13) and the output signal from the strain gauge arch sutured to the myocardium of the left ventricle (14). Although we are well aware of the limitations of both methods, we believe our conclusions regarding increased contractility are permissible from the results, when interpreted in light of the similar changes we observed when heart rate was unaltered (group 3) and ventricular afterload unchanged (group 5). Changes in dp/dt were particularly consistent and impressive. Within 2 to 3 sec after injection of nicotine into the base of the aorta and concomitant with the onset of the systemic pressure rise, a rise in peak dp/dt began; this rise was found to be statistically significant from the first 5-sec period on. Not only did the rate of rise of pressure increase during isometric contraction, but the maximum rate of isometric relaxation also increased frequently. Such an increase has also been interpreted as evidence of increased myocardial contractility (15). Additional evidence of improved myocardial performance was obtained from the increase in the output signal from the strain gauge arch sutured to the myocardium of the left ventricle. This signal, representative of the force being developed by the myocardium (14), also began to rise 2 to 3 sec after the injection. If the strain gauge arch had been sutured to the right rather than the left ventricle, we would have obviated the difficulties in interpretation occurring as a result of simultaneous changes in arterial pressure. However, this would have been countered by the disadvantage that the right ventricle also faces an increased impedance within the pulmonary circulation as a result of reflex aortic chemoreceptor stimulation (16). Further evidence for immediate enhancement of ventricular performance is suggested by the fact that the over-all flow did not decrease during a period when nicotine evoked a significant rise in peripheral vascular resistance.

Since an increase in myocardial contractility occurring 2 to 3 heart beats after raising aortic pressure was demonstrated by Sarnoff and co-workers (7) and confirmed by Levy and co-workers (8), we believed it important to exclude the possibility that such autoregulatory effects were responsible for the changes observed in our experiments. Furthermore, it
might be argued that the increase in ventricular afterload resulting from the rise in peripheral vascular resistance might directly increase left ventricular dp/dt without necessarily affecting contractility. These possibilities appear to be excluded by the studies in group 5, in which nicotine injections were repeated after blocking the alpha-adrenergic receptors with dibenzyline and thus largely preventing the usually observed peripheral vasoconstrictive response (12). The significant rise in dp/dt and signal from the strain gauge arch proved that improvement in myocardial contractility took place even in the absence of an appreciable change in aortic outflow impedance (Fig. 2). Additional evidence of improvement in myocardial contractility in this group was provided by the observation that the peak velocity of the ascending aortic flow increased significantly now that the left ventricle no longer had to work against an increased aortic outflow impedance.

In another group of animals pre-treated with propranolol (which induced beta-adrenergic blockade and prevented direct sympathetic stimulation to the heart) (17), stimulation of the aortic chemoreceptors failed to induce a significant increase in the parameters used to judge myocardial performance, in spite of the significant rise in aortic mean pressure (group 6). This reinforces the conclusion that the degree of aortic pressure rise produced by aortic chemoreceptor stimulation in these studies was not producing a direct increase in peak dp/dt independent of changes in myocardial contractility. With this rise in aortic pressure during the first 5 sec, we also observed an increase in calculated systemic vascular resistance and a significant decrease in stroke volume. In this group there was also a rise in left ventricular end-diastolic pressure during all three experimental periods, while after selective aortic stimulation this was significantly less; this suggests that the enhanced myocardial contractility observed with group 1 was also being mirrored by the absence of change in left ventricular filling pressure as systemic pressure rose. The injection of propranolol itself produced a marked deterioration in myocardial function in the experimental animals; this has also been observed by others (18). In our study, it was evidenced by a decrease in the signal from the strain gauge arch, a drop in peak dp/dt and a fall in peak aortic velocity values during the control period. Two animals in this group were given intravenous digitalis following conclusion of these experiments. Both showed a significant increase in peak dp/dt and the force developed by the myocardium underneath the strain gauge arch, indicating that these dogs were still able to increase myocardial contractility by means other than beta-adrenergic stimulation.

Combined blockade of both alpha- and beta-receptors (control group C) prevented the changes in response to nicotine, thus showing that the adrenergic fibers provide the efferent arm for all the reflex cardiovascular effects of aortic chemoreceptor stimulation by nicotine. The cholinergic fibers apparently play no part in these effects; their blockade by large doses of atropine (group 3) did not influence the improvement in left ventricular performance or the increase in peripheral vascular resistance. The pretreatment with atropine itself induced no significant hemodynamic changes, as demonstrated by statistical evaluation of the control values. This is in accordance with the observations of Page and Olmstedt, who found only small and variable effects of atropine on the cardiovascular system (19). The postnicotine effect was about the same in group 3 as it was in the group with selective aortic stimulation. At times even a slight enhancement in the responses was noted, similar to the slight augmentation of sympathetic actions in animals pretreated with atropine observed by other investigators (19).

The effect of hypoxic stimulation of the aortic and carotid chemoreceptors on myocardial contractility was studied by Kahler and co-workers (4). Their experimental design was so constructed that no clear separation between the effect of aortic and carotid body stimulation could be made, and the authors concluded that "aortic and carotid

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chemoreceptors form the afferent limb for the reflex augmentation of myocardial contractile force. Our results demonstrate that the reflex increase in myocardial contractility in the dog originates from the aortic, and not from the carotid chemoreceptors. Thus, the response remained intact after bilateral surgical elimination of the carotid body. Furthermore, the insertion of 140 cm-long plastic coils that delayed the arrival of any nicotine injected at the base of the aorta at the carotid chemoreceptor site by at least 15 sec (11) did not alter the immediate response observed within the first 15 sec. Finally, surgical vagotomy, by interrupting afferent fibers from the aortic body (12), abolished the response, confirming the origin of the reflex to the aortic chemoreceptors.

Selective stimulation of the carotid chemoreceptors in our study was achieved by injection of nicotine directly into the brachiocephalic artery or into the upstream end of the carotid coil (group 4). This failed to evoke improvement in myocardial performance, and in a certain number of experiments even induced a slight decrease. Following anoxic stimulation of the carotid region, Downing and co-workers (1) found no change in myocardial contractility in one-third of their experiments and a decrease in the remaining two-thirds, while Salem and co-workers (2) and DeGeest and co-workers (3) found a pure negative inotropic effect on the myocardium following anoxic stimulation of the carotid region. Kahler and co-workers (4) described an increase in myocardial contractility when stimulating the carotid chemoreceptors by hypoxia.

The change in systemic vascular resistance after carotid chemoreceptor stimulation was slight and inconsistent in our study, though Downing, Remensnyder and Mitchell (1), and Daly and Scott (10) found an increase after hypoxic stimulation of the carotid chemoreceptors. However, these investigators studied the changes 1 to 3 min after the beginning of stimulation, while our study deals with changes during the first 15 sec. Our study also revealed that selective carotid stimulation produces a decrease in heart rate; although the stroke volume increases during this bradycardic period, overall flow does not change significantly. The present study confirms the findings of Comroe and Mortimer (11) that in the artificially ventilated dog, aortic chemoreceptor stimulation increases heart rate and blood pressure, while carotid chemoreceptor stimulation in most cases decreases both, and demonstrates again how markedly these two sets of receptors differ in their cardiovascular action.

Previous investigators have not studied changes in cardiac output immediately following chemoreceptor stimulation. The available information on this subject generally deals with changes 1 to 3 min after applying a stimulus to these receptors (9, 10). The use of an electromagnetic flowmeter in the present study permitted us to follow beat-to-beat changes. Consequently, we were able to demonstrate that stroke volume decreased during the first 10 sec after initiating selective aortic body stimulation. However, with the concomitant tachycardia, the over-all flow did not change significantly. The systemic vascular resistance increased significantly after stimulation of the aortic chemoreceptors, similar to the results obtained in our previous investigation (16) and with the recent results of Daly and Ungar (6). This rise in peripheral vascular resistance appears to be effectively opposed by the enhanced ventricular performance and, thus, flow is maintained without significant change. An additional factor in maintaining stroke volume may be an increase in venous return, since Kahler, Goldblatt and Braunwald (4) demonstrated that chemoreceptor stimulation induces systemic venoconstriction.

The possibility that catecholamine liberation from the adrenals may, in part, produce the effects demonstrated by us, was excluded by the negative results achieved in control group A. In this group, nicotine was injected into the upper part of the descending aorta, and thus the drug reached the adrenals in a similar or even higher concentration than after ascending aortic injection. However, no
response was observed in this group. Catecholamine liberation from the heart also seems to be excluded, since the ascending aortic injection evoked the response only when the vagus nerve was intact; after vagotomy (control group B), the effect was absent. We do not think that direct stimulation of sympathetic ganglia by nicotine occurred in our experiments, since the dose range used in this study was well below the minimum of 32 μg/kg needed to accomplish this (5).

Injection at the base of the ascending aorta raises the question whether part of the response we observed may have been due to some of the nicotine reaching the coronary circulation. However, the intracoronary injection of nicotine always induces a drop in arterial pressure in the dog (20), while in our experiments this pressure always rose immediately after the injection. Bradycardia is a further consequence of intracoronary injection of nicotine (20); bradycardia in our experiments was demonstrated to arise only from selective carotid body stimulation and never occurred when selective aortic chemoreceptor stimulation was induced by the ascending aortic injection. Furthermore, vagotomy abolished the response, although the nicotine was injected into the same part of the ascending aorta. We think it unlikely, therefore, that nicotine reaching the coronary circulation influenced our results.

Acknowledgment

We wish to acknowledge the helpful technical assistance of L. Samuel Vickers.

References

17. Black, J. W., Crowther, A. F., Shanks,
CHEMORECEPTORS AND VENTRICULAR PERFORMANCE


Comparison of the Reflexes Elicited from Combined or Separate Stimulation of the Aortic and Carotid Chemoreceptors on Myocardial Contractility, Cardiac Output and Systemic Resistance

SHLOMO STERN and ELLIOT RAPAPORT

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