Effect of Sympathetic Nerve Stimulation on Cerebral Blood Flow and on Large Cerebral Arteries of Dogs

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SUMMARY **This study was performed to determine whether sympathetic stimulation reduces or redistributes cerebral blood flow. Total and regional cerebral blood flows were measured with the use of microspheres. Left stellate and superior cervical ganglia were stimulated electrically in anesthetized dogs. Sympathetic stimulation did not alter blood flow to ipsilateral cerebrum, cerebellum, or brainstem. Responsiveness of cerebral vessels to vasoconstrictor stimuli was intact, since cerebral blood flow decreased during systemic hypocapnia. Sympathetic stimulation dilated the ipsilateral pupil and reduced flow to ipsilateral temporalis and genioglossus muscles, which indicates that sympathetic pathways to the head were activated. We tested the hypothesis that sympathetic stimulation might constrict large cerebral arteries while dilation of small vessels through autoregulation maintains flow constant. Sympathetic stimulation during systemic hypercapnia, which interferes with autoregulation, did not decrease ipsilateral cerebral blood flow. In additional studies responses of large arteries which supply the brain were evaluated by determining the gradient between common carotid artery pressure and vertebral artery wedge pressure. Serotonin constricted large arteries that supply the brain, but bilateral stimulation of superior cervical ganglia did not increase the resistance of these arteries. As a result of these studies, we conclude that (1) sympathetic stimulation does not reduce or redistribute cerebral blood flow, (2) sympathetic stimulation does not constrict large cerebral arteries significantly, and (3) serotonin constricts large arteries to the brain but dilation of small cerebral vessels tends to maintain cerebral blood flow constant.**

A NUMBER of investigators have evaluated the possible significance of cerebral vascular innervation by examining responses to stimulation of sympathetic nerves. Electrical stimulation of cervical sympathetic nerves that innervate cerebral vessels has been reported to have no effect on resting cerebral blood flow (CBF) in the cat[1] and dog.[2] Conflicting reports have suggested that sympathetic stimulation decreases CBF profoundly in the baboon,[3] goat,[4] and dog.[5] Discrepancies in results may be attributed in part to the different methods that have been used to measure CBF.[6]

In this study, we have examined effects of stimulation of sympathetic nerves on total and regional CBF. Labeled microspheres were used to measure CBF.[7] This technique circumvents the methodological problems created by the presence of multiple arteries and veins to and from the brain and allows measurement of both total and regional CBF. The measurement of regional CBF allowed us to determine whether sympathetic stimulation decreases or redistributes CBF to the ipsilateral hemisphere and to compare the total and regional flows with those in the contralateral "control" hemisphere.

Several studies were performed. Total and regional CBF were measured during (1) stimulation of a superior cervical ganglion, (2) stimulation of a stellate ganglion, (3) unilateral stimulation of both ganglia, and (4) unilateral stimulation of both ganglia during systemic hypercapnia. The rationale for sympathetic stimulation during hypercapnia is as follows. Cerebral vessels autoregulate extremely effectively, so that changes in arterial pressure have little effect on CBF.[8, 9] It has been suggested that sympathetic stimulation might constrict large cerebral arteries and thereby decrease pressure in smaller cerebral arteries, but that autoregulation by the distal arteries might maintain CBF constant.[10] Because hypercapnia interferes with cerebral autoregulation,[8] it seemed possible that hypercapnia might unmask a cerebral vasoconstrictor effect of sympathetic nerve stimulation.

Additional studies were performed to determine more directly whether large arteries to the brain constrict during sympathetic stimulation. Rapela and Martin[11] have described recently a technique to estimate resistance of large cerebral arteries. They determined the gradient between the common carotid artery pressure and vertebral artery wedge pressure. Rapela and Martin found that serotonin increases this gradient and concluded that serotonin constricts large cerebral arteries. In this study we measured the gradient between common carotid pressure and vertebral artery wedge pressure during stimulation of both superior cervical ganglia. These studies tested the hypothesis that sympathetic nerves might constrict large arteries

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that supply the brain and increase the gradient between carotid pressure and vertebral artery wedge pressures, but a decrease in distal artery resistance might maintain CBF constant.

Methods

Thirty-eight mongrel dogs weighing 17–25 kg were anesthetized with chloralose (50 mg/kg) and urethane (500 mg/kg) intravenously, with supplemental doses given as needed. Each dog was anticoagulated with heparin (500 U/kg, iv), paralyzed with decamethonium bromide (0.3 mg/kg, iv), and artificially ventilated with a respirator. Systemic arterial Po_2, Pco_2, and pH were measured (Instrumentation Laboratories Ultramicro gas analyzer) before each injection of microspheres. Systemic arterial pressure was measured in a brachial artery.

MEASUREMENT OF CBF

The heart was exposed through a left thoracotomy at the 4th intercostal space. A flanged cannula of polyethylene tubing was placed in the left atrial appendage for the injection of isotope-labeled microspheres. Additional cannulas for withdrawal of reference blood samples were placed in a brachial and femoral artery. In four dogs, a catheter was inserted into the dorsal sagittal sinus through a burr-hole, to obtain blood samples for estimating the percentage of microspheres shunted through arteriovenous channels. Dorsal sagittal sinus pressure was recorded in these dogs to monitor changes in intracerebral pressure. Maximal changes in sinus pressure were less than 2 mm Hg during sympathetic stimulation, and would not be expected to affect CBF.

Microspheres with a mean diameter of 15 μm were injected into the left atrium. Injections of microspheres labeled with either ^{46}Sc, ^{85}Sr, ^{141}Ce, or ^{125}I allowed us to make four separate measurements of CBF in each dog. The vials containing microspheres [mixed with 1 drop of polysorbate 80 (Tween 80)] were vigorously agitated in a Vortex mixer for 3–5 minutes before injection. The number of microspheres in each injection varied between 1.6 and 10.9 $\times$ 10^6. The microspheres were injected in approximately 10 seconds; the cannula was flushed with 10 ml of saline at 37°C during the subsequent 20 seconds. Beginning 30 seconds before injection of microspheres and continuing until 2 minutes after injection, reference arterial blood samples were withdrawn from the brachial and femoral arteries, and venous blood samples (in four dogs) were withdrawn from the dorsal sagittal sinus at a rate of 2.06 ml/min with Harvard pumps. The interval between subsequent injections varied from 15 to 45 minutes.

At the end of each study the dogs were killed and the brains were removed. The brain was cut into 39 samples: right and left medulla, pons, thalamus-midbrain, cerebellum, and multiple cerebral samples. In the dogs in which large cerebral artery resistance was measured, we also obtained samples of gray matter (occipital gray matter and caudate nucleus) and white matter (centrum ovale and corpus callosum). Tissue samples were also taken from temporalis muscles and either cervical muscles or the tongue. The weights of brain and other tissue samples ranged from 0.4 to 4.9 g, net weight.

After weighing, specimens were placed in plastic tubes and counted for 5 minutes in a 3-inch well-type gamma counter. The reference blood samples were divided in portions so that their counting geometry was similar to that of the tissue samples. The energy windows for ^{46}Sc, ^{85}Sr, ^{141}Ce, and ^{125}I were 700–1,500 keV, 400–600 keV, 125–175 keV, and 20–50 keV, respectively. The isotope separation was performed by standard techniques.[7, 12]

Tissue weights and output from the gamma counter were punched onto paper tapes and processed on a PDP-11 computer. CBF was calculated with the formula, $CBF = C_b \times 100\ RBF/C_r$, where CBF = cerebral blood flow in ml/min per 100 g of brain, C_b = counts/g of brain tissue, RBF = reference blood flow (rate of withdrawal of blood samples from arteries), and C_r = total counts in reference arterial blood. The counts in the two reference blood samples were averaged. Blood flows to muscle were calculated in a similar fashion. Results are expressed as mean ± SE. Statistical analysis was performed with the *t*-test for paired data.

The amount of arteriovenous shunting of microspheres in the brain was estimated by dividing the number of counts in venous blood from the dorsal sagittal sinus by the number of counts in the averaged arterial blood samples. Shunting was less than 3% during control measurements and sympathetic stimulation.

STIMULATION OF THE SUPERIOR CERVICAL GANGLION

Seven dogs were studied. The left superior cervical ganglion was isolated by a frontal approach high in the cervical region. The body of the ganglion was dissected free, a tie was secured just below the caudal end, and the sympathetic nerve leading caudally from the ganglion was cut. A bipolar electrode was placed on the body of the ganglion. Voltage, frequency, and duration of the impulses were adjusted to achieve maximal dilation of the pupil. The parameters varied as follows: voltage = 5–20 V, frequency = 10–20 Hz, and duration = 3 msec. Microspheres were injected during a control period and during stimulation of the left superior cervical ganglion. Stimulation was applied for 2–3 minutes, with injection of microspheres 40–60 seconds after the onset of stimulation.

STIMULATION OF THE STELLATE GANGLION

Eight dogs were studied; in one of these we had also measured responses to stimulation of the superior cervical ganglion. Although the superior cervical ganglion provides virtually all of the sympathetic innervation to cerebral vessels,[13] it seemed important to examine responses to stimulation of the stellate ganglion in light of a previous report that stellate stimulation reduces CBF profoundly.[5] The body of the ganglion was dissected free from the pleura, and a tie was secured caudal to the ganglion. Cardiac fibers arising from the stellate ganglion were severed to minimize changes in systemic arterial pressure produced by stimulation. Sympathetic stimulation was performed at 10–30 V, 10–20 Hz, and 3 msec. The injection of microspheres was carried out as described above.

STIMULATION OF BOTH GANGLIA

Eleven dogs were studied; in three of these we had also measured responses to stimulation of the superior cervical ganglion alone. Ganglia were stimulated as described above.

RESPONSE TO SYSTEMIC HYPOCAPNIA

In five dogs, CBF was measured during systemic hypocapnia. In all five dogs we had measured responses to stimulation of the stellate ganglion and in one dog we had measured responses to stimulation of the superior cervical ganglion. Responses to systemic hypocapnia were measured to determine whether cerebral vasoconstrictor responses were intact in these dogs. Hypocapnia was induced by increasing ventilatory rate.

RESPONSES TO SYMPATHETIC STIMULATION DURING SYSTEMIC HYPERCAPNIA

Ten dogs were studied, five of which had also been studied during sympathetic stimulation while normocapnic. Arterial P_{CO_2} was increased by mixing 10% CO_2 with the inspired air. Measurements were made after the dogs had been hypercapnic for a period of at least 15 minutes. In half the dogs, CBF was measured first during hypercapnia without sympathetic stimulation and then during sympathetic stimulation; in the other half the order was reversed. Both the left stellate and superior cervical ganglia were stimulated.

MEASUREMENT OF RESISTANCE OF LARGE ARTERIES THAT SUPPLY THE BRAIN

In seven dogs we evaluated the effects of sympathetic nerve stimulation on large arteries, using the technique of Rapela and Martin.[11] The difference between common carotid artery pressure and vertebral artery wedge pressure was determined. Common carotid artery pressure was measured with a catheter inserted in the thyroid artery. Vertebral wedge pressure was obtained by inserting catheters into both vertebral arteries before they entered the transverse foramina of the 6th cervical vertebra. Large (PE 200) catheters were advanced until they wedged. Small (PE 50) catheters were inserted through the large catheters until they wedged. At autopsy the small catheters were found to be wedged either at the 2nd cervical vertebra or at the C1-C2 or C2-C3 interspace.

We tested the adequacy of the placement of vertebral wedge catheters by observing the response to brief periods (about 10–15 seconds) of bilateral common carotid artery occlusion (Fig. 1). Carotid occlusion increased systemic arterial pressure from 86 ± 4 (mean ± SE) mm Hg to 103 ± 5 mm Hg and decreased vertebral wedge pressure from 65 ± 5 to 31 ± 5 mm Hg. In three of the seven dogs, carotid occlusion produced a marked decrease in pressure in one vertebral artery but did not reduce pressure in the other vertebral artery. In all three of these dogs the vertebral artery catheter on the side that did not respond to carotid occlusion was wedged in a muscular branch of the vertebral artery, and the catheter on the "responsive" side was wedged in an appropriate position in the vertebral artery. In those three dogs we used vertebral artery pressures obtained on the "responsive" side; in the other four dogs we averaged pressure from both vertebral arteries to obtain vertebral wedge pressure.

Both superior cervical ganglia were exposed. The ganglia were stimulated at 15 V, 15 Hz, and 4 msec.

Serotonin was infused in these studies to test responsiveness of large arteries. Small catheters were inserted into both lingual arteries. Serotonin was infused at 300 μg/min through each catheter into the common carotid arteries. This large dose of serotonin was selected because serotonin was used as an internal control (to demonstrate constrictor responsiveness of vessels to the brain) and because an earlier study[11] had suggested that this dose of serotonin constricts large cerebral arteries.

Microspheres were injected four times during each experiment to measure CBF: during the control period, sympathetic stimulation, control period, and infusion of serotonin. The microspheres were injected during infusion of serotonin when vertebral artery wedge pressure reached its nadir.

Total cerebral vascular resistance was calculated by dividing systemic arterial pressure by total cerebral blood flow. Large artery resistance was estimated by dividing large artery pressure gradient (mean systemic arterial pressure minus vertebral artery wedge pressure) by total CBF.

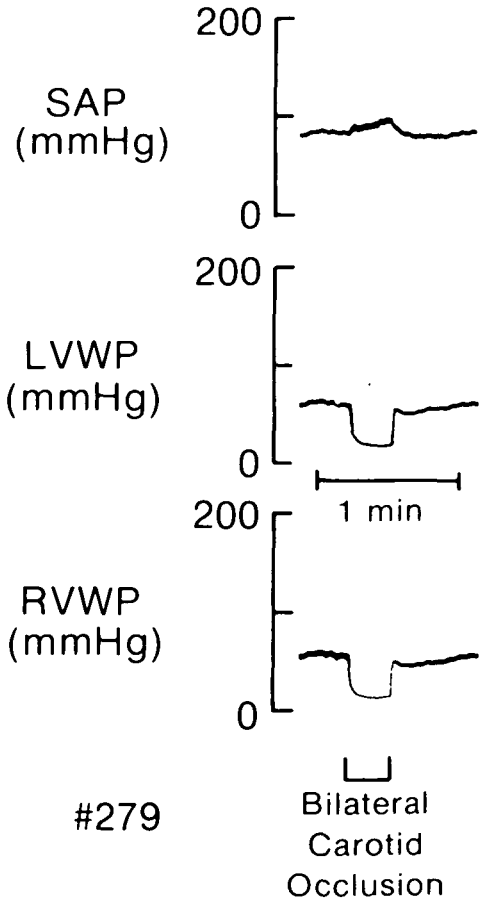

FIGURE 1 *Measurements are mean systemic arterial pressure (SAP), left vertebral artery wedge pressure (LVWP), and right vertebral artery wedge pressure (RVWP). Bilateral carotid occlusion increased systemic pressure and profoundly decreased vertebral artery wedge pressure.*

TABLE 1 *Effect of Stimulation of Left Superior Cervical Ganglion on Cerebral Blood Flow (CBF)**

	Control		Sympathetic stimulation	
Total CBF (ml/min per 100 g)	48 ± 6		52 ± 7	
Mean arterial pressure (mm Hg)	115 ± 4		120 ± 5	
Total cerebral vascular resistance (mm Hg per ml/min per 100 g)	2.6 ± 0.3		2.5 ± 0.3	
Systemic blood gases and pH				
$Paco_2$ (mm Hg)	37 ± 0.7		37 ± 0.7	
pH	7.38 ± 0.01		7.37 ± 0.01	
Pao_2 (mm Hg)	143 ± 14		140 ± 14	
Regional CBF (ml/min per 100 g)	*Right*	*Left*	*Right*	*Left*
Hemibrain	47 ± 6	47 ± 6	52 ± 6	51 ± 7†
Cerebrum	45 ± 6	45 ± 6	49 ± 6	48 ± 6
Cerebellum	55 ± 6	58 ± 6	63 ± 9	63 ± 10
Brainstem				
Thalamus	54 ± 11	53 ± 11	58 ± 9	62 ± 11
Pons	39 ± 6	42 ± 6	41 ± 7	39 ± 8
Medulla	48 ± 8	47 ± 8	51 ± 9	52 ± 9
Cranial muscle blood flow (ml/min per 100 g)	6.7 ± 1	14.1 ± 4	9.2 ± 2	2.1 ± 1.0‡

* Values were obtained in 7 dogs and are expressed as mean ± SE.
† Blood flow to stimulated side of brain (left) was not significantly less than flow to contralateral side ($P > 0.05$).
‡ Blood flow to ipsilateral temporalis muscle was significantly lower during stimulation than during control ($P < 0.01$).

Additional studies were performed to determine whether constriction of extracranial arteries contributes to responses to sympathetic stimulation or serotonin. As we will describe below, serotonin increased large artery resistance. It seemed important to determine whether serotonin or sympathetic stimulation constricted large intracranial (cerebral) arteries or large extracranial arteries that supply the brain (the internal carotid artery and the external carotid artery, through the anastomotic branch). In four dogs a PE 50 catheter was advanced distally in the external carotid artery, about 3 inches past the carotid bifurcation. The purpose of these experiments was to determine whether sympathetic stimulation or serotonin constricts large extracranial arteries that supply the head and brain and reduces distal external carotid artery pressure.

We also attempted to measure pressure in the distal internal carotid artery. The measurement was not technically feasible because a catheter could not be advanced distally in the internal carotid artery.

Results

EFFECTS OF SYMPATHETIC STIMULATION AND HYPOCAPNIA

Stimulation of the superior cervical and stellate ganglia did not alter total or regional CBF (Tables 1–3). In each dog the ipsilateral pupil dilated maximally during sympathetic stimulation and blood flow to ipsilateral temporalis muscle decreased. An incidental finding was that blood flow during the control period was greater in the ipsilateral

TABLE 2 *Effect of Stimulation of Left Stellate Ganglion on Cerebral Blood Flow (CBF)**

	Control		Sympathetic stimulation	
Total CBF (ml/min per 100 g)	59 ± 5		62 ± 5	
Mean arterial pressure (mm Hg)	110 ± 7		114 ± 6	
Total cerebral vascular resistance (mm Hg per ml/min per 100 g)	1.9 ± 0.2		1.9 ± 0.1	
Systemic blood gases and pH				
$Paco_2$ (mm Hg)	36 ± 0.5		37 ± 0.3	
pH	7.36 ± 0.01		7.36 ± 0.005	
Pao_2 (mm Hg)	128 ± 10		124 ± 7	
Regional CBF (ml/min per 100 g)	*Right*	*Left*	*Right*	*Left*
Hemibrain	58 ± 5	58 ± 4	61 ± 4	61 ± 5†
Cerebrum	57 ± 5	56 ± 4	59 ± 4	59 ± 4
Cerebellum	80 ± 5	80 ± 5	83 ± 8	84 ± 9
Brainstem				
Thalamus	65 ± 8	63 ± 6	68 ± 7	67 ± 7
Pons	49 ± 4	48 ± 4	50 ± 5	48 ± 5
Medulla	59 ± 6	58 ± 6	61 ± 6	62 ± 6
Cranial muscle blood flow (ml/min per 100 g)	11 ± 3	18 ± 4	12 ± 3	7 ± 3‡

* Values were obtained in 8 dogs.
† Blood flow to stimulated side was not less than flow to the contralateral side ($P > 0.05$).
‡ Blood flow to ipsilateral temporalis muscle was significantly lower during stimulation than during control ($P < 0.02$).

TABLE 3 *Effect of Stimulation of Left Stellate and Superior Cervical Ganglia on Cerebral Blood Flow (CBF)**

	Control		Sympathetic stimulation	
Total CBF (ml/min per 100 g)	55 ± 7		58 ± 8	
Mean arterial pressure (mm Hg)	115 ± 4		119 ± 5	
Total cerebral vascular resistance (mm Hg per ml/min per 100 g)	2.4 ± 0.2		2.3 ± 0.2	
Systemic blood gases and pH				
$Paco_2$ (mm Hg)	37 ± 0.4		37 ± 0.4	
pH	7.36 ± 0.004		7.36 ± 0.004	
Pao_2 (mm Hg)	142 ± 10		134 ± 11	
Regional CBF (ml/min per 100 g)	*Right*	*Left*	*Right*	*Left*
Hemibrain	54 ± 7	54 ± 7	59 ± 8	57 ± 8†
Cerebrum	52 ± 7	52 ± 7	57 ± 8	56 ± 8
Cerebellum	68 ± 9	73 ± 9	75 ± 9	76 ± 9
Brainstem				
Thalamus	56 ± 7	56 ± 7	59 ± 8	57 ± 7
Pons	44 ± 6	44 ± 6	44 ± 6	42 ± 7
Medulla	54 ± 8	56 ± 7	52 ± 7	53 ± 8
Cranial muscle blood flow (ml/min per 100 g)	4.1 ± 0.5	14.2 ± 4	4.9 ± 1.6	1.7 ± 0.6‡

* Values were obtained in 11 dogs.
† Blood flow to stimulated side of brain was not significantly less than flow to contralateral side ($P > 0.05$).
‡ Blood flow to ipsilateral temporalis muscle was lower during stimulation than during control ($P < 0.005$).

muscle than in contralateral muscle. This hyperemia was presumably produced by section of the sympathetic nerve caudal to the ganglion, as described in Methods. Stimulation of the stellate ganglion did not increase arterial pressure, as it did in previous studies,[5] because we had cut fibers that passed from the stellate ganglion to the heart.

In five dogs, CBF decreased from 54 ± 8 to 29 ± 6 ml/min per 100 g of brain when Pco_2 was decreased from 36 ± 0.4 to 23 ± 0.5 mm Hg. This indicates that cerebral vasoconstrictor responsiveness was intact in these dogs (Fig. 2).

EFFECT OF SYMPATHETIC STIMULATION DURING HYPERCAPNIA

Hypercapnia increased CBF to 160 ± 7 ml/min (Table 4). Stimulation of stellate and superior cervical ganglia did not decrease ipsilateral CBF or redistribute CBF, but reduced blood flow to the ipsilateral genioglossus muscle.

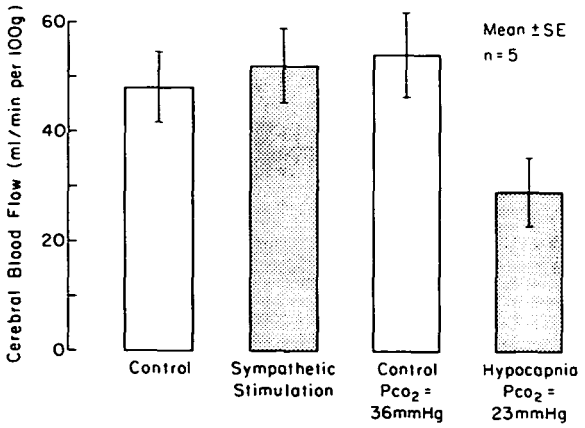

FIGURE 2 *Electrical stimulation of superior cervical ganglia did not alter cerebral blood flow. Cerebral vasoconstrictor responses to hypocapnia were intact.*

EFFECT OF SYMPATHETIC STIMULATION ON LARGE ARTERY RESISTANCE

Stimulation of both superior cervical ganglia did not decrease total CBF or redistribute blood flow (Table 5); sympathetic stimulation tended to increase, rather than decrease, flow to cerebral gray matter, but the changes were not statistically significant. Sympathetic stimulation did not increase large artery pressure gradient or resistance (Fig. 3 and Table 5). Distal external carotid artery pressure did not decrease during sympathetic stimulation in the two dogs in which it was measured, which suggests that sympathetic stimulation does not constrict extracranial arteries that supply the brain.

EFFECT OF SEROTONIN ON LARGE ARTERY RESISTANCE

Intracarotid infusion of serotonin significantly increased large artery pressure gradient and resistance (Fig. 4 and Table 5). Distal external carotid artery pressure decreased during infusion of serotonin in the four dogs in which it was measured. The gradient between systemic arterial pressure and distal external carotid artery pressure increased 21 ± 9 mm Hg during administration of serotonin. The data suggest that a major part of the constrictor effect of serotonin on large arteries that supply the brain is on large extracranial, rather than intracranial, arteries.

Total cerebral vascular resistance increased less than large artery resistance; this suggests that small cerebral vessels may have dilated during administration of serotonin. CBF decreased with serotonin in four of five experiments, but this effect was small and not statistically significant.

Discussion

This study indicates that electrical stimulation of sympathetic ganglia does not decrease or redistribute CBF. Several possible deficiencies which might have invalidated the conclusion were considered.

TABLE 4 *Effect on Cerebral Blood Flow (CBF) of Stimulation of Left Superior Cervical and Stellate Ganglia during Hypercapnia**

	Control		Sympathetic stimulation	
Total CBF (ml/min per 100 g)	160 ± 17		172 ± 12	
Mean arterial pressure (mm Hg)	109 ± 7		113 ± 7	
Total cerebral vascular resistance (mm Hg per ml/min per 100 g)	0.7 ± 0.1		0.7 ± 0.1	
Systemic blood gases and pH				
$Paco_2$ (mm Hg)	53 ± 1.0		53 ± 0.7	
pH	7.17 ± 0.02		7.21 ± 0.02	
Pao_2 (mm Hg)	118 ± 6		114 ± 7	
Regional CBF (ml/min per 100 g)	*Right*	*Left*	*Right*	*Left*
Hemibrain	161 ± 17	158 ± 16	168 ± 14	169 ± 12†
Cerebrum	156 ± 15	153 ± 16	168 ± 13	164 ± 12
Cerebellum	187 ± 18	188 ± 16	195 ± 14	197 ± 12
Thalamus	189 ± 22	165 ± 17	199 ± 19	175 ± 14
Pons	126 ± 14	122 ± 13	132 ± 12	128 ± 10
Medulla	158 ± 17	161 ± 19	167 ± 14	167 ± 17
Cranial muscle blood flow (ml/min per 100 g)	8.8 ± 2	12.4 ± 4	8.9 ± 2	2.5 ± 1.2‡

* Values were obtained in 10 dogs.
† Blood flow to stimulated side of brain was not less than flow to the contralateral side ($P > 0.05$).
‡ Blood flow to ipsilateral genioglossus muscle was lower during stimulation than during control ($P < 0.02$).

First, it was necessary to demonstrate that the level of sympathetic stimulation was adequate to produce a response. The observations of maximal pupillary dilation and profound decreases in blood flow to temporalis and genioglossus muscles during sympathetic stimulation indicate that the stimulus activated sympathetic pathways. These responses in cranial muscle did not demonstrate that we had stimulated fibers that innervate cerebral vessels. However, our finding in another study[14] that cerebrovascular catecholamine levels were depleted several days after sympathetic ganglionectomy indicates that the ganglia which were stimulated during the blood flow studies were indeed supplying sympathetic innervation to cerebral vessels.

Another consideration was that the normal responsiveness of cerebral vessels was impaired by the experimental

TABLE 5 *Effect of Sympathetic Stimulation and Serotonin on Large Arteries that Supply the Brain and on Cerebral Blood Flow (CBF)**

	Control	Sympathetic stimulation	Control	Intracarotid serotonin
Total CBF (ml/min per 100 g)	32.6 ± 3.3	37.5 ± 4.0	36.9 ± 4.0	31.4 ± 7.2
Mean systemic arterial pressure (mm Hg)	82 ± 3	86 ± 6	80 ± 4	81 ± 5
Total cerebral vascular resistance (mm Hg per ml/min per 100 g)	2.7 ± 0.3	2.4 ± 0.2	2.3 ± 0.3	3.2 ± 0.7‡
Mean vertebral arterial wedge pressure (mm Hg)	58 ± 4	61 ± 6	58 ± 6	35 ± 5‡
Large artery pressure gradient (mm Hg)†	24 ± 3	25 ± 2	22 ± 4	46 ± 6‡
Large artery resistance (mm Hg per ml/min per 100 g)†	0.8 ± 0.2	0.7 ± 0.1	0.7 ± 0.2	2.0 ± 0.6‡
Systemic blood gases and pH				
$Paco_2$ (mm Hg)	37 ± 0.6	38 ± 0.4	37 ± 0.7	36 ± 0.8
pH	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01
Pao_2 (mm Hg)	158 ± 13	148 ± 11	140 ± 11	136 ± 9
Regional CBF (ml/min per 100 g)				
Cerebrum	33 ± 4.2	39 ± 4.5	38 ± 5.0	36 ± 6.8
Gray matter				
Cortical gray	36 ± 4.6	45 ± 5.3	42 ± 5.2	42 ± 7.4
Caudate nucleus	46 ± 5.4	62 ± 8.4	54 ± 6.0	50 ± 13
White matter				
Centrum ovale	18 ± 1.5	16 ± 2.0	18 ± 2.7	15 ± 4.0
Corpus callosum	18 ± 2.0	17 ± 3.1	17 ± 2.3	12 ± 2.8
Cerebellum	37 ± 3.3	39 ± 4.4	41 ± 4.2	36 ± 5.5
Brainstem				
Thalamus	34 ± 2.3	39 ± 4.4	38 ± 4.8	40 ± 7.6
Pons	26 ± 2.3	26 ± 4.1	28 ± 3.6	25 ± 4.3
Medulla	30 ± 3.1	33 ± 4.8	33 ± 3.6	32 ± 6.7
Cranial muscle blood flow (ml/min per 100 g)	6.8 ± 1.9	2.6 ± 1.5‡	8.7 ± 3.8	2.0 ± 0.8‡

* Values in first three columns were obtained in seven dogs; values in last column were obtained in five dogs.
† Large artery pressure gradient (systemic arterial pressure − vertebral artery wedge pressure) was divided by total cerebral blood flow to estimate large artery resistance.
‡ Values were significantly different from those during preceding control period ($P < 0.05$).

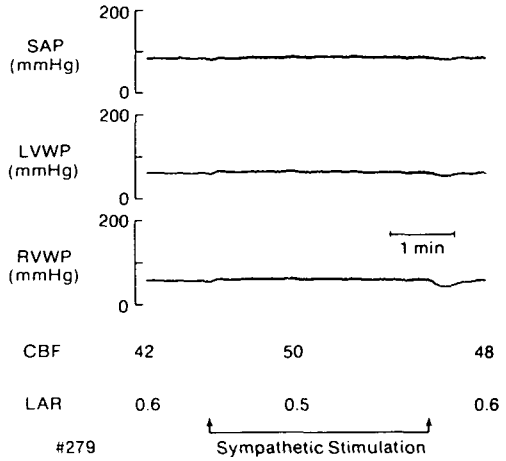

FIGURE 3 *Abbreviations are summarized in legend to Figure 1. In addition, CBF = cerebral blood flow (ml/min per 100 g) and LAR = resistance of large arteries (in mm Hg per ml/min per 100 g). Stimulation of both superior cervical ganglia did not increase the gradient between common carotid arterial pressure (SAP) and the vertebral artery wedge pressure, and did not increase resistance of large arteries. Cerebral blood flow measurements before and after sympathetic stimulation (indicated as 42 and 48 ml/min) were obtained several minutes before and after, respectively, sympathetic stimulation.*

procedures. If the capacity of cerebral vessels to constrict were impaired in these dogs, a significant vasoconstrictor effect of sympathetic stimulation could be masked. However, systemic hypocapnia produced profound cerebral vasoconstriction, which indicates that the cerebral vessels were capable of constricting in the presence of appropriate stimuli.

Several studies have suggested that sympathetic stimulation decreases CBF.[3-5, 10, 15] These studies used isotope clearance techniques,[3, 10, 15] carotid flowmeter measurements,[4] and a modified venous outflow technique[5] to measure CBF. As Harper[16] has pointed out, the accuracy of the isotope clearance technique may be compromised when temporal muscles and scalp are not removed.[3, 15] Despite ligation of the external carotid artery, it is possible that extracranial contamination with ^{133}Xe or ^{85}Kr may distort the clearance curves and that the curves could detect effects of sympathetic stimulation on extracranial structures. The accuracy of the other techniques[4, 5] is also limited by the possibility that measurement of CBF includes contamination by flow from extracranial structures.

Several studies have used labeled microspheres to measure CBF during sympathetic stimulation.[1, 17-19] Two studies indicated that, during unilateral stimulation of superior cervical ganglion in the cat and monkey,[1, 18] cerebral flow does not differ in the ipsilateral and contralateral side of the brain. These studies used only one injection of microspheres so that flow could not be compared during control period and sympathetic stimulation, and vasoconstrictor responsiveness to hypocapnia was not demonstrated. In another study, stimulation of the caudal cervical ganglion did not alter CBF,[17] but responses to stimulation of the superior cervical ganglion, which supplies most of the sympathetic fibers to cerebral vessels, were not examined. A recent study suggests that sympathetic stimulation during severe hypertension (mean arterial pressure between 160 and 300 mm Hg) may reduce ipsilateral CBF.[19] Although only one injection of microspheres was made, so that flow could not be compared during control period and during sympathetic stimulation, the study is of interest because it suggests that sympathetic nerves may affect cerebral vessels during an extreme stress.

Previous studies in which the diameter of pial vessels was measured have demonstrated consistently that large pial vessels constrict during sympathetic stimulation.[20] The question then arises as to why we and others[1, 2, 17, 18] have been unable to demonstrate a decrease in CBF during sympathetic stimulation. One possibility is that sympathetic stimulation constricts cerebral arteries, but the response is not sufficient to have hemodynamic effects. In support of this possibility, Wei et al.[20] found that sympathetic stimulation produces only modest constriction (7%) of large pial arteries of the cat and no response in small pial arteries. A second possibility is that, although sympathetic stimulation produces constriction of large cerebral arteries, autoregulation by distal cerebral arterioles[10] maintains CBF constant. If this were true, autoregulation might mask a constrictor response to sympathetic stimulation. To test this hypothesis we observed the effect of sympathetic stimulation during hypercapnia, which interferes with cerebral autoregulation.[21] Our data do not support the hypothesis: sympathetic stimulation did not decrease CBF during hypercapnia. Our data contrast with those of Harper et al.,[10] who found that unilateral sympathetic stimulation in baboons reduces CBF during hypercapnia. It is possible that the level of hypercapnia in our experiments (Pco_2 = 53 mm Hg), which was less severe than in the experiments of Harper et al. (Pco_2 = 58 mm Hg), did not abolish autoregulation. This possibility is not a likely explanation for the different results in the two studies, since the physiological effects of hypercapnia in our study appeared to be profound; CBF increased to 160

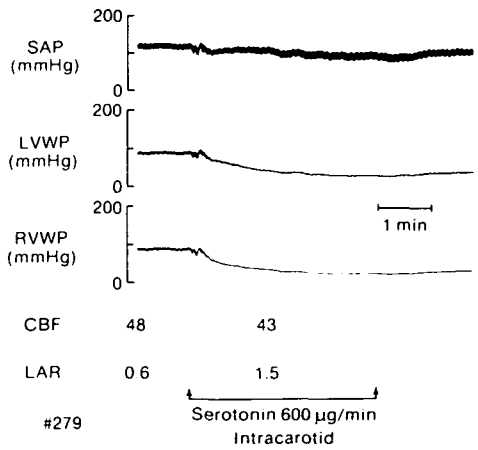

FIGURE 4 *Infusion of serotonin into both common carotid arteries increased the gradient between common carotid arterial pressure and vertebral artery wedge pressure. Serotonin increased resistance of large arteries and produced only a small decrease in cerebral blood flow. Cerebral blood flow measured before serotonin infusion (indicated as 48 ml/min) was obtained several minutes before the time indicated. Abbreviations as in Figures 2 and 3.*

ml/min per 100 g during hypercapnia in this study and to 111 ml/min per 100 g in the study of Harper et al.[10] Our findings are in agreement with those of Traystman and Rapela,[2] who also found that sympathetic stimulation does not reduce CBF during hypercapnia.

Another approach was used in this study to determine whether large arteries that supply the brain constrict during sympathetic nerve stimulation. The technique of Rapela and Martin[11] was used to determine the gradient between common carotid artery pressure and wedged vertebral artery pressure, as an estimate of resistance of large arteries that supply the brain. We first considered two questions concerning this technique. First, does the pressure in the wedged vertebral artery catheter reflect vertebral artery pressure or, because of communications between intra- and extracranial vessels,[8] does it reflect systemic arterial pressure? The finding that vertebral wedge pressure decreases profoundly during bilateral carotid occlusion, despite increases in systemic arterial pressure, suggests that vertebral wedge pressure reflects vertebral artery pressure. Second, can large arteries respond to vasoconstrictor stimuli? Constriction of large arteries has been demonstrated in both the cerebral circulation[11, 22] and other vascular beds.[23–25] This study confirms the findings of Rapela and Martin[11] and Grimson et al.[22] that intracarotid infusion of serotonin produces profound constriction of large arteries.

The calculation of large artery resistance is not a precise determination. It is determined by dividing the pressure gradient of the large arteries by total CBF. This calculation assumes that all of the CBF traverses the entire length of the large cerebral arteries from the carotid arteries to the wedged vertebral artery catheters. Since only a portion of the cerebral flow traverses the length of these arteries, this calculation must underestimate large artery resistance. An important question is whether this underestimation of resistance of large arteries might be greater during sympathetic stimulation, and we might therefore fail to detect an increase in resistance. This could occur if sympathetic stimulation redistributed CBF. For example, if sympathetic stimulation redistributed blood flow to favor cerebrum rather than cerebellum and brainstem, a smaller proportion of total brain blood flow would traverse the length of the large cerebral arteries to the wedged vertebral artery catheters. Large artery resistance would then be underestimated, and a constrictor effect of sympathetic stimulation could be masked. This is not the case in our study, since sympathetic stimulation did not redistribute blood flow within the brain. We conclude therefore that large arteries to the brain can constrict (in response to serotonin) but that they do not constrict during sympathetic stimulation to a sufficient degree to produce detectable hemodynamic effects.

In this study we found that the increase in total cerebral resistance was less than the increase in large artery resistance during infusion of serotonin. This finding suggests that serotonin constricted large arteries to the brain but dilated small vessels. A similar effect has been observed in another vascular bed: serotonin constricts large arteries of the dog foreleg but dilates small vessels.[24]

In summary, the present study indicates that stimulation of the sympathetic ganglia that innervate cerebral vessels, at levels of stimulation that produce vasoconstriction in cranial muscles and maximal pupillary dilation, does not decrease or redistribute CBF during normocapnia or systemic hypercapnia. The findings also indicate that large arteries that supply the brain constrict in response to serotonin but not to sympathetic nerve stimulation. It seems unlikely that stimuli that activate sympathetic neural pathways have a direct effect on cerebral vessels except, perhaps, during extreme hypertension.[19]

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Total and Regional Cerebral Blood Flow during Hypotension, Hypertension, and Hypocapnia

Effect of Sympathetic Denervation in Dogs

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SUMMARY **This study was performed to determine whether acute or chronic sympathetic denervation increases or redistributes cerebral blood flow (CBF) during hypotension or during the action of vasoconstrictor stimuli (hypocapnia and hypertension). Left superior cervical and stellate ganglionectomy was performed in anesthetized dogs. Total and regional CBF were measured by using microspheres. In acute experiments, hemorrhagic hypotension produced a redistribution of CBF which tended to preserve blood flow to the brainstem and to cerebral gray matter. Hypertension and hypocapnia did not redistribute CBF. Blood flows were similar in the acutely denervated and nondenervated half of the brain during control conditions, hypotension, hypertension, and hypocapnia. Completeness of sympathetic denervation was demonstrated by large increases in blood flow to the masseter muscle on the denervated side. Similar studies were undertaken 6-7 days after sympathetic ganglionectomy, at which time cerebral vascular catecholamines were depleted on the denervated side: norepinephrine content in innervated and denervated middle cerebral arteries was 3.1 ± 0.5 and 0.1 ± 0.02 ng/g, respectively. Blood flows in the chronically denervated and nondenervated half of the brain were similar during control conditions and during interventions. The major new findings in this study are, first, that hypotension produces a redistribution of CBF which tends to preserve blood flow to brainstem and to cerebral gray matter, and second, that acute or chronic sympathetic denervation does not alter distribution of CBF over a wide range of arterial pressure or during hypocapnia.**

CEREBRAL blood vessels are innervated by adrenergic nerve fibers from the cervical sympathetic chain.[1, 2] The main source of this sympathetic innervation is the superior cervical ganglion,[3] with a small contribution in dogs from the stellate ganglion.[4] Although cerebral vessels are densely innervated, the significance of these sympathetic nerves in regulation of cerebral blood flow (CBF) is controversial.

Several previous studies have evaluated the functional significance of sympathetic nerves by examining regulation of cerebral flow after acute[5, 6] or chronic[7, 8] sympathetic denervation. Acute cervical sympathectomy has been reported to increase CBF over a wide range of arterial pressure,[5] particularly at normal and elevated levels of pressure. In contrast, a recent report suggests that acute cervical sympathectomy does not increase CBF at normal levels of arterial pressure but does increase flow during hypotension.[6] Chronic sympathetic denervation has been reported to have no effect on CBF,[6-8] but effectiveness of denervation was not confirmed by demonstrating depletion of vascular catecholamines. It seems reasonable to suggest that previous studies have not resolved the question of the effect of sympathetic denervation on control of CBF. Furthermore, the methods that were used to measure CBF have not allowed examination of the effect of denervation on distribution of blood flow within the brain.

In this study, we have examined effects of acute and chronic unilateral sympathetic denervation on total and regional CBF. Labeled microspheres were used to measure CBF.[9] The microsphere technique circumvents the problems created by the presence of multiple vessels to and from the brain and allows measurement of both total and regional CBF. The measurement of regional CBF allowed us to compare distribution of CBF simultaneously in the hemisphere ipsilateral to the sympathetic denervation and in the contralateral "control" hemisphere. We postulated that unilateral acute sympathetic denervation or depletion of cerebral vascular catecholamines might increase CBF to the ipsilateral hemisphere or redistribute CBF in the ipsilateral hemibrain.

Several studies were performed to test this hypothesis. Total and regional CBF were measured during control

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