Baroreceptor Reflexes and Autoregulation of Cerebral Blood Flow in the Dog

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ABSTRACT
Cerebral venous outflow was measured in anesthetized dogs at the confluence of the sagittal and straight sinuses, with the lateral sinuses occluded. Denervation of the carotid bifurcation increased systemic arterial pressure (+ 25.8; se ± 7.7 mm Hg) and decreased cerebral vascular conductance (—0.018; se ± 0.005 ml/min·mm Hg); stimulation of the carotid sinus nerve decreased systemic arterial pressure and increased cerebral vascular conductance. Graded constrictions of the common carotid arteries induced transient responses of the cerebral blood flow that were characteristic of an autoregulatory process. Plots of the steady-state pressures and flows during the decreases of perfusion pressure were concave toward the pressure axis, were similar before and after denervation of the carotid bifurcation, and were indicative of autoregulation.

We conclude that pressoreceptors in the carotid bifurcation or other pressoreceptors in systemic vessels upstream from the carotid bifurcation are not necessary for the control of the "tone" of the cerebral vasculature or in the mechanism of the autoregulation of cerebral blood flow.

ADDITIONAL KEY WORDS
carotid sinus nerve
cerebral vasomotor tone
carotid bifurcation denervation
cerebral blood perfusion pressure
reactive vascular bed
sympathetic nerves and cerebral vascular tone

Previous studies demonstrate that the cerebral blood flow remains almost constant, in the face of changes in pressure in the carotid arteries, due to compensatory changes in cerebral vascular resistance; these compensatory changes occur whether this pressure is altered by changes in aortic arch blood pressure (1, 2) or by graded compression of the carotid arteries (3).

According to Rein (4) cerebral vasodilation might be induced by decreased pressure in the carotid sinus, but Heymans and Bouckaert (5) considered that baroreceptors had no effect on the cerebral vasculature. Yoshida et al. (6) obtained autoregulatory responses in monkeys in which the carotid sinuses had been denervated in order to abolish the depressor reflexes and so obtain higher aortic arch pressures during occlusion of the thoracic aorta. Their studies suggest that the carotid sinuses are not essential but do not show to what extent they might modify the autoregulatory flow responses. They also studied the effect of cervical sympathectomy and concluded that autoregulation is composed of two components: (1) a quick (myogenic) component in which the sympathetic nerves play a role and (2) a slower, metabolically mediated component. As we point out in the discussion, the technique they used for measuring cerebral blood flow actually measures a significant component of extracranial flow (55%). Furthermore, studies from this laboratory (7, 8) have demonstrated that neither intraarterial injections of adrenergic mediators (levarterenol) nor stimulation of the headward end of the vago sympathetic trunk in the dog has significant effect on the cerebral re-
sistance vessels, whereas they had a striking effect on extracranial vessels.

In view of the above studies, we believe that the interpretation of the data of Yoshida et al. (6) may be in error due to the inclusion of extracranial beds in their flow measurements, particularly in reference to the "fast neurogenic component of autoregulation."

Methods

GENERAL PROCEDURES

Dogs weighing 12 to 17 kg were used. They were anesthetized as follows: 5 dogs received sodium pentobarbital, 30 mg/kg iv; 6 received morphine, 3.5 mg/kg sc, followed 45 min later by chloralosane, 100 mg/kg iv in 3 dogs, by Dial urethane, 0.125 ml/kg iv in 2 dogs, and by sodium pentobarbital, 30 mg/kg iv; 6 received dog. Subsequently, anesthesia was maintained with additional doses of sodium pentobarbital, chloralosane, or Dial urethane, as required. Dissection to expose the femoral artery and vein, carotid arteries, vertebral arteries and left jugular vein, and to approach the calvarium, was performed with a cautery. Mepesulfate, 125 mg/kg iv, was given to prevent clotting just before diverting the outflow from the confluence of the sinuses to the jugular vein (see below); later, 500 mg was given every half hour. The trachea was intubated and the secretions from the respiratory tract were aspirated as necessary to maintain a free airway; the animals breathed room air spontaneously. To prevent cooling, the animals were covered with a plastic sheet; to prevent loss of water by evaporation and consequent cooling, the inguinal and neck regions were sutured with skin surgical clips, except for the space occupied by the cannulas and the carotid clamps. Rectal temperatures, recorded in several experiments, were never below 37°C.

DENERVATION OF CAROTID BIFURCATIONS

Both carotid bifurcations were exposed before the surgical approach to the confluence of the cerebral venous sinuses. After the external carotid artery, the internal carotid artery and sinus, and the occipital artery were identified, the mass of nervous and fascial tissue, including the carotid sinus nerve, was exposed in each side for later ligation and section. This procedure denervated both the carotid sinuses and the carotid bodies.

CEREBRAL BLOOD FLOW

The technique used to measure cerebral venous outflow has been described in a previous paper (3). Both lateral sinuses were occluded with bone wax to prevent communication between the intra- and extracranial circulation; the blood from the sagittal and straight sinuses was diverted to the jugular vein. With this technique 50 to 70% of the mass of the brain is drained at the confluence of the sagittal and straight sinuses. To estimate the cerebral blood flow in relation to the mass of the brain perfused, a cast of the venous vascular bed drained at the confluence of the sinuses was obtained by retrograde injection of Silastic® at the end of the experiment; the mass of the brain thus delineated was weighed and referred to the flow measured to express it in milliliters per 100 g of brain.

CEREBRAL PERFUSION PRESSURE

The common carotid arterial blood pressure was measured through tubes inserted into the thyroid arteries, just downstream to the snap-release screw clamps used to produce graded constrictions of both common carotid arteries (Fig. 1). Constriction of both common carotid arteries was not sufficient to reduce cerebral perfusion pressure, as the four major arteries supplying blood to the brain, the two internal carotids and the two vertebral arteries communicate via the circle of Willis. To decrease the cerebral perfusion blood pressure by graded narrowing of both common carotid arteries, it was necessary to occlude the vertebral arteries and obstruct communications between the vertebral arteries and other cephalic arteries. The latter was accomplished by cannulating both vertebral arteries at their entrance in the transverse canal with polyethylene catheters, which were advanced into the vertebral arteries until they were wedged at the levels of the second or third cervical vertebra; also, this procedure allowed us to measure the blood pressure as closely as possible to the circle of Willis (Fig. 1). Thus changes in blood pressure at the circle of Willis, induced by constricting the carotid arteries, were transmitted to the catheters wedged in the vertebral arteries. The venous outflow pressure was measured upstream from the flowmeter (9) (Fig. 1). This pressure measures merely the resistance to flow of blood induced by the flow transducer as the outflow was open to atmospheric pressure at a level corresponding to the zero reference plane for all blood and spinal fluid pressure measurements. The mean of the carotid and vertebral artery pressures minus the venous outflow pressure was used as the best approximation of the true perfusion pressure of the cerebral vascular bed. Mean carotid, vertebral arterial, and venous outflow pressures were measured at corresponding phases of respiration (usually at a midpoint between the maximum and minimum in the fluctuations of

1Room-temperature curing silicon rubber, Medical Grade Elastomer 382, Dow Corning.

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blood pressure induced by respiration) during control and experimental periods. The conductance (1/PRU or ml/min•mm Hg) through the cerebral vascular bed was computed from the cerebral venous outflow and the perfusion pressure.

SPINAL FLUID PRESSURE

The spinal fluid pressure was measured at the level of the cisterna magna with a 19-gauge needle. All pressures were measured with Stat-ram transducers and recorded on a 6-channel Brush oscillograph.

Results

CONTROL VALUES

In 11 experiments the initial value of the systemic blood pressure was 120.5 (SE ± 5.6) mm Hg, the cerebral perfusion pressure 100 (SE ± 4.7) mm Hg and the cerebral blood flow 12.5 (SE 1.3) ml/100 g per min. In 8 of the 11 experiments the brain weight was measured; the cerebral blood flow was 26.2 (SE ± 3.8) ml/min•100 g of brain and the spinal fluid pressure was 14.8 (SE 1.2) mm Hg. In the early stages of four experiments the Po2 was 70 to 89 mm Hg and the Pco2 between 40 and 48 mm Hg in the arterial blood.

The type of anesthesia did not influence the flow responses to changes in perfusion pressure resulting from carotid constriction, denervation of the carotid bifurcation, or stimulation of the cranial end of either sinus nerve.
Denervation of the carotid bifurcation increased the systemic blood pressure, but the cerebral blood flow did not increase in the same proportion as the cerebral perfusion pressure; consequently, the conductance decreased. In a representative experiment (Fig. 2A), the systemic arterial blood pressure increased from 107 to 157 mm Hg and the perfusion pressure from 93 to 131 mm Hg after section of the carotid sinus nerves; the conductance decreased from 0.105 to 0.076. Denervation of the carotid bifurcation increased the systemic arterial pressure and decreased the cerebral vascular conductance in all experiments but one; the mean of the paired differences was significantly different from zero (Table 1, columns 5 and 6). The decrease in pressure following denervation of the carotid bifurcation observed in 1 experiment was due to the accidental bleeding that occurred when sectioning the mass of the tissue including the carotid nerves. Denervation did not affect the arterial PCO₂ (46 mm Hg) in 1 experiment in which it was measured before and after section of both carotid nerves.

**EFFECTS OF STIMULATION OF THE CAROTID SINUS NERVE ON CEREBRAL VASCULAR CONDUCTANCE**

During stimulation of the central end of either the left or right sectioned carotid sinus nerve, the heart rate increased (167/min to 104/min) and the cerebral venous outflow decreased (10.076 ml/min to 7.016 ml/min). The conductance increased from 0.076 to 0.105, indicating a decrease in vascular resistance. The systemic arterial pressure was also affected, increasing from 157 mm Hg to 170 mm Hg during stimulation.

**FIGURE 2**

Effect of section and stimulation of carotid sinus nerves on arterial blood pressure and cerebral blood flow of the dog. A, during tying and sectioning both carotid sinus nerves. B, during stimulation of the cranial end of the right carotid sinus nerve after section of both nerves. Figures in parentheses in the bottom channel indicate conductances. See Figure 1 for reference to the sites where the pressures and flow were measured.
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TABLE 1

Effect of Denervation of the Carotid Bifurcations on Systemic Arterial Blood Pressure and Cerebral Vascular Conductance

<table>
<thead>
<tr>
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<th>Before denervation</th>
<th>After denervation</th>
<th>Mean of difference between paired values</th>
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<td>Systemic arterial pressure (mm Hg)</td>
<td>Cerebral vascular conductance (ml/min - mm Hg)</td>
<td>Systemic arterial pressure (mm Hg)</td>
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<td>(1)</td>
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<tr>
<td>Mean</td>
<td>123</td>
<td>0.122</td>
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<td>6.3</td>
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<td>11</td>
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*All 11 experiments are included in this table.

nerve, the arterial blood pressure and heart rate decreased; the cerebral venous outflow decreased proportionately less because of an accompanying increase in conductance (Fig. 2B).

EFFECT OF DENERVATION ON THE CEREBRAL VASCULAR RESPONSES TO DECREASED PERFUSION PRESSURE

Transient Responses.—Prior to denervation (Fig. 3A) a decrease of perfusion pressure was produced for 1 min. Within 4 sec, cerebral blood flow decreased but not in proportion to the decreased blood pressure. This disproportion between the decrease in blood pressure and that in the flow was more marked at the end of the period of decreased pressure, as is shown by the values of the conductance at the respective times. With restoration of the perfusion pressure to control values, the flow overshot and then returned to control values after 2 min (Fig. 3A). Similar responses of blood flow to induced pulses of decreased perfusion pressure were obtained after denervation of the carotid bifurcations, although at each point the conductance was less after than before denervation (Fig. 3B). The arterial Pco2 measured in other series of experiments (unpublished data) during the 1-min periods of decreased perfusion pressure did not vary from the preceding control values.

Steady State Pressure-Flow Relationship.—The steady state pressure in the carotid arteries is normally higher than that in the vertebral arteries with the technique we used; in most of the experiments, there was some resistance to blood flow in the arterial system between the carotid arteries and the vertebral arteries at the level where the vertebral catheters were wedged (see Methods). However, during constriction of the common carotid arteries, the steady pressure in the vertebral arteries often was higher than that in the carotid arteries especially at the end of a period of decreased carotid artery pressure (Fig. 3). This was due to remaining unoccluded arterial communications between the subclavian, the anterior spinal artery, and the cephalic arterial system downstream to both the wedged vertebral catheters and the carotid clamps (see Methods).

A plot of the mean of the blood flows vs. the perfusion pressure observed in all experiments shows the lack of proportional changes in steady state blood pressure and flow before as well as after denervation (Fig. 4.). The values plotted were measured at times of stable flows and pressures (Fig. 4 insert, a and c). The resulting curves showed, before as well as after denervation, a concavity towards the pressure axis characteristic of active vascular beds (10). The increase in blood pressure following denervation extended the pressure-flow curve further to the right. This plot also shows that the flow during denervation was significantly lower than before denervation only at pressures between 70 and 100 mm Hg.

The completeness of the carotid sinus de-
nervation was certain because reduction of the cerebral arterial perfusion pressure to 60 to 40% of the control by constricting the carotid arteries produced an increase in the femoral artery pressure of 19.8 ± SE 3.2 mm Hg before denervation; after denervation the systemic arterial blood pressure did not increase (−0.5 ± SE 1.3 mm Hg) during comparable reductions of cerebral arterial perfusion pressure.

Discussion

The existence of autoregulation in the cerebral vasculature in response to alterations of cerebral arterial perfusion pressure has been a controversial subject. Data obtained with direct methods in monkeys and dogs supported the view that autoregulation of blood flow does not occur since cerebral blood flow varied in direct linear relationship with the perfusion pressure (11, 12). Furthermore, Heymans and Neil (13) stated that “the constancy of cerebral blood flow depends primarily on the constancy of the blood pressure,” showing

FIGURE 3
Cerebral blood flow responses to a decreased pulse of perfusion pressure before (A) and after denervation of carotid bifurcations (B). Same experiment as Figure 2.
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FIGURE 4
Cerebral vascular responses to periods of decreased perfusion pressure before and after carotid bifurcation denervation. Plot of data from all experiments in the series. Abscissa = cerebral arterial perfusion pressure. Ordinate = blood flow expressed as percentage of the flow observed at 70 mm Hg before denervation. Insert shows a typical record of blood flow and pressure; plotted points were measured at a for the controls and at c during the periods of decreased pressure. For each experiment, points at a and at c for different periods of decreased pressure were joined by a smooth curve; the values of flow corresponding to the pressure indicated on the abscissa were obtained from these curves; these flows were then normalized to the flow observed at 70 mm Hg. Numbers at each point indicate number of observations.

that they did not recognize the occurrence of cerebral blood flow autoregulation.

The existence of an autoregulation of blood flow was found in measurements of cerebral blood flow in humans (1, 14) during direct observation of the pial vessels in cats (15), and during blood flow estimations by indirect methods in rabbits and dog (16, 17). Using a method to isolate the intracranial from the extracranial venous circulation, which was less traumatic than that used by other authors, we have consistently demonstrated the existence of a marked autoregulatory phenomena of the cerebral blood flow in the dog (3). In the present experiments, autoregulation is apparent from the fact that the plots of cerebral perfusion pressure and flow resulted in curves concave to the pressure axis; this is indicative of a highly reactive vascular bed (10) (Fig. 4). The existence of an autoregulatory phenomenon of blood flow is apparent also from the consistent decrease in cerebral vascular conductance during the increase in blood pressure following carotid bifurcation denervation (Fig. 3A; Table 1, last column). Moreover, the stimulation of the cephalic end of the sinus nerve induced changes in systemic arterial blood pressure and in cerebral vascular conductance, the latter in the same direction as those expected to result from autoregulation of blood flow in the face of blood pressure changes (Fig. 2B).
The mechanism of autoregulation is still unknown. It is generally agreed that it is intrinsic to the vascular bed in beds other than that of the brain (10, 18). Most likely, a similar intrinsic mechanism is responsible also for the responses of the cerebral vascular bed to changes in perfusion pressure (3); however, participation of a nervous reflex mechanism has not been ruled out.

Autoregulation conceivably could be mediated by a nervous reflex initiated by the carotid sinuses. The evidence currently available has led to diverse conclusions. Rein (4) stated that a decreased pressure in the carotid sinus may induce cerebral vasodilation, while Heymans and Bouckaert (5) considered that the baroreceptor reflexes had no effect on the cerebral vasculature. In Rein's experiments the blood flow in one carotid artery was measured before and after occlusion of the opposite carotid; in Heyman's and Bouckaert's, the intraluminal pressure was changed in one vascularly isolated but innervated carotid artery and the blood flow measured in the other carotid, or the carotid artery flow was recorded before and after carotid sinus nerve section. These observations can be objected because they did not estimate cerebral vascular resistance, and they measured only common carotid artery blood flow, which cannot be considered representative of the cerebral vascular bed.

Similar objections could be raised to the conclusions reached by Yoshida et al. (6), who reported autoregulatory flow responses to increases in blood pressure in monkeys with carotid sinus nerves sectioned. They measured "internal carotid flow" by recording the flow in the common carotid with the external carotid artery ligated. When this group of investigators (19) tested for communications between the internal carotid and extracranial vessels, they observed that the common carotid artery flow decreased only to 55% of control after ligation of the internal carotid artery, at a point proximal to the posterior communicating artery, i.e., proximal to the circle of Willis. We believe that 55% of the flow recorded by Yoshida et al. (6) was going through extracranial structures.

Measurement of extracranial flow as part of the "internal carotid flow" may explain the proportionately greater increase in flow than in blood pressure observed by Yoshida et al. (6) in cervical sympathectomized monkeys, immediately after the aortic blood pressure was increased. This passive flow response in the common carotid was in contrast to the initial "fast component" of the autoregulatory flow response they observed before sympathectomy; this fast component was explained as effected by the sympathetic. We believe that sympathectomy might have decreased the resistance to flow in the extracranial vascular bed and consequently increased the proportion of "external carotid" flow measured in the common carotid artery. The predominance of flow responses of the extracranial passive vascular bed over those of the active intracranial vascular bed may explain the change in the autoregulatory response induced by sympathectomy in the experiments of Yoshida et al. (6). This interpretation is supported by the fact that the responses in the "external carotid" to changes in aortic pressure reported in Table 3 of the paper by Yoshida et al. (6) are characteristic of a passive vascular bed. Furthermore, stimulation of the cervical sympathetic nerves (7) does not seem to have significant effect on the cerebral vasculature, whereas section of sympathetic nerves produces vasodilation of the extracranial vasculature.

In our own observations, denervation of the carotid bifurcation did not change the responses of the cerebral venous flow to alterations in perfusion pressure. Denervation of both common carotid bifurcations (Fig. 2A; Table 1) and stimulation of the cranial end of the carotid sinus nerve (Fig. 2B) decreased and increased, respectively, cerebral vascular conductance. These cerebrovascular responses were similar to those expected to occur in other vascular beds following a decrease in the activity of the carotid sinus nerves. However, when a decrease in the activity of the carotid sinus nerves was induced by reducing...
the carotid artery blood pressure (Fig. 3A), the cerebral vascular conductance increased. The direction of this vascular response was opposite to that expected as the result of a decreased activity of the baroreceptor nerves, but it was in accord with autoregulatory responses of blood flow to changes in cerebral perfusion pressure. The opposing effects of the section of the carotid nerves and of the constriction of the common carotid arteries on the cerebral vascular conductance rule out the possibility that the carotid sinus pressor receptors could be responsible for the cerebral vascular changes that accompany alterations of arterial blood pressure; in both instances the afferent impulses in the carotid sinus nerves are decreased.

The cerebral vasoconstriction induced by denervation of the carotid sinus (Fig. 2A) and the cerebral vasodilation induced by the reduction of the carotid artery pressure (Fig. 3A) were both accompanied by a rise of aortic pressure. These opposing responses of the cerebral vascular conductance in the presence of a similar increase in aortic pressure rule out the possibility that aortic pressor receptors are responsible for the changes in cerebral vasmotor activity that accompany alterations of aortic pressure. In further experiments we observed that pulses of decreased cerebral arterial perfusion pressure still induced cerebral vasodilation after carotid bifurcation denervation, despite the fact that there was then no significant rise of the systemic arterial blood pressure (Fig. 3B). The above studies thus provide almost conclusive evidence that neither the carotid sinus nor the aortic pressor receptors play a necessary role in cerebral vascular autoregulation.

Baroreceptor nerves arising in the common carotid arteries (20) might be a possible source of afferent impulses for reflex mediation of autoregulation, but in our experiments these nerves were sectioned during exposure of the common carotid and superior thyroid arteries, and therefore such receptors are not necessary for autoregulation. Boss and Green (20) also described pressor receptors along the common carotid arteries upstream from the thyroid arteries and from the points where we occluded the carotid arteries. The same arguments can be applied to these as to the pressor receptors in the aorta—that, if such receptors exist, they could not be responsible for cerebrovascular autoregulation.

The fact that pressure receptor reflexes at or upstream from the carotid sinuses do not participate in the mechanism of the autoregulatory processes does not exclude the possibility that other nervous reflexes may be involved. Thus it is conceivable that a nervous mechanism may participate as a link in a reflex involving a controlled metabolic variable (21). Previous data (3, 18, 21) suggest that a controlled metabolic variable plays a role in the regulation of cerebral vascular tone; such a metabolic factor might initiate nervous reflex responses at appropriate chemoreceptors in the capillary bed or in the postcapillary venous channels draining the cerebral vasculature.

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