Total and Regional Cerebral Blood Flow During Stimulation of Carotid Baroreceptors

DONALD D. HEISTAD, M.D.,* AND MELVIN L. MARCUS, M.D.*

SUMMARY The concept that reflex control of cerebral vessels is unimportant has been challenged by recent studies which suggest that carotid baroreceptors have an important role in regulation of cerebral blood flow (CBF). In this study we have tested the hypothesis that arterial baroreceptors contribute to regulation of total or regional CBF. CBF was measured in anesthetized dogs with 15 μm microspheres. Stimulation of carotid baroreceptors, by raising carotid sinus pressure, did not alter or redistribute cerebral flow. Responses to baroreceptor stimulation were intact, as manifested by vasoconstriction in skeletal muscle. CBF decreased during systemic hypotension in response to increases in neurogenic tone initiated by arterial baroreceptors. These studies tested the hypotheses that stimulation of baroreceptors reduces total CBF or redistributes cerebral flow without surgical manipulation, permits measurement of regional as well as total cerebral blood flow. We have performed two studies to examine the role of baroreceptors in regulation of cerebral blood flow. First, CBF was measured during stimulation of carotid sinus baroreceptors. Baroreceptors were stimulated by raising pressure in the isolated, perfused carotid sinuses. CBF was measured using labeled microspheres. This technique, in addition to separating intracranial and extracranial blood flow without surgical manipulation, permits measurement of regional as well as total cerebral blood flow. Second, we measured CBF during elevation of systemic arterial pressure before and after denervation of carotid and aortic baroreceptors. These studies tested the hypotheses that stimulation of baroreceptors reduces total CBF or redistributes blood flow within the brain and that arterial baroreceptors contribute to the increase in cerebrovascular tone during systemic hypertension.

Methods and Design

Twenty-two mongrel dogs weighing 16 to 29 kg were anesthetized with chloralose (50 mg per kilogram) and urethane (500 mg per kilogram) intravenously, paralyzed with decamethonium bromide (0.3 mg per kilogram i.v.), anticoagulated with heparin (500 units per kilogram i.v.), and ventilated artificially with room air and supplemental oxygen. Suplemental doses of chloralose and urethane were given each one to two hours. Rectal temperature was maintained at 37° to 38°C.

Measurement of CBF

Microspheres were used to measure CBF. We have described the technique in detail. A cannula was placed in the left atrium for injections of microspheres. Cannulas for withdrawal of reference blood samples were placed in brachial and lingual or common carotid arteries. In two dogs, a catheter was inserted into the dorsal sagittal sinus through a burr hole to obtain venous blood samples for estimation of the amount of arteriovenous shunting of microspheres. Less than 3% of the microspheres shunted to the cerebral venous blood during all the measurements, and there was minimal change in dorsal sagittal sinus pressure during the interventions. Microspheres, 15 μm in diameter, were injected into the left atrium. Injection of microspheres labeled with 153Ce, 85Sr, 82Sc, and 125I allowed us to make four measurements of CBF. The interval between each injection was usually 10 to 30 minutes.

At the end of the study the animals were killed and the brain was cut into 41 samples: right and left medulla, pons, thalamus-midbrain; white matter (corpus callosum; centrum ovale and optic chiasm), gray matter (caudate nucleus; cortical gray [sensory-motor and visual]); multiple cerebral samples, and right and left cerebellum. Tissue samples were obtained from muscles in the head and neck region. The brain and muscle samples weighed 0.4 to 4.9 gm. The tissues were weighed, placed in plastic tubes, and counted for five minutes in a three-inch well-type gamma counter. Reference blood samples were divided into aliquots so that their counting geometry was similar to that of the tissue samples. The energy windows and methods of isotope separation have been described previously. Output from the scintillation counter was punched on paper tape and processed on a PDP-11 computer. CBF was calculated using the formula: CBF = C T × 100 RBF/C R, where CBF = cerebral blood flow in milliliters per minute per...
100 gm brain, $C_n$ = counts per gram brain tissue, $RBF$ = reference blood flow (rate of withdrawal of blood samples from arteries in milliliters per minute), and $C_r$ = total counts in reference arterial blood. Blood flows to muscle were calculated with a similar formula.

**Stimulation of Carotid Baroreceptors**

The carotid bifurcations were exposed. The internal carotid and all branches of the external carotid artery were ligated. Arterial blood was pumped at 45 ml per minute into one or each common carotid artery. Blood flowed out through a cannula in the external carotid artery and through Starling resistors to the external jugular vein. Changes in carotid perfusion pressure were made with a Starling resistor. Baroreceptors were stimulated unilaterally in live dogs and bilaterally in 11 dogs. In dogs in which only one carotid was perfused, the contralateral carotid vessels were not ligated but the contralateral carotid sinus baroreceptors were denervated. Systemic arterial pressure (measured in a brachial artery) was prevented from decreasing during stimulation of baroreceptors by inflation of a cuff around the descending aorta. Systemic arterial PO$_2$, PCO$_2$, and pH were measured before each injection of microspheres.

Vascular responses to baroreceptor stimulation were observed during each study in the isolated, perfused gracilis muscle. Perfusion pressure was recorded. At constant flow, changes in gracilis muscle vascular resistance are reflected in changes in perfusion pressure.

**Baroreceptor Stimulation During Normocapnia**

In 14 dogs, microspheres were injected during a control period (carotid perfusion pressure 100 ± 3 mm Hg) and one to four minutes after increasing perfusion pressure in the isolated carotid sinus to 199 ± 1 mm Hg to stimulate carotid baroreceptors.

In ten of these dogs microspheres were injected during another control period and during hypocapnia. CBF was measured during hypocapnia, produced by hyperventilation, to determine whether cerebral vasconstrictor responses were intact.

In the five dogs in which the right internal carotid artery was ligated (to permit unilateral stimulation of baroreceptors), there was no difference in control blood flow or responses to hypocapnia in the two hemispheres: blood flow to the right and left cerebrum was 45 ± 5.4 (mean ± SE) and 47 ± 5.5 ml per minute per 100 gm, respectively, during control, and 21 ± 4 and 22 ± 4 ml per minute per 100 gm, respectively, during hypocapnia.

**Baroreceptor Stimulation During Hypercapnia**

In six dogs we injected microspheres during hypercapnia and during hypocapnia with bilateral carotid baroreceptor stimulation. In four of these dogs we had measured responses to baroreceptor stimulation during normocapnia. The rationale for studying responses to baroreceptor stimulation during hypercapnia was that James, Millar, and Purves have suggested that cerebrovascular responses to neural stimuli may be minimal during normal blood gases and accentuated during hypercapnia. Measurements were made about 15 minutes after starting hypercapnia, which was produced by adding 3% CO$_2$ to the inspired air.

**Systemic Hypertension Before and After Denervation**

Six dogs were studied. A cuff was placed around the thoracic aorta near the diaphragm. Inflation of the cuff occluded or obstructed the aorta and increased arterial pressure in the cephalad part of the body by 26 to 70 mm Hg. Microspheres were injected approximately three minutes after raising arterial pressure.

Microspheres were injected four times in each animal: during a control period and during elevation of systemic arterial pressure, before and after barodenervation. Denervation was accomplished by bilateral cervical vagotomy and denervation of both carotid bifurcations. Completeness of barodenervation was confirmed by the absence of bradycardia after intravenous injection of angiotensin.

Statistical analysis was performed with the t-test for paired data.

**Results**

**Effects of Stimulation of Carotid Baroreceptors During Normocapnia**

Stimulation of baroreceptors by raising carotid sinus pressure did not alter total CBF or redistribute flow within the brain (table 1, fig. 1). Stimulation of baroreceptors decreased heart rate $32 ± 5$ (mean ± SE) beats per minute ($P < 0.01$) and produced profound vasodilatation in skeletal muscle: blood flow to muscle (measured with microspheres) increased from $3.2 ± 0.7$ to $13.4 ± 2.6$ ml per minute per 100 gm during baroreceptor stimulation ($P < 0.01$) and gracilis muscle perfusion pressure decreased from $124 ± 10$ mm Hg to $87 ± 8$ mm Hg during baroreceptor stimulation ($P < 0.01$). Cerebral vessels were responsive to a constrictor stimulus as shown by the decrease in blood flow during hypocapnia (table 1).

Responses to unilateral and bilateral stimulation of baroreceptors are not separated in table 1 because they did not...
differ. In five dogs in which baroreceptors were stimulated in one carotid, total CBF was 46.8 ± 5.5 ml per minute during control and 45.6 ± 7.4 ml per minute per 100 gm during baroreceptor stimulation. In nine dogs in which baroreceptors were stimulated in both carotids, cerebral flow was 42.5 ± 2.4 during control and 46.0 ± 4.1 ml per minute during baro-receptor stimulation. Regional distribution of cerebral flow also did not differ in dogs with unilateral and those with bilateral stimulation of baroreceptors.

Effects of Stimulation of Carotid Baroreceptors During Hypercapnia

Bilateral stimulation of carotid baroreceptors during hypercapnia did not alter total cerebral blood flow or redistribute cerebral flow (table 2). Baroreceptor stimulation during hypercapnia decreased heart rate 34 ± 4.7 beats per minute (P < 0.01), increased muscle blood flow from 3.8 ± 0.5 to 15.7 ± 5.2 ml per minute per 100 gm (P < 0.05), and decreased gracilis muscle perfusion pressure from 152 ± 19 to 112 ± 16 (P < 0.01).

Effects of Raising Systemic Arterial Pressure Before and After Barodenervation

CBF was less during the control period after barodenervation than during control before barodenervation (table 3). We attribute this to a nonspecific effect rather than an effect of barodenervation, since a small decrease in flow was also seen in the two control periods in the first study (columns 1 and 3, table 1). The time required to perform barodenervation may account for the slightly greater decrease in CBF during control in table 3 than in table 1.

When arterial baroreceptors were intact, systemic hypertension did not alter CBF (table 3). After denervation of baroreceptors, systemic hypertension again did not increase CBF. The distribution of CBF was similar during elevation of systemic arterial pressure before and after denervation of baroreceptors (table 3).

Discussion

We conclude from this study that stimulation of carotid baroreceptors does not alter total CBF and does not redistribute cerebral flow. In addition, the results indicate that CBF does not increase during elevations of systemic arterial pressure within the range of 80 to 155 mm Hg even

---

**Table 1** Effects of Baroreceptor Stimulation and Hypocapnia on Cerebral Blood Flow

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Baroreceptor Stimulation*</th>
<th>Normocapnia</th>
<th>Hypocapnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CBF (ml/min/100 gm)</td>
<td>44.7 ± 2.6</td>
<td>48.3 ± 3.9†</td>
<td>40.4 ± 4.1</td>
<td>21.5 ± 2.0†</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>103 ± 4.4</td>
<td>104 ± 10.0</td>
<td>97 ± 8.0</td>
<td>102 ± 8.3</td>
</tr>
<tr>
<td>Systemic blood gases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>39 ± 0.4</td>
<td>22 ± 0.8</td>
<td>21 ± 2.3</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.37 ± 0.003</td>
<td>7.37 ± 0.002</td>
<td>7.47 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>126 ± 5.0</td>
<td>112 ± 7.9</td>
<td>123 ± 9.4</td>
<td></td>
</tr>
<tr>
<td>Regional CBF (ml/min/100 gm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrum</td>
<td>43 ± 2.6</td>
<td>45 ± 3.7</td>
<td>39 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>Gray matter</td>
<td>53 ± 3.2</td>
<td>55 ± 5.3</td>
<td>52 ± 5.6</td>
<td></td>
</tr>
<tr>
<td>Medulla</td>
<td>44 ± 2.9</td>
<td>45 ± 4.4</td>
<td>36 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>

*During baroreceptor stimulation carotid perfusion pressure was increased from 100 ± 3 to 194 ± 3 mm Hg. Systemic arterial pressure was prevented from decreasing by occluding the aorta.
†Total CBF was significantly less during hypocapnia than during normocapnia (P < 0.01). Total CBF was not significantly different during control and baroreceptor stimulation (P > 0.05). Total CBF was significantly less during hypocapnia than during normocapnia (P < 0.05).

**Table 2** Effects of Stimulation of Baroreceptors on Cerebral Blood Flow During Systemic Hypercapnia

<table>
<thead>
<tr>
<th></th>
<th>Hypercapnia</th>
<th>Baroreceptor stimulation during hypercapnia*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CBF (ml/min/100 gm)</td>
<td>72.3 ± 8.8†</td>
<td>70.7 ± 11.9†</td>
</tr>
<tr>
<td>Mean systemic arterial pressure (mm Hg)</td>
<td>102.6 ± 4.4</td>
<td>104.4 ± 10.0</td>
</tr>
<tr>
<td>Systemic blood gases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>51 ± 1.3</td>
<td>51 ± 1.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.25 ± 0.02</td>
<td>7.26 ± 0.02</td>
</tr>
<tr>
<td>Paco2 (mm Hg)</td>
<td>133 ± 9.4</td>
<td>127 ± 9.7</td>
</tr>
<tr>
<td>Regional CBF (ml/min/100 gm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrum</td>
<td>65 ± 7.2</td>
<td>66 ± 10.9</td>
</tr>
<tr>
<td>Gray matter</td>
<td>88 ± 7.3</td>
<td>86 ± 15.7</td>
</tr>
<tr>
<td>Medulla</td>
<td>33 ± 5.1</td>
<td>33 ± 6.0</td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>112 ± 14.1</td>
<td>103 ± 18.8</td>
</tr>
<tr>
<td>Thalamus-midbrain</td>
<td>94 ± 15.3</td>
<td>85 ± 19.8</td>
</tr>
<tr>
<td>Pons</td>
<td>58 ± 8.9</td>
<td>54 ± 13.1</td>
</tr>
</tbody>
</table>

*During baroreceptor stimulation carotid perfusion pressure was increased from 98 ± 2 to 194 ± 3 mm Hg.
†Total CBF during hypercapnia was significantly more than during normocapnia (column 1, table 1) (P < 0.05). Statistical comparison was made using the four dogs for which paired data (during normocapnia and hypercapnia) are available.
‡Total CBF during hypercapnia was significantly more than during hypocapnia (P < 0.05).
after denervation of arterial baroreceptors. Thus arterial baroreceptors do not contribute to increases in cerebrovascular resistance during increases in systemic pressure. These results, in conjunction with our previous observation that chemoreceptor stimulation does not alter CBF or contribute to cerebral vasodilatation during systemic hypoxemia, support the concept that reflex control of cerebral vessels is not of primary importance.

We considered several questions before concluding that baroreceptor stimulation does not produce cerebral vasoconstriction. First, were baroreceptors active in these animals? Elevation of carotid perfusion pressure produced the expected bradycardia, hypotension, and vasodilatation in skeletal muscle. Second, was the responsiveness of cerebral vessels intact? CBF decreased during hypocapnia and increased during hypercapnia, which indicates that the absence of cerebrovascular responses during baroreceptor stimulation was not the result of absence of vasoconstrictor or vasodilator responsiveness. Third, could changes in carotid pressure depress chemoreceptors, affect CBF, and mask an effect of baroreceptors? A previous study has suggested that changes in arterial pressure have little effect on chemoreceptor discharge. In addition, we have found no effect of chemoreceptor stimulation on CBF.

Fourth, did ligation of one or both internal carotid arteries interfere with responses to baroreceptor stimulation? There was no difference in blood flow to the two cerebral hemispheres when one carotid artery was ligated. CBF tended to be less when one or both internal carotid arteries were ligated than when both internal carotid arteries were patent (tables 1 and 3, respectively), but cerebral responses to hypocapnia and hypercapnia were nevertheless intact. This indicates that ligation of one or both carotid arteries in the dog does not prevent cerebrovascular responses.

The results of this study should be placed in perspective with the results of previous studies. Rapela et al. measured cerebral venous blood flow and also concluded that carotid baroreceptors have no significant effect on CBF. Rapela et al. used the cerebral venous outflow technique. It has been suggested that this technique might damage vessels and reduce cerebrovascular responsiveness as a result of ligation of veins during isolation of venous outflow. Nevertheless, our studies with the microsphere technique, in which veins are not ligated, support Rapela's observations and further indicate that carotid baroreceptors do not alter regional CBF.

Our findings conflict with two recent studies which concluded that carotid baroreceptor stimulation produces cerebral vasoconstriction. The explanation for the divergent conclusions is not clear to us but may relate to the methods used to measure CBF. Ponte and Purves used a xenon clearance technique in baboons and James et al. used a krypton clearance technique in dogs to measure CBF. Thus these investigators used isotope clearance techniques whereas we used microspheres to measure cerebral flow. We have recently examined several aspects of the microsphere technique in measurement of CBF. The major conclusion of the study was that 15 μ spheres are an appropriate size for measurement of CBF in dogs since arteriovenous shunting is minimal, intracerebral distribution is not artifactually distorted (as it is with 50 μ spheres), and measurements of both total and regional flow are reproducible. In contrast to the microsphere technique, the isotope clearance techniques measure blood flow to only a small portion of the cerebrum and involve assumptions related to partition coefficients and extrapolation of curves which have multiple slopes. The microsphere technique therefore appears to be a more direct measurement of CBF.

An incidental but interesting observation in this study was that there was no significant redistribution of CBF during increases in systemic arterial pressure. In other words, the cerebrovascular autoregulatory response was not associated with preferential increases in blood flow to the brain stem, cerebrum, or cerebellum and the usual ratio of blood flow to gray and white matter was preserved (table 3). This suggests that autoregulation maintains regional as well as total CBF.
MODEL FOR SPASM OF THE ANTERIOR CEREBRAL ARTERY / Peters et al.

This study does not establish the mechanism by which CBF is regulated during changes in arterial pressure. We conclude, however, that the failure of CBF to increase during increases in arterial pressure is not the result of baroreceptor-induced cerebral vasoconstriction. These findings favor the concept that neural control of CBF is unimportant1, 5, 9, and support a predominant role of local factors.

Acknowledgment

We thank Donald Piegors and Dennis Beach for technical assistance; James Ehrhardt, Ph.D., for assistance with isotope separation; Oscar Lim for assistance with computer programming; and Violetta Pusack for secretarial assistance.

References


A Model for Spasm of the Anterior Cerebral Artery

NORMAN D. PETERS, M.D., AND GIOVANNI DI CHIRO, M.D.

SUMMARY A model for production of spasm of the anterior cerebral artery in primates is presented. The model consists of injection of 0.35 cc of fresh blood into the chiasmatic cistern through the optic canal after orbital exenteration. Clinical and angiographical follow-up is possible. The clinical appraisal of acute and chronic changes can be accomplished in the awake animal.

THE PATHOPHYSIOLOGICAL MECHANISMS OF spasm of the cerebral arteries are not well understood. A variety of theories have been proposed to explain a confusing, and sometimes contradictory, body of clinical and radiographical evidence.1-13 The complexity of the problem is borne out by the large number of proposed models.13-23 Experimental vasospasm is produced either by mechanical trauma to a vessel or by application into the subarachnoid space (SAS) or directly on the vessel of a variety of spasmogenetic agents in a wide range of volumes and concentrations. The applicability of the proposed models to the naturally occurring spasm in man remains sub judice.24 In particular, no experimental method is available to investigate the immediate as well as the prolonged clinical effects of subarachnoid hemorrhage (SAH) and subsequent vasospasm in the awake animal.

A method for the production and evaluation of cerebrovascular spasm in primates is proposed. The model, which is a derivation of the Hudgins and Garcia approach for creating experimental cerebral infarction,24, 25 has two distinctive and advantageous features: (1) production of segmental vasospasm in the anterior circle of Willis using a small amount of spasmogenetic agent, and (2) the possibility of clinical appraisal of acute and chronic changes in the awake animal.

Methods

A total of 29 rhesus monkeys weighing 5 to 7 kg were used. The experimental protocol included two phases: (A) placement of an indwelling catheter into the chiasmatic cistern, and (B) introduction of spasmogenetic agent into the cistern followed by clinical and angiographical evaluation.

Phase A

The anesthetized animal was appropriately positioned in a standard primate headholder. The left eye was enucleated along with all muscle attachments and orbital fat, and extenteration of the orbit was accomplished using the operating microscope. The optic nerve was severed, and bleeding from the ophthalmic artery was controlled with bipolar coagulation. Using sharp curettes, the optic canal was enlarged until the dura overlying the chiasmatic cistern was encountered. Under 25X magnification, the dura and arachnoid were opened, and the tip of a 7-cm Raimondi peritoneal catheter* was placed in the chiasmatic cistern. Final positioning of the

*Heyer-Schulte Corporation, Goleta, California.
Total and regional cerebral blood flow during stimulation of carotid baroreceptors.
D D Heistad and M L Marcus

Stroke. 1976;7:239-243
doi: 10.1161/01.STR.7.3.239

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/7/3/239

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/