Interaction of Baroreceptor and Chemoreceptor Reflexes

MODULATION OF THE CHEMORECEPTOR REFLEX BY CHANGES IN BARORECEPTOR ACTIVITY

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ABSTRACT The purpose of this study was to determine whether the level of arterial pressure and degree of baroreceptor activation affect responses to stimulation of chemoreceptors. Chemoreceptors were stimulated by injecting nicotine into the common carotid artery of anesthetized and paralyzed dogs. Responses were observed in the innervated gracilis muscle, perfused at constant flow while perfusion pressure was measured. Arterial pressure was lowered by bleeding the animals and raised by transient occlusion of the descending aorta. Vasoconstrictor responses to stimulation of chemoreceptors were enhanced by hypotension and inhibited by elevation of arterial pressure. Potentiation of the chemoreceptor reflex by hemorrhagic hypotension was not the result of altered vascular resistance in the gracilis muscle, sensitization of chemoreceptors by catecholamines or acidosis, or changes in cerebral perfusion pressure.

Additional studies were done in which we excluded the possibility that the changes resulted from direct effects of changes in arterial pressure on chemoreceptors. Both carotid bifurcations were isolated and perfused. On one side, pressure was raised to stimulate the carotid sinus baroreceptors. On the other side, the carotid body chemoreceptors were stimulated by nicotine or by hypoxic and hypercapnic blood. Activation of baroreceptors on one side attenuated the vasoconstrictor response to chemoreceptor stimulation on the other side. This excludes a direct effect of changes in arterial pressure on the chemoreceptors and suggests a central interaction of these reflexes.

We conclude that vasoconstrictor responses to stimulation of chemoreceptors are potentiated by hypotension and inhibited by transient hypertension. These effects appear to result at least in part from a central interaction of chemoreceptor and baroreceptor reflexes.

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INTRODUCTION

Hypotension and hypoxemia often occur together in the clinical setting, so the baroreceptors and chemoreceptors are affected simultaneously. In most studies of baroreceptor and chemoreceptor reflexes, however, the reflexes have been activated individually, and the possibility of interaction of reflexes has received little attention (2). Previous studies of the effect of systemic hypoxia on changes in heart rate in relation to changes in arterial pressure (3–5) do not permit definite conclusions concerning a possible interaction between baroreceptor and chemoreceptor reflexes.

The purpose of this study was to examine the possibility that responses to stimulation of chemoreceptors might be affected by the level of arterial pressure. Chemoreceptors were activated by injection of nicotine into the common carotid artery (6) or by perfusing the carotid artery with hypoxic blood. The magnitude of reflex vasoconstrictor responses in the perfused gracilis muscle indicated the magnitude of the chemoreceptor reflex. Arterial pressure was lowered by bleeding the animals or raised transiently by inflating a balloon in the descending aorta.

Further studies were undertaken to consider systematically mechanisms by which the level of arterial pressure affects the chemoreceptor reflex. First, studies were done to test the hypothesis that release of catecholamines during hypotension (7) might sensitize chemoreceptors (8, 9) and potentiate chemoreceptor responses. Second, we examined the possibility that decreases in cerebral perfusion pressure during hypotension might account for augmented responses to stimulation of chemoreceptors. Third, because changes in arterial pressure might affect the magnitude of the chemoreceptor reflex by a direct effect on chemoreceptors (10), experiments were done in which we excluded direct effects of changes in pressure on chemoreceptors. The results will indicate that changes in baroreceptor activity modulate the chemoreceptor reflex and suggest that there is major central interaction of the baroreceptor and chemoreceptor reflex.

METHODS

Male mongrel dogs weighing 14–26 kg were anesthetized with chloralose (50 mg/kg) and urethane (500 mg/kg) and treated with decamethonium bromide (0.3 mg/kg). The animals were ventilated with room air and supplemental oxygen to maintain normal systemic arterial blood gases.

The gracilis muscle was dissected free from surrounding tissues except for the gracilis artery, vein, and nerve. The gracilis artery was cannulated and perfused at constant flow with heparinized blood, while perfusion pressure was recorded. Flow ranged from 3 to 10 ml/min. With flow constant, changes in perfusion pressure reflected changes in vascular resistance in the gracilis muscle. Systemic arterial pressure was measured in the left brachial artery.

One of the carotid artery bifurcations was exposed. A small needle was inserted into the common carotid artery for injection of nicotine bitartrate (10 and 40 μg). The catheter was loaded with 0.1 and 0.4 ml of solution and flushed into the artery with 1.5 ml of saline within approximately 1 s. Nicotine stimulates carotid chemoreceptors and causes reflex vasoconstriction in the gracilis muscle. This response can be abolished by denervating either the carotid body or the gracilis muscle (6), indicating that this is a neurogenic response.

A balloon catheter was inserted into a femoral artery and advanced to the descending aorta below the subclavian artery. Inflation of the balloon with about 15 ml of air obstructed or occluded the aorta, increased arterial pressure in the cephalad body by 20–40 mm Hg, and stimulated the baroreceptors. Responses to stimulation of chemoreceptors by nicotine were observed in eight dogs during elevation of arterial pressure and compared to responses obtained before and after aortic occlusion.

13 dogs were studied during hypotension. The animals were bled rapidly into a reservoir until mean arterial pressure was between 65 and 85 mm Hg and bled further to a mean arterial pressure of 40–50 mm Hg, then, all the blood which had been removed was transfused. Responses to chemoreceptor stimulation by nicotine were measured during both levels of hypotension and compared to responses obtained before and after hemorrhage. In four studies, bilateral cervical vagotomy was done to eliminate afferent impulses from aortic baroreceptors and chemoreceptors. We also measured responses to *l*-norepinephrine bitartrate, 1.0 μg (expressed as the base) injected into the gracilis artery, to determine whether hemorrhagic hypotension (which increases resistance in the gracilis muscle) affects responses to the neurotransmitter.

We considered the possibility that systemic release of catecholamines during hemorrhagic hypotension might sensitize chemoreceptors and alter responses to nicotine. Responses to chemoreceptor stimulation by nicotine were measured before, during, and after an intravenous infusion of norepinephrine, 12 μg/min (as the base) in six dogs.

Additional studies were done to examine the possibility that changes in cerebral perfusion pressure might account for altered responses to stimulation of chemoreceptors. The left and right carotid artery bifurcations were exposed in five dogs. The internal carotid and all branches of the external carotid arteries were ligated. The occipital arteries were ligated 1–2 cm from their origin from the external carotid arteries, which preserved the blood supply to the carotid chemoreceptors. The common carotid and external carotid arteries were cannulated. Arterial blood was pumped at constant flow (60–90 ml/min) into each common carotid artery separately, and perfusion pressures were measured. Blood flowed out through cannulas in the external carotid arteries and through Starling resistors to a jugular vein.

Chemoreceptors were stimulated by injecting nicotine into one carotid artery. The carotid sinus baroreceptors were stimulated by increasing perfusion pressure in both carotids from 100 to 200 mm Hg by increasing pressure in the Starling resistors. Before the interventions, the dogs were bled to achieve a systemic arterial pressure less than 100 mm Hg. Because of the complex blood supply of the carotid body (11), and even though no other vascular supply to the carotid body was visualized, the precaution of maintaining systemic pressure below the perfusion pressure in the carotid was taken to assure perfusion of the carotid body through the carotid artery. Bilateral cervical vagotomy was done to eliminate afferent impulses from the aortic baroreceptors and chemoreceptors.

Vasoconstrictor responses to stimulation of chemoreceptors were measured when carotid perfusion pressure was increased from 100 to 200 mm Hg. When carotid perfusion pressure was raised, systemic arterial pressure decreased; systemic pressure (and cerebral perfusion pressure) were restored to normal by occluding the descending aorta with a balloon, and responses to chemoreceptor stimulation again were observed.

In another group of studies, direct effects of changes in arterial pressure on the chemoreceptors were excluded. Both carotid bifurcations were perfused, and both vagi were cut. The dogs were bled initially to achieve a systemic arterial pressure less than perfusion pressure in the carotid.[1] In one carotid, perfusion pressure was maintained constant at 75–100 mm Hg with a Starling resistor, and chemoreceptors were stimulated by injecting nicotine in 17 dogs and by infusing hypoxic and hypercapnic blood in 7 dogs. In the dogs in which hypoxic and hypercapnic blood was used to stimulate chemoreceptors, blood was obtained from a femoral artery, passed through a Travenol regional perfusion bubble oxygenator (Travenol Labora-

[1] In three experiments, systemic pressure was higher than carotid perfusion pressure at the start of the interventions, but the results were nevertheless similar to those of the other experiments.

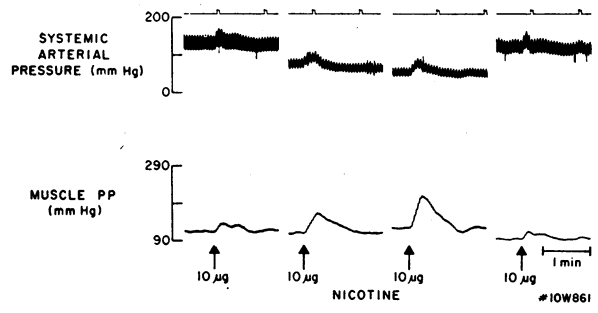

FIGURE 1 Responses to stimulation of chemoreceptors by nicotine before hemorrhage, during two levels of hypotension induced by successive hemorrhage, and after transfusion. Bilateral cervical vagotomy had been done in this study.

This experiment is unusual in that the base-line muscle perfusion pressure (PP) did not increase after the first hemorrhage, and the increase was small after the second hemorrhage; responses to nicotine were augmented nevertheless. This supports the concept that augmented responses to chemoreceptor stimulation during hemorrhagic hypotension are not the result of an increase in base-line vascular tone during hypotension.

tories, Artificial Organs Div., Morton Grove, Ill.), rewarmed, and pumped at constant flow past an oxygen electrode into the carotid artery. A gas mixture with 13% oxygen, 5% CO_2, and 82% nitrogen was bubbled through the oxygenator to maintain normoxia. To stimulate chemoreceptors, nitrogen with approximately 10% CO_2 was bubbled through the oxygenator.

The contralateral carotid artery was perfused with normoxic blood, and the carotid sinus baroreceptors were stimulated by increasing perfusion pressure with a Starling resistor. In six of these experiments the occipital artery was ligated at its origin from the external carotid artery, so that the induced changes in pressure in the carotid artery were not transmitted to the carotid body. Ligation of the occipital artery (after ligating the other arteries) eliminated chemoreceptor responses to intracarotid injections of nicotine on the ipsilateral side in all six dogs. Thus possible activation of the carotid body by changes in pressure was excluded.

Vasoconstrictor responses were observed in the gracilis muscle during stimulation of the carotid chemoreceptors on one side while the perfusion pressure in the contralateral carotid sinus was 75–100, 200, and 75–100 mm Hg. If activating the carotid baroreceptors on one side affected the response to chemoreceptor stimulation on the other side, this would suggest a central interaction of the reflexes.

The interaction of baroreceptor and chemoreceptor reflexes was evaluated statistically by comparing responses to chemoreceptor stimulation (changes in gracilis perfusion pressure) at high and low levels of systemic arterial pressure or carotid perfusion pressure (which reflect the degree of baroreceptor activity) by using orthogonal contrasts (12). Statistical results are summarized in Table VI.

RESULTS

Effects of elevating systemic arterial pressure. Transient occlusion of the descending aorta by inflating a balloon raised arterial pressure in vessels upstream from the occlusion by an average of 30 mm Hg and caused vasodilatation in the muscle (Tables I and VI). Vasoconstrictor responses to stimulation of chemoreceptors by nicotine were inhibited profoundly during elevation of arterial pressure and restored promptly af-

TABLE I

*Effect of Raising Arterial Pressure on Responses to Chemoreceptor Stimulation**

	Control	Aortic occlusion	Control
	mm Hg	*mm Hg*	*mm Hg*
Base-line mean systemic arterial pressure	102±4.7	132±4.9	106±4.8
Δ mean arterial pressure in response to nicotine‡			
10 μg	+10±3.6	+6±2.6 NS§	+7±2.6
40 μg	+18±4.5	+8±2.9 NS§	+16±6.3
Baseline gracilis perfusion pressure	109±7.4	79±5.0	118±9.7
Δ gracilis perfusion pressure in response to nicotine			
10 μg	+20±4.4	+4±1.7‖	+22±7.9
40 μg	+52±18.2	+27±11.2‖	+58±20.8

* Values are mean±SE obtained in eight dogs. Nicotine was injected into one common carotid artery.

‡ The values reported are the maximal pressor response which, in some experiments, followed initial transient bradycardia and hypotension.

§ NS indicates that increases in arterial pressure after nicotine were not significantly different during aortic occlusion and during the control periods.

‖ Variance referred to in Table VI represents comparison of responses to the two doses of nicotine observed during the period of aortic occlusion with corresponding responses during the two control periods. Vasoconstrictor responses in the muscle to intracarotid nicotine were significantly less during aortic occlusion than during the control periods before and after aortic occlusion.

ter deflation of the balloon and return of systemic arterial pressure to normal.

Effects of hypotension. Hemorrhagic hypotension increased baseline perfusion pressure in the muscle and reduced vasoconstrictor responses to the intra-arterial administration of norepinephrine (Tables II and VI). Despite the reduced responsiveness of the gracilis muscle (as indicated by slightly reduced responses to the neurotransmitter, norepinephrine), the vasoconstrictor and systemic pressor responses to chemoreceptor stimulation by nicotine were enhanced markedly during hypotension (Tables II and VI, Fig. 1). In terms of relative potency, four times the dose of nicotine was required during the control period to trigger the same reflex vasoconstrictor response occurring during moderate hypotension (at a mean arterial pressure of 73 mm Hg). This potentiation was related to the severity of hypotension.

Similar potentiation of responses to chemoreceptor stimulation were observed during hemorrhagic hypotension after cervical vagotomy in four dogs. 10 μg nicotine increased gracilis perfusion pressure by 10±5.4 mm Hg (mean±SE) when systemic pressure was 118± 9.2 mm Hg during the control period; after hemorrhage, systemic pressure was 50±2.0 mm Hg, and the response to 10 μg of nicotine was augmented ($P < 0.05$) to 39± 12.4 mm Hg. 40 μg nicotine increased gracilis perfusion pressure 17±7.2 mm Hg during the control period, and after hemorrhage the response was augmented ($P < 0.05$) to 50±14.4 mm Hg.

Effects of intravenous infusion of norepinephrine. Norepinephrine was infused intravenously to determine whether systemic release of catecholamines during hypotension might sensitize chemoreceptors and augment vasoconstrictor responses to nicotine. Intravenous norepinephrine did not alter the vasoconstrictor response to chemoreceptor stimulation. Norepinephrine raised mean arterial pressure from 94±5.1 (mean±SE) to 107±7.8 mm Hg. 10 μg nicotine increased gracilis perfusion pressure 12±4.1 (average of values before and after norepinephrine) and 12±3.6 mm Hg during norepinephrine. 40 μg nicotine increased gracilis perfusion pressure 42±18 (before and after norepinephrine) and 44±20 mm Hg during norepinephrine.

Effects of cerebral perfusion pressure. When perfusion pressure in the isolated perfused carotid arteries was increased from 100 to 200 mm Hg, vasoconstrictor and systemic pressor responses were inhibited (Tables III and VI, Fig. 2). The increase in carotid perfusion pressure also decreased systemic arterial pressure (and cerebral perfusion pressure). When carotid perfusion pressure was maintained at 200 mm Hg and the aorta was occluded with a balloon to restore systemic and cerebral perfusion pressures, responses to chemoreceptor stimulation remained depressed. It appears, therefore, that changes in cerebral perfusion pressure do not account for the altered responses to chemoreceptor stimulation when systemic pressure is changed.

Responses to carotid chemoreceptor stimulation during activation of the contralateral carotid baroreceptors. Vasoconstrictor and systemic pressor responses to stimulation of chemoreceptors by injecting nicotine into one carotid artery perfused at constant pressure were inhibited by elevation of pressure in the contralateral

TABLE II

*Effect of Hemorrhagic Hypotension on Responses to Chemoreceptor Stimulation and Norepinephrine**

	Control	Hemorrhage$_1$	Hemorrhage$_2$	Recovery
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*
Baseline mean systemic arterial pressure (n = 13)	127±4.8	73±1.4	46±1.4	115±3.9
Δ mean arterial pressure in response to nicotine				
10 μg (n = 6)	+4±3.3	+16±12‡	+22±11‡	+3±2.5
40 μg (n = 13)	+12±3.0	+20±4.9‡	+28±4.8‡	+7±2.2
Baseline gracilis perfusion pressure (n = 13)	79±5.2	133±13	141±10	82±8.6
Δ gracilis perfusion pressure in response to nicotine				
10 μg (n = 6)	+7±2.8	+20±3.0‡	+32±10‡	+6±2.9
40 μg (n = 13)	+21±5.6	+43±9.7‡	+47±7.7‡	+20±6.1
Δ gracilis perfusion pressure in response to norepinephrine (n = 13)	+35±2.9	+28±3.2‡	+28±3.6‡	+40±2.8

* Nicotine was injected into one common carotid artery to stimulate the carotid chemoreceptor. 1.0 μg norepinephrine was injected into the gracilis artery.

‡ Increases in arterial pressure and vasoconstrictor responses in the gracilis muscle after nicotine were significantly augmented during hypotension. Vasoconstrictor responses to norepinephrine were significantly depressed during hypotension. Variance referred to in Table VI represents comparison of responses during the two levels of hypotension with responses during control and recovery.

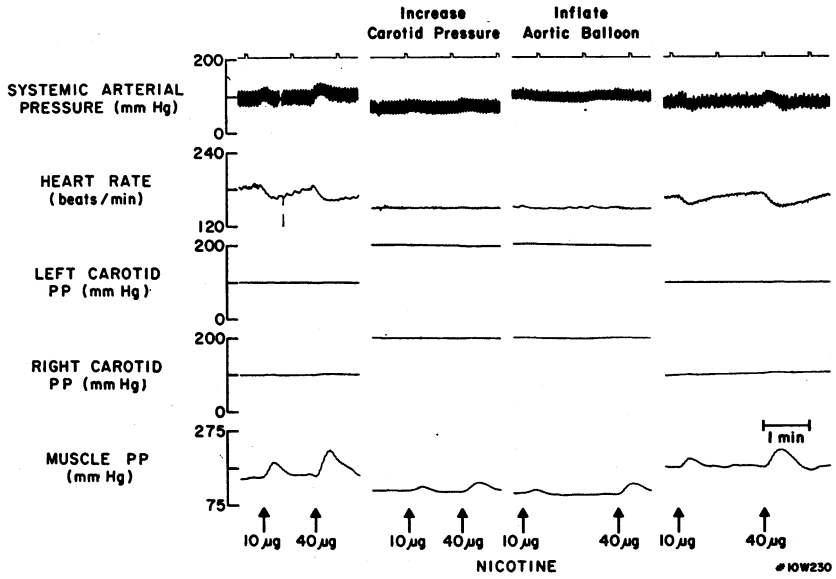

FIGURE 2 Effect of changes in carotid and cerebral perfusion pressure on responses to chemoreceptor stimulation by nicotine. In the second panel, carotid perfusion pressure was raised, which resulted in a decrease in systemic pressure (and cerebral perfusion pressure) and depression of the vasoconstrictor response to chemoreceptor stimulation in the muscle. In the third panel, inflation of the balloon in the descending aorta raised systemic pressure (and cerebral perfusion pressure), but responses to chemoreceptor stimulation were still depressed. In the fourth panel, carotid perfusion pressure was lowered (and the balloon in the aorta deflated), and vasoconstrictor responses to chemoreceptor stimulation were restored.

TABLE III

*Effect of Carotid Hypertension and Systemic Normotension on Responses to Chemoreceptor Stimulation**

	Carotid perfusion pressure			
	100	200	200‡	100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*
Baseline mean systemic arterial pressure*	89±9.7	53±11.6	91±7.1	79±3.1
Δ mean arterial pressure in response to nicotine				
10 μg	+19±7.9	+3±1.4§	+3±1.9 NS‖	+13±3.2
40 μg	+33±14	+8±3.3§	+5±2.4 NS	+25±9.1
Baseline gracilis perfusion pressure	154±7.3	88±21	83±20	142±15
Δ gracilis perfusion pressure in response to nicotine				
10 μg	+36±6.3	+8±2.1§	+5±2.3 NS	+25±5.3
40 μg	+71±15	+19±4.5§	+22±3.9 NS	+47±4.1

* Values were obtained in five dogs. The animals were bled to achieve a systemic arterial pressure lower than carotid perfusion pressure.

‡ The descending aorta was occluded with a balloon to restore systemic (and cerebral perfusion) pressure. Systemic pressure here refers to arterial pressure upstream from the site of the balloon in the descending aorta.

§ Responses to nicotine were significantly less when carotid perfusion pressure was 200 mm Hg than when it was 100 mm Hg. Variance referred to in Table VI (Effect of Raising Carotid Pressure) represents comparison of the first and fourth columns of this table with the second and third columns; in Table VI, "Effect of inflating aortic balloon" represents comparison of the second column of this table with the third column.

‖ Responses to nicotine when carotid perfusion pressure was 200 mm Hg were not altered significantly by raising systemic arterial pressure (NS).

baroreceptors (Tables IV and VI, Figs. 3 and 5). Responses to stimulation of chemoreceptors by hypoxic and hypercapnic blood also were inhibited by elevation of pressure in the contralateral baroreceptors (Tables V and VI, Figs. 4 and 5).

DISCUSSION

This study indicates that the baroreceptor reflex modulates the chemoreceptor reflex. Hypotension potentiates vasoconstrictor responses to chemoreceptor stimulation, and transient hypertension inhibits these responses.

We considered the possibility that altered baseline vascular resistance in the muscle might have contributed to altered responses. For example, hemorrhage might increase vasoconstrictor responses to chemoreceptor stimulation simply by changing the baseline resistance. The changes in resistance, however, would tend to alter responses to chemoreceptor stimulation in a direction opposite to the one observed. Hemorrhage increases vascular resistance and with increased resistance one would expect smaller vasoconstrictor responses (13, 14). This was confirmed in the present study by injecting norepinephrine into the arterial inflow to the muscle. Vasoconstrictor responses to norepinephrine in the muscle were reduced during hemorrhagic hypotension. This indicates that the increased responses to chemoreceptor stimulation during hypotension occur despite, and not because of, the increased base-line vascular resistance in the muscle.

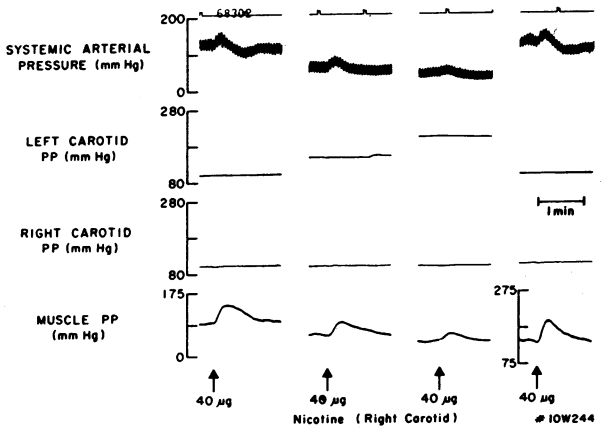

FIGURE 3 Response to stimulation of chemoreceptors during activation of the contralateral baroreceptor. Perfusion pressure (PP) was maintained at 100 mm Hg in the right carotid and nicotine was injected to stimulate the chemoreceptor. The left carotid sinus baroreceptor was activated by raising perfusion pressure from 100 to 150 and 200 mm Hg.

In this experiment, systemic pressure was higher than carotid perfusion pressure (100 mm Hg) in the first and last panels (see footnote 1).

Using norepinephrine to test responses during hemorrhage (that is, superimposing a humoral stimulus on a neural one) is not exactly analogous to observing responses to two neural stimuli (that is, chemoreceptor stimulation and hemorrhage). We have considered the

TABLE IV

*Effect of Raising Perfusion Pressure in One Carotid Artery on Responses to Nicotine Injected in the Contralateral Carotid Artery Perfused at Constant Pressure**

	Left carotid perfusion pressure			
	75–100	150	200	75–100
	mm Hg	*mm Hg*	*mm Hg*	*mm Hg*
Baseline mean systemic arterial pressure‡	75±7.7	52±4.5	42±3.8	74±7.7
Δ mean arterial pressure in response to nicotine				
10 μg	+21±5.1	+12±2.9§	+6±1.3§	+17±4.9
40 μg	+26±4.7	+18±3.7§	+10±1.4§	+26±5.6
Baseline gracilis perfusion pressure	148±16	110±13	103±12	151±13
Δ gracilis perfusion pressure in response to nicotine				
10 μg	+36±12	+25±9.4§	+15±3.5§	+26±5.7
40 μg	+55±11	+43±11§	+26±4.2§	+50±7.2

* Values were obtained in 13–17 dogs.

‡ The animals were bled to achieve a systemic arterial pressure lower than the carotid perfusion pressure.

§ Nicotine was injected into the right common carotid artery which was perfused at constant pressure; responses to nicotine were significantly less when perfusion pressure in the contralateral carotid was elevated (to 150 and 200 mm Hg) than when perfusion pressure was 75–100 mm Hg. Variance referred to in Table VI represents comparison of responses during the two levels of elevation of carotid pressure (columns 2 and 3) with responses during the two periods of perfusion at 75–100 mm Hg (columns 1 and 4).

TABLE V

*Effect of Raising Perfusion Pressure in One Carotid Artery on Responses to Perfusion of Contralateral Carotid Artery with Hypoxic and Hypercapnic Blood at Constant Pressure**

	Left carotid perfusion pressure		
	75–100	200	75–100
	mm Hg	*mm Hg*	*mm Hg*
Blood perfusing right carotid during hypoxia			
P_{O_2}	33±3.0	34±3.0	33±2.2
P_{CO_2}	84±5.6	83±4.6	86±5.5
pH	7.12±0.04	7.14±0.04	7.15±0.04
Baseline mean systemic arterial pressure‡ (mm Hg)	45±2.6	28±2.9	42±2.4
Δ mean arterial pressure during hypoxia (mm Hg)	23±6.5	+8±4.2§	+22±7.7
Baseline gracilis perfusion pressure (mm Hg)	157±21	105±14	174±20
Δ gracilis perfusion pressure during hypoxia (mm Hg)	+85±21	+45±14§	+70±16

* Values are mean±SE obtained in seven dogs during 2–3 min perfusion with hypoxic and hypercapnic blood. In six of these seven dogs, the occipital artery originating from the carotid which was perfused at high pressure was ligated at its origin to eliminate possible effects on chemoreceptors with increases in pressure.
‡ The animals were bled to achieve a systemic arterial pressure lower than the carotid perfusion pressure.
§ Responses to hypoxia were significantly less when carotid perfusion pressure was 200 mm Hg than when carotid perfusion pressure was 75–100 mm Hg. Variance referred to in Table VI represents comparison of responses observed when carotid perfusion was 200 mm Hg with responses during the two periods of perfusion at 75–100 mm Hg.

TABLE VI

*Statistical Analyses**

	Sum of squares	F	*P*
Table I: effect of raising arterial pressure			
ΔMAP with nicotine	360	3.85	NS
Δ GPP with nicotine	5,281	8.32	<0.01
Table II: effect of hemorrhage			
Δ MAP with nicotine	4,140	15.69	<0.01
Δ GPP with nicotine	7,512	13.28	<0.01
Δ GPP with norepinephrine	1,215	9.17	<0.01
Table III: effect of raising carotid pressure			
Δ MAP with nicotine	3,151	26.92	<0.01
Δ GPP with nicotine	9,797	46.54	<0.01
effect of inflating aortic balloon (restoring cerebral perfusion pressure)			
Δ MAP with nicotine	7	<1	NS
Δ GPP with nicotine	0.4	<1	NS
Table IV: effect of raising carotid pressure			
Δ MAP with nicotine	4,014	15.79	<0.01
Δ GPP with nicotine	6,844	6.19	<0.05
Table V: effect of raising carotid pressure			
Δ MAP with hypoxia	788	8.65	<0.05
Δ GPP with hypoxia	5,363	9.72	<0.01

* MAP indicates mean arterial pressure; GPP indicates gracilis perfusion pressure; NS indicates not statistically significant ($P > 0.05$). Sources of variance that account for the sum of squares are indicated in the footnotes to Tables I–V.

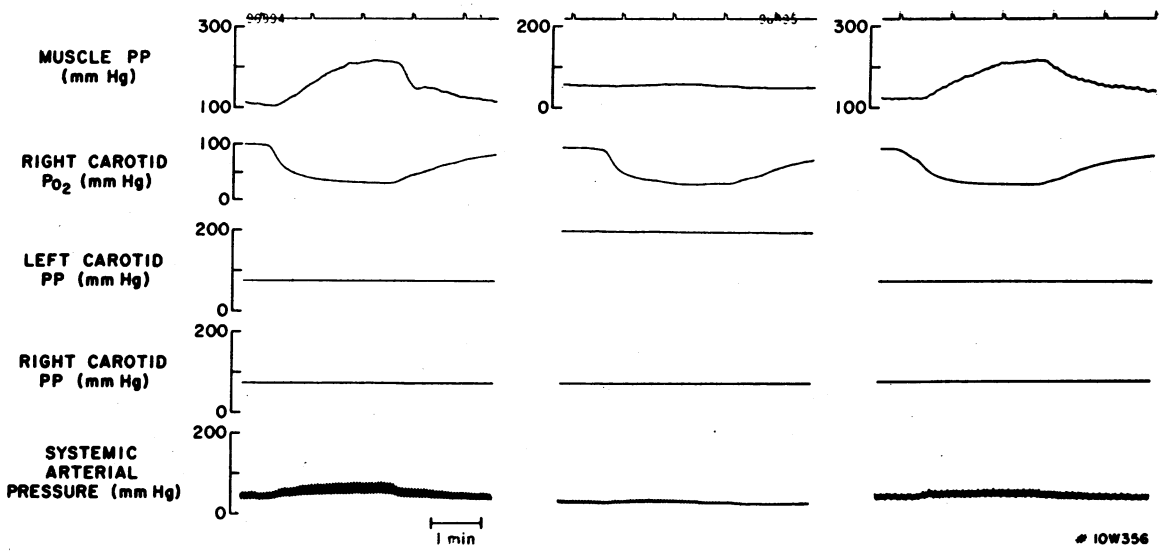

FIGURE 4 Response to stimulation of chemoreceptors by hypoxic and hypercapnic blood during activation of the contralateral baroreceptor. Perfusion pressure (PP) was maintained at 75 mm Hg in the right carotid, and the chemoreceptor was stimulated by hypoxic and hypercapnic blood for 2.5–2.7 min. The left carotid baroreceptor was activated by raising perfusion pressure from 75 to 200 mm Hg. The left occipital artery had been ligated in this study, and there was no reflex response to injection of nicotine into the left common carotid artery.

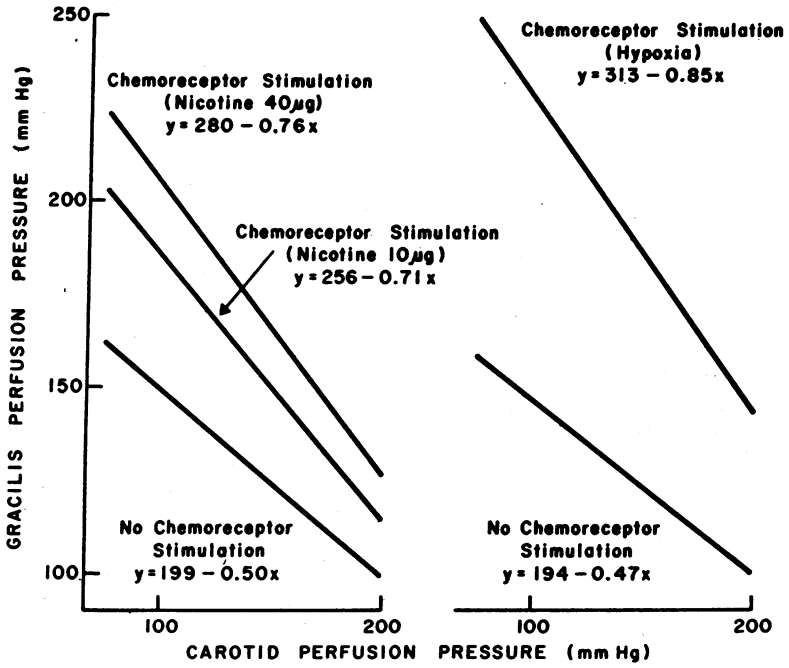

FIGURE 5 Relationship between carotid perfusion pressure (which reflects the degree of baroreceptor activity) and gracilis perfusion pressure, during stimulation of carotid chemoreceptors with 10 and 40 μg nicotine (left) and hypoxia (right) and with no chemoreceptor stimulation. The slopes during chemoreceptor stimulation are significantly different from the slopes with no chemoreceptor stimulation.

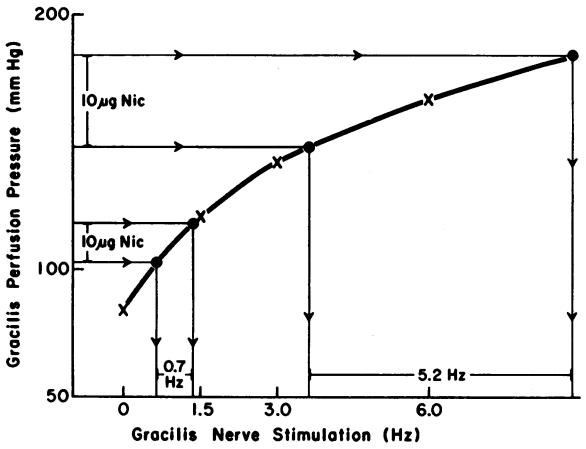

FIGURE 6 Frequency-response curve of responses in gracilis muscle to electrical stimulation of peripheral sympathetic nerve. The curve is plotted from data obtained in a previous study (Table VI, ref. 15, during "normal sodium solution"). Data points from that study were obtained during electrical stimulation at 0, 1.5, 3.0, and 6.0 Hz and are indicated by x. The curve indicates that increasing levels of nerve stimulation cause progressively smaller responses in the gracilis muscle. Responses to chemoreceptor stimulation obtained in the present study (Table IV, responses to 10 μg nicotine (Nic) when carotid perfusion pressure was 75–100 and 200 mm Hg) have been superimposed on the frequency-response curve, and are indicated by solid circles (●). For example, when carotid pressure was 200 mm Hg, 10 μg nicotine (Nic) increased perfusion pressure from 103 to 118 mm Hg, which is equivalent to sympathetic stimulation at 0.7 Hz. The responses to the same chemoreceptor stimulus elicited from two different levels of resting sympathetic tone (the low level when carotid pressure was 200 mm Hg; the high level when carotid pressure was 75–100 mm Hg) were equivalent to electrical stimuli of 0.7 Hz and 5.2 Hz, respectively. This suggests a more than sevenfold augmentation of the efferent sympathetic stimulus to the same afferent chemoreceptor activation.

question of superimposition of two neural stimuli by examining responses to increasing levels of nerve stimulation (Fig. 6). We have examined data from a previous study (15). Increasing the frequency of stimulation from 5 to 6 Hz, for example, causes a smaller response than increasing the frequency from 1 to 2 Hz. Therefore at higher levels of resting sympathetic tone (during hemorrhage and when carotid pressure is low), one would expect smaller responses to a superimposed neural stimulus, such as chemoreceptor stimulation. Because responses to chemoreceptor stimulation were larger, rather than smaller, during hemorrhage and when carotid pressure was low, we conclude that the increased responses to chemoreceptor stimulation occur despite the tendency for a neural stimulus to cause a smaller response when resting neural tone is high.

The rate of blood flow through the carotid body decreases during hypotension (16). Because of low blood flow through the carotid body during hemorrhagic hypotension, the concentration of nicotine after an injection may be increased. However, increased concentration of nicotine does not appear to account for the augmented responses to chemorecetpor stimulation during hypotension. The vasoconstrictor response to chemoreceptor stimulation with 40 and 80 μg nicotine (in 12 dogs) averaged 21±5.6 and 24±7.8 mm Hg, respectively, during the control period. This indicates that the response to 40 μg nicotine was near the top (flat portion) of the dose-response curve. In contrast, the response to 40 μg nicotine increased to 47±7.7 mm Hg during hemorrhagic hypotension. These findings suggest that an increase in concentration of nicotine would not account for the marked potentiation of the chemoreceptor reflex during hypotension. We cannot totally exclude the possibility that altered rate of blood flow through the carotid body may have contributed to augmented responses during hypotension, perhaps by altering the temporal profile of concentration, so that receptors are exposed to nicotine for a longer time. Possible changes in rate of blood flow through the carotid body were minimized in the study in which nicotine was injected into carotid arteries perfused at constant flow and pressure.

Catecholamines may sensitize chemoreceptors to other stimuli (8–10). We considered the possibility that release of catecholamines during hemorrhagic hypotension (7) might sensitize chemoreceptors and augment the chemoreceptor reflex independently of the fall in systemic pressure. A systemic infusion of norepinephrine did not significantly augment the chemoreceptor reflex, so we can exclude this as the primary mechanism for augmented chemoreceptor responses during hypotension. It is possible that norepinephrine has a small effect on chemoreceptors, because the small elevation of arterial pressure during infusion of norepinephrine did not reduce responses to chemoreceptor stimulation.

Acidosis during hypotension also might sensitize the chemoreceptors (17) and account for augmented responses. Arterial pH decreased from 7.34±0.01 during the control to 7.33±0.01 and 7.32±0.01 during the two levels of hypotension, and the chemoreceptor reflex was augmented. After transfusion had restored arterial pressure to normal, the pH continued to fall, to 7.24±0.03, but the response to chemoreceptor stimulation was reduced. Therefore, the magnitude of the chemoreceptor reflex did not parallel changes in pH, and acidosis cannot account for the potentiation of the chemoreceptor reflex during hypotension.

There are several other mechanisms by which changes in arterial pressure might affect the magnitude of the chemoreceptor reflex. Changes in arterial pressure might affect chemoreceptors directly. Biscoe, Bradley, and Purves (18), in a study which modifies an earlier conclusion (19), observed that arterial pressure has little effect on carotid chemoreceptors over the range 60–160 mm Hg. In our study of hypotension, the first level of hemorrhage did not lower arterial pressure below 60 mm Hg in any dogs, so the direct effect on carotid chemoreceptors of changes in arterial pressure was minimal. The second level of hemorrhage lowered arterial pressure below 60 mm Hg, so there may have been a direct effect of pressure on resting neural discharge of carotid chemoreceptors. Although resting chemoreceptor discharge may increase when arterial pressure is below 60 mm Hg, there is no evidence that the increase in rate of discharge after nicotine or hypoxia is potentiated at low levels of arterial pressure. In any event, a direct effect of pressure on carotid chemoreceptors is excluded in the study in which changes in pressure were induced in one carotid and nicotine was injected in the other carotid which was being perfused at constant pressure.

The level of arterial pressure affects the rate of discharge of aortic chemoreceptors (10), although this effect is small (20). In the present studies, a direct effect of arterial pressure on aortic chemoreceptors may have contributed to potentiation of responses during hypotension and inhibition of responses during hypertension. Such an effect, however, is not the primary mechanism for alteration of the chemoreceptor reflex, because profound alterations of the reflex were still observed after denervation of aortic baro- and chemoreceptors with cervical vagotomy.

Changes in sympathetic tone have been shown to affect chemoreceptor activity (21, 22). In our studies, changes in arterial pressure and carotid perfusion pressure still altered the chemoreceptor reflex after vagotomy; because low cervical vagotomy probably interrupts sympathetic input to the superior cervical ganglion (23) and carotid body, it appears that changes in sympathetic tone within the carotid body are not the primary mechanism for the interaction which we have observed.

Another possible mechanism for altered responses to chemoreceptor stimulation is a change in cerebral perfusion pressure. Ischemia of the central nervous system has been reported to increase sympathetic discharge, (24) and it seemed possible that hypotension might cause cerebral ischemia and potentiate the chemoreceptor reflex. In this study, hypotension from hemorrhage augmented the chemoreceptor reflex, but systemic hypotension from elevation of the carotid sinus perfusion pressure was associated with depression of the chemoreceptor reflex. Since systemic hypotension and a fall in cerebral perfusion pressure were associated with both increases (during hemorrhage) and decreases (during perfusion of the carotids at high pressure) in the chemoreceptor reflex, the effect of arterial pressure on the chemoreceptor reflex cannot be the result primarily of changes in cerebral perfusion pressure. Further evidence for this statement is provided by the study summarized in Table III. Responses to chemoreceptor stimulation were still suppressed when carotid perfusion pressure was elevated and cerebral perfusion pressure was maintained at control levels. We conclude that changes in arterial pressure in the brain do not account for the effects observed in the present study. Of interest is a more recent study by Hainsworth and Karim (25) in which these investigators concluded that cerebral hypotension is of minor importance in vascular control unless it is associated with systemic and cerebral hypoxemia.

Another mechanism by which changes in arterial pressure might alter responses to chemoreceptor stimulation is a central interaction of the baroreceptor and chemoreceptor reflexes. This study indicates that physiologic activation of the baroreceptor reflex, by elevation of pressure in one carotid sinus, inhibits the vasoconstrictor response to activation of the contralateral carotid chemoreceptors. The findings suggest a central interaction between the baroreceptor and chemoreceptor reflexes. A study of Miura and Reis (26) provides a neurophysiologic explanation for this interaction. These investigators found that bilateral lesions of the paramedian reticular nucleus of the medulla, which serves to mediate the baroreceptor reflex, augmented systemic pressor responses to chemoreceptor stimulation. In light of the recent observation (27) that baroreceptor stimulation inhibits sympathetic nerve discharge at a spinal as well as a medullary locus, it is possible that central interaction of the baroreceptor and chemoreceptor reflexes may occur at both the brainstem and spinal levels.

We might speculate about the clinical importance of the finding that hypotension potentiates the chemoreceptor reflex. Other studies have demonstrated that stimulation of chemoreceptors produces reflex vasoconstriction in muscle and vasodilatation in the coronary bed (6, 28). This favors redistribution of blood flow toward the coronary circulation. We speculate that potentiation of the chemoreceptor reflex during hypotension would promote this favorable redistribution of blood flow when oxygen availability is limited by hypoxemia and hypotension.

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