Influence of Cardiopulmonary Vagal Afferent Activity on Carotid Chemoreceptor and Baroreceptor Reflexes in the Dog

By Hiroyuki Koike, Allyn L. Mark, Donald D. Heistad, and Phillip G. Schmid

ABSTRACT

The goal of this study was to determine if physiological levels of cardiopulmonary vagal afferent activity modulate carotid chemoreceptor and baroreceptor reflexes. In anesthetized, ventilated dogs, the aortic nerves and the cervical sympathetic trunks were cut, and atropine was administered so that vagotomy would interrupt only cardiopulmonary afferent impulses. Reflex vascular responses were observed in perfused gracilis muscle and hindpaw. Carotid chemoreceptors were activated with nicotine or hypoxic, hypercapnic blood; carotid baroreceptors were stimulated by changes in carotid pressure. Interruption of vagal afferents augmented reflex vascular responses during changes in carotid pressure from 75 to 125 mm Hg. Interruption of cardiopulmonary vagal afferents potentiated reflex vasoconstrictor (muscle), vasodilator (paw), and vasopressor responses to activation of the carotid chemoreceptors. The potentiation of the chemoreceptor reflex frequently occurred in the absence of increases in base-line vascular resistance. Vagotomy also potentiated ventilatory responses to stimulation of the carotid chemoreceptors in spontaneously breathing dogs. The results indicate that interruption of cardiopulmonary afferents potentiates the vascular and ventilatory responses to activation of the carotid chemoreceptors and augments the gain of the carotid baroreceptor reflex at low carotid pressures. These findings suggest that physiological levels of cardiopulmonary vagal afferent impulses suppress carotid baroreceptor and chemoreceptor reflexes through an interaction in the central nervous system. The suppressive effect on the chemoreceptor reflex may be distinct from tonic restraint of the vasomotor center by vagal afferents, since it involves sympathetic vasodilator as well as vasoconstrictor responses and may occur without suppression of base-line adrenergic constrictor tone.

Vagal afferent pathways originating in cardiopulmonary receptors have been recognized for many years (1-4), and investigators (5-9) have recently demonstrated that impulses arising in these receptors exert a tonic restraint on adrenergic discharge and contribute to physiological control of the circulation.

In delineating the role of cardiopulmonary vagal afferents in circulatory control, it is important to consider an influence of vagal afferent impulses on other reflexes, such as the carotid chemoreceptor and baroreceptor reflexes. The observation of Heistad et al. (10) and of Mancia (11) that afferent impulses arising in carotid baroreceptors inhibit the chemoreceptor reflex through a central interaction prompted us to test the hypothesis that afferent impulses originating in cardiopulmonary receptors inhibit the chemoreceptor reflex. Toubes and Brody (12) have reported that activation of vagal afferents during myocardial ischemia does not alter the chemoreceptor reflex, but inhibition of the chemoreceptor reflex by vagal afferents might have been masked in their study by hypotension, which is reported to potentiate the chemoreceptor reflex (10).

Previous investigators (5, 6) have reported that interruption of vagal afferent activity potentiates the response to carotid occlusion. Although these studies suggest that vagal afferent activity inhibits the carotid baroreceptor reflex, quantitative conclusions regarding interaction of cardiopulmonary and carotid baroreceptor reflexes are difficult without knowledge of the magnitude of change in carotid sinus pressure. In the previous studies (5, 6), carotid sinus pressures were not controlled or measured. Since base-line systemic arterial blood pressure increased after vagotomy, the magnitude of fall in carotid arterial blood pressure during coronary carotid occlusion, i.e., the stimulus to the carotid baroreceptor reflex, was probably greater after vagotomy; this situation may have been responsible for some of the potentiation.

The purpose of the present study was, thus, to determine the influence of physiological levels of cardiopulmonary vagal afferent activity (1) on
vascular responses to graded stimulation of carotid baroreceptors under conditions in which base-line carotid sinus pressure and changes in carotid pressure are controlled and (2) on vascular and ventilatory responses to pharmacologic and physiologic activation of carotid chemoreceptors. A goal of this study was to determine if physiological levels of vagal afferent activity exert a suppressive effect on the carotid chemoreceptor reflex that is distinct from restraint of tonic adrenergic discharge by cardiopulmonary vagal afferents.

**Methods**

Mongrel dogs weighing 17-25 kg were anesthetized with chloralose (50 mg/kg, iv) and urethane (500 mg/kg, iv) and treated with decamethonium bromide (0.3 mg/kg, iv) and heparin (500 units/kg, iv). The dogs were ventilated artificially (tidal volume 15 ml/kg and rate 12-14/min) through an endotracheal tube with room air and supplemental oxygen at 1-2 liters/min to maintain normal blood gases. Blood gases and pH were measured with an Instrumentation Laboratory blood-gas analyzer before and after vagotomy. Systemic arterial and right atrial pressures were measured. Atropine (0.2 mg/kg, iv) was administered each hour to block vagal cholinergic effects on the heart.

**SECTION OF AORTIC DEPRESSOR NERVES**

Through a longitudinal midline incision in the neck, the nodose ganglion was exposed bilaterally. Using a dissecting microscope, the aortic nerves were located near the junction of the cranial laryngeal nerve and the nodose ganglion (13). The aortic nerves were identified by electrically stimulating the central cut end of the nerves. High-voltage, low-frequency (10 v, 10 Hz, 0.1-1 msec) stimulation produced hypertension; low-voltage, high-frequency (4 v, 100 Hz, 0.1-1 msec) stimulation produced hypotension (13).

The efficacy of interrupting the aortic nerves was demonstrated by injecting sodium cyanide (0.2-0.4 mg/kg) into the aortic root while the carotid sinuses were being perfused with a delay circuit. When the aortic nerves were intact, an aortic injection of sodium cyanide promptly increased systemic arterial blood pressure and muscle perfusion pressure (13). After the aortic depressor nerves had been sectioned, an aortic injection of sodium cyanide failed to increase systemic arterial blood pressure and muscle perfusion pressure (13). Although these procedures directly indicate only denervation of aortic chemoreceptors, Edis and Shepherd (13) have demonstrated that they also confirm denervation of aortic baroreceptors. Cervical sympathetic nerves were identified and cut just below the superior cervical ganglia bilaterally. Thus, the aortic depressor nerves and the cervical sympathetic nerves were eliminated from the vago sympathetic trunk, and vagal cholinergic effects were blocked with atropine (0.2 mg/kg, iv). Preservation of intact vagal cardiopulmonary afferents after dissection was demonstrated by observing vasodepressor responses to right atrial injections of veratrine (2-4 μg/kg) (13).
Effects of Vagotomy on Responses to Carotid Chemoreceptor Stimulation with Nicotine

<table>
<thead>
<tr>
<th></th>
<th>Muscle perfusion pressure (mm Hg)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>ΔNicotine&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Before vagotomy</td>
<td>158 ± 6.3</td>
<td>+23 ± 2.2</td>
</tr>
<tr>
<td>After vagotomy</td>
<td>168 ± 5.9</td>
<td>+46 ± 5.7</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
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All values are means ± SE for experiments on 14 dogs except for those for the responses to local intracarotid injection of norepinephrine (NE) where n = 9. ΔNicotine<sup>1</sup> and ΔNicotine<sup>2</sup> indicate the responses to intracarotid injections of low and high doses, respectively. The low dose was 0.3 or 0.6 μg/kg, and the high dose was twice the low dose. The same doses were administered before and after vagotomy. ΔNE indicates the responses to an injection of norepinephrine (0.5 μg) into the tubing perfusing the gracilis muscle. Systemic arterial P<sub>O</sub><sub>2</sub> averaged 106 ± 9 mm Hg, P<sub>CO</sub><sub>2</sub> averaged 36 ± 1 mm Hg, and pH averaged 7.36 ± 0.02 before vagotomy; after vagotomy P<sub>O</sub><sub>2</sub> averaged 165 ± 9 mm Hg, P<sub>CO</sub><sub>2</sub> averaged 35 ± 1 mm Hg, and pH averaged 7.35 ± 0.02. *P* values are for the comparison of values determined before and after vagotomy.
INFLUENCE OF CARDIOPULMONARY AFFERENTS

absence of increases in base-line vascular resistance (Figs. 1 and 2).

Base-line right atrial pressure averaged $4.1 \pm 0.7$ mm Hg before vagotomy and $4.3 \pm 0.8$ mm Hg after vagotomy ($P > 0.05$). Right atrial pressure did not change during stimulation of the carotid chemoreceptors.

Vagotomy also potentiated the reflex responses to stimulation of the carotid chemoreceptor reflexes with local hypoxia and hypercapnia (Table 2). The magnitude of potentiation of responses to hypoxia and hypercapnia was similar to the magnitude of potentiation of responses to nicotine.

Effects of Cardiopulmonary Vagal Afferent Activity on Ventilatory Responses.

—Vagotomy tended to increase base-line minute volume and to decrease base-line ventilatory rate and end-tidal CO$_2$ (Table 3).

Vagotomy augmented reflex changes in minute volume and end-tidal CO$_2$ during stimulation of chemoreceptors and tended to augment reflex increases in ventilatory rate (Table 3).

Effects of Sham Vagotomy.

—Base-line muscle perfusion pressure and responses to carotid chemoreceptor stimulation were not altered by sham vagotomy. Increases in muscle perfusion pressure in response to the intracarotid administration of nicotine (0.6 and 1.2 μg/kg) averaged $25 \pm 7.1$ and $28 \pm 11.1$ mm Hg before sham vagotomy and $25 \pm 7.2$ and $30 \pm 12.2$ mm Hg after sham vagotomy, respectively, after sham vagotomy.

Changes in systemic arterial blood pressure with chemoreceptor stimulation were also not altered by sham vagotomy.

![Figure 2](image)

**Figure 2**

Lack of correlation ($r = -0.16$) between change in chemoreceptor stimulation and changes in baseline muscle perfusion pressure (MPP) after vagotomy.

<table>
<thead>
<tr>
<th>Muscle perfusion pressure (mm Hg)</th>
<th>Mean arterial blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control</strong></td>
<td><strong>ΔNicotine$^1$</strong></td>
</tr>
<tr>
<td>Before vagotomy</td>
<td>$120 \pm 7.1$</td>
</tr>
<tr>
<td>After vagotomy</td>
<td>$120 \pm 9.4$</td>
</tr>
<tr>
<td>$P$</td>
<td>$&gt; 0.05$</td>
</tr>
</tbody>
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All values are means ± se for three experiments that were separate from the experiments reported in Table 1. Systemic blood gases and pH were: $P_O_2 213 \pm 3$ mm Hg, $P_CO_2 39 \pm 3$ mm Hg, and pH 7.42 ± 0.04. ΔHypoxia and hypercapnia indicates the responses to perfusion of the carotid bifurcations with blood having a $P_O_2$ of $54 \pm 6$ mm Hg, a $P_CO_2$ greater than $100$ mm Hg, and a pH of 7.10 ± 0.12 before vagotomy and a $P_O_2$ of $59 \pm 6$ mm Hg, a $P_CO_2$ greater than $100$ mm Hg, and a pH of 7.10 ± 0.13 after vagotomy. See the legend to Table 1 for additional explanations.
CAROTID BARORECEPTOR REFLEX

Effects of Cardiopulmonary Afferent Activity.—Changes in muscle perfusion pressure and systemic arterial blood pressure in response to changes in carotid sinus pressure from 75 to 125 mm Hg were potentiated after vagotomy (Figs. 3 and 4), but changes in muscle perfusion pressure and systemic arterial blood pressure during changes in carotid pressure from 125 to 175 mm Hg were not augmented after vagotomy (Figs. 3 and 4).

Right atrial pressure did not change significantly during stimulation of carotid baroreceptors either before or after vagotomy.

Effects of Sham Vagotomy.—Muscle perfusion pressures during changes in carotid sinus pressure were similar before and after sham vagotomy. Muscle perfusion pressures at carotid pressures of 75, 125, and 175 mm Hg averaged 147 ± 4.9, 125 ± 7.1, and 92 ± 7.6 mm Hg, respectively, before sham vagotomy and 145 ± 13.1, 122 ± 14.2, and 97 ± 8.3 mm Hg, respectively, after sham vagotomy. Changes in systemic arterial blood pressure during carotid baroreceptor stimulation also were not altered by sham vagotomy.

Discussion

This study suggests that reflexes arising in cardiopulmonary receptors exert an inhibitory effect on carotid chemoreceptor and baroreceptor reflexes.

CAROTID CHEMORECEPTOR REFLEX

 Interruption of cardiopulmonary afferents augmented vasoconstrictor (muscle), vasodilator (paw), and ventilatory responses to activation of chemoreceptors.

 Interruption of cardiopulmonary afferents increased base-line vascular resistance and arterial blood pressure in some experiments, but these effects were not consistent. This finding suggests that under the conditions of these experiments (carotid sinus pressure 125 mm Hg) the cardiopulmonary vagal afferents inhibited the vasomotor center in some but not all experiments. Since potentiation of the chemoreceptor reflex with vagotomy often occurred in the absence of an increase in base-line vascular resistance, it appears that suppression of the chemoreceptor reflex by the cardiopulmonary afferents may not have resulted from tonic restraint of the vasomotor center by the cardiopulmonary afferents.

Mancia et al. (8) have found that cardiopulmonary restraint of the vasomotor center decreases rapidly when the carotid sinus pressure is increased from 100 to 160 mm Hg but does not disappear until the carotid pressure reaches 160–200 mm Hg.
As just mentioned, we were frequently unable to demonstrate cardiopulmonary restraint of the vasomotor center with the carotid sinus pressure at 125 mm Hg. This difference might be explained by the fact that central venous or right atrial pressure—and, therefore, the stimulus to cardiopulmonary stretch receptors—was higher in their study (5.1 ± 0.6-5.7 ± 0.6 mm Hg) than it was in ours (4.1 ± 0.7 mm Hg). This difference would not seem to be important. Instead, the important point in interpreting our results is that under physiological conditions cardiopulmonary vagal afferents frequently exerted a suppressive effect on the chemoreceptor reflex in the absence of demonstrable tonic restraint of adrenergic discharge to the muscle resistance vessels.

Another observation also suggests that suppression of the chemoreceptor reflex did not result simply from inhibition of adrenergic discharge: interruption of cardiopulmonary afferents potentiated reflex vasodilation in the paw in addition to vasoconstriction in muscle. Reflex vasodilation in the paw during chemoreceptor stimulation has been reported to result from activation of a sympathetic dilator pathway (14). If cardiopulmonary afferents suppressed responses to chemoreceptor stimulation simply by restraining adrenergic discharge, potentiation of vasodilation in the paw after vagotomy would not have occurred. Since suppression of the chemoreceptor reflex involved reflex vasodilation in addition to vasoconstriction and since suppression frequently occurred in the absence of demonstrable tonic restraint of adrenergic discharge, we speculate that cardiopulmonary vagal afferents exert a specific suppressive effect on the chemoreceptor reflex.

We should consider the possibility that the chemoreceptor reflex was potentiated because the stimulus to carotid chemoreceptors or the firing of carotid chemoreceptors was greater after interruption of cardiopulmonary vagal afferents. It is unlikely that the stimulus was greater after vagotomy, since the carotid bifurcations were vascularly isolated and perfused at constant pressure and the doses of nicotine and the degree of hypoxia and hypercapnia were similar before and after vagotomy. Increases in adrenergic discharge to the carotid body can decrease blood flow to the carotid body and increase chemoreceptor activity and the firing of carotid chemoreceptors in response to a
given stimulus (15), but adrenergic vasoconstrictor influences on the carotid body were interrupted at the start of each experiment by sectioning the cervical sympathetic nerves. Thus, it seems doubtful that the stimulus and the firing of carotid chemoreceptors were greater after vagotomy.

The effects of vagotomy presumably did not result from interruption of afferents originating below the diaphragm, since Mancia et al. (8) have demonstrated that sectioning the vagi at the diaphragm does not exert cardiovascular effects. Ito and Scher (16) have demonstrated that some fibers originating in aortic baroreceptors course in the vagal trunk and are not interrupted by sectioning the cervical aortic depressor nerves as was done in this study. Although it might be suggested that inhibition of the chemoreceptor reflex resulted from aortic baroreceptor afferents that travel in the vagal trunk, we believe this possibility is improbable for two reasons. First, Ito and Scher (16) have found evidence for functionally significant aortic baroreceptor afferents in the vagal trunks only in a minority of dogs. Thus, if inhibition of the carotid chemoreceptor reflex in our study resulted from aortic baroreceptor afferents in the vagal trunk, one would have anticipated potentiation by vagotomy in only a minority of the experiments. In contrast, vagotomy potentiated the carotid chemoreceptor reflex in almost all of our experiments. Therefore, it seems improbable that the inhibition resulted from aortic baroreceptor afferent activity. Second, Edis and Shepherd (13) have demonstrated that the methods employed in this study to identify and section the aortic depressor nerves result in the selective denervation of aortic baroreceptors and chemoreceptors and in the preservation of cardiopulmonary vagal afferents. We suggest, therefore, that inhibition of the carotid chemoreceptor reflex resulted from the influence of cardiopulmonary vagal afferents on carotid chemoreceptor reflexes. Reflexes arising in atria, ventricles, and lung have been implicated in circulatory control, and a recent study (9) indicates that each contributes to tonic inhibition of the vasomotor center in the dog, but the precise location and characteristics of the cardiopulmonary receptors which modulate the carotid chemoreceptor reflex are not clear from this study.

Previous studies (17) suggest that the interaction of cardiovascular reflexes may be selective and involve one component of a reflex response, e.g., cardiac, but not another, e.g., vascular. Because of this selectivity, we studied the effects of interrupting cardiopulmonary afferents on ventilatory in addition to vascular responses to chemoreceptor activation. The increase in ventilatory responses to chemoreceptor stimulation after vagotomy suggests that the influence of cardiopulmonary reflexes involves both vascular and ventilatory responses.

We suggest from these studies that cardiopulmonary vagal afferent impulses exert a suppressive effect on the chemoreceptor reflex within the central nervous system. This effect appears to be distinct from vagal afferent tonic restraint of the vasomotor center. Although it is tempting to speculate that cardiopulmonary afferents act presynaptically on chemoreceptor afferent fibers, the data from this study do not permit conclusions regarding the location and mechanism of the interaction within the central nervous system.

**CAROTID BARORECEPTOR REFLEX**

 Interruption of cardiopulmonary vagal afferents augmented the gain of the carotid baroreceptor reflex when carotid sinus pressure was changed from 75 to 125 mm Hg but not when carotid sinus pressure was increased from 125 to 175 mm Hg. Guazzi et al. (5) and Pillsbury et al. (6) have demonstrated that interruption of cardiopulmonary vagal afferents potentiates the response to carotid occlusion. Although their observations suggest that vagal afferents modulate the carotid baroreceptor reflex through a central interaction, the possibility that the potentiation in their studies resulted from a greater stimulus to the carotid baroreceptors after vagotomy cannot be excluded. Base-line systemic arterial blood pressure increased after vagotomy, and, therefore, the decrease in carotid arterial blood pressure (the stimulus to carotid baroreceptors) during carotid occlusion was probably greater after vagotomy. In the present study, base-line carotid sinus pressure and the changes in pressure during the stimulation of the carotid baroreceptors were controlled to exclude the possibility that augmentation of the carotid sinus reflex after vagotomy resulted from augmentation of the stimulus.

As indicated previously, blockade of the cardiopulmonary vagal afferents augmented the gain of the carotid sinus over the range of carotid sinus pressures from 75 to 125 mm Hg but not over the range of pressures from 125 to 175 mm Hg. In accord with this observation, several investigators (7, 8) have reported that responses to interruption of cardiopulmonary afferents are greatest when carotid sinus pressure is low and least when carotid sinus pressure is high.
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Based on these observations under physiological conditions, we can speculate on the possible significance of an inhibitory effect of exaggerated cardiopulmonary vagal afferent activity in pathologic states. For example, Higgins et al. (18) have demonstrated that reflex vasoconstrictor responses to carotid hypotension are attenuated in dogs with heart failure; we raise the possibility that this inhibition might result from exaggerated inhibitory cardiopulmonary afferent activity associated with stretch of the cardiac receptors. The results of this study also may relate to abnormalities in neurogenic control in several hypertensive states. For example, reflexes arising in cardiac receptors have been implicated in pathologic states such as coronary artery occlusion, myocardial infarction, and left ventricular outflow obstruction (12, 19–23). The results of the present study raise the possibility that reflexes arising in cardiopulmonary receptors might contribute to abnormal neurogenic control in these states partly by suppressing reflex adjustments to systemic hypotension and hypoxia through an inhibitory interaction with carotid baroreceptor and chemoreceptor reflexes.

In closing, it should be noted that this study has identified an inhibitory influence of cardiopulmonary vagal afferent activity. There is now substantial evidence supporting the existence of cardiopulmonary receptors with spinal sympathetic afferent pathways (24, 25). We did not in this study test for an interaction of cardiopulmonary sympathetic afferents and carotid reflexes.

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