Cerebral Vascular Response to Moderate Blood Loss: Modification by Hypertension

FRANK P. HOLLADAY, M.D., JAMES R. BEAN, M.D., BYRON YOUNG, EDWARD P. TODD, M.D.,* AND MARK W. ROY, PH.D.

SUMMARY To study the effect of non-hypotensive hemorrhage on cerebral blood flow in normo- and hypertensive states, chloralose anesthetized cats were subjected to graded blood loss (5 ml/kg) every 30 min. Cerebral blood flow was measured using radiolabeled microspheres or H₂ clearance. Hypertension was produced by infusion of phenylephrine to a diastolic blood pressure of 100 mm Hg. Control animals suffered no net blood loss. PCO₂ was between 28 and 32 mm Hg for all groups over the entire experiment. In normotensive cats, cerebral blood flow increased following withdrawal of 10 ml/kg of blood. In hypertensive cats, cerebral blood flow increased after withdrawal of 20 ml/kg of blood. These findings were consistent for all brain regions examined. Animals without blood loss, whether normo- or hypertensive showed no consistent change in cerebral blood flows. Possible explanations for these findings, particularly neurally mediated responses, are discussed.

SEVERAL STUDIES HAVE DEMONSTRATED that cerebral blood flow (CBF) decreases following hemorrhage severe enough to cause hypotension. This reduction in CBF is attributed to decreased cerebral perfusion pressure secondary to systemic hypotension. When moderate hemorrhage occurs acute volume contraction ensues, while normotension is maintained by numerous protective cardiovascular reflexes. The effects of volume contraction produced by hemorrhage on CBF have not been assessed independent of systemic blood pressure. Similarly, the interactions between volume status and arterial blood pressure which influence cerebral blood flow remain largely unexplored. To determine the effects of volume contraction on CBF and to delineate a possible interaction between volume status and arterial blood pressure in determining CBF, the effects were studied of graded, non-hypotensive hemorrhage on CBF in normotensive and hypertensive cats.

Materials and Methods

Cats of both sexes (2–4 kg) were anesthetized with alpha chloralose maintaining diastolic blood pressure around 80 mm Hg (60–80 mg/kg). The animals were intubated and mechanically ventilated with room air. Tidal volume and respiratory rate were adjusted to maintain arterial PCO₂ between 28 and 32 mm Hg (Instrumentation Laboratories, Wilmington, MD). Femoral arterial and venous catheters were implanted. Temperature was measured rectally (Telethermometer, Yellow Springs Instruments, Yellow Springs, Ohio).

Methods for Measurement of Cerebral Blood Flow

Both microsphere and H₂ clearance techniques were used to measure regional CBF in animals after graded blood loss. This was to assure that the changes associated with hemorrhage were not dependent upon the alterations in left ventricular pressure induced by microsphere injection.

1) Microsphere Method

A catheter was guided from the femoral artery into the left ventricle for microsphere injection. Catheter position was confirmed at autopsy. Microsphere preparation and injection, reference blood collection, tissue handling and data analysis have been previously described. In the present study, tissue samples were taken from multiple cortical, cerebellar, and brainstem regions with no attempt to distinguish between grey and white matter flows.

2) Hydrogen Clearance Method

Polarographic electrodes were constructed from 25 micron platinum/Iridium (90%/10%) wire. The electrodes were insulated with Teflon and polystyrene except for 0.5 mm at the tip. Ten electrodes per cat were implanted bilaterally in frontal, parasagittal, temporal, parietal and occipital cortices. The electrodes were implanted through burr holes, and held in place with Coe Flex® dental impression material, which also sealed the skull. To avoid experimental bias, data from all implanted electrodes was used unless the electrode failed to detect inhaled H₂ (5–7%). Currents from the platinum electrodes were monitored using amplifiers similar to that described by Pastzor. Amplifier outputs were recorded every other second using a computer directed scanning voltmetter (Model 2497A, Hewlett-Packard, Corvallis, Oregon). The voltages were stored and the corresponding curves analyzed later by performing linear regression calculations on the separate components of the biexponential curves or on the single component of monoeexponential curves. For biexponential curves, linear regression calculations were performed over the first 2 min of clearance to determine mean CBF. All calculations were performed with an HP85 computer (Hewlett-Packard, Corvallis, Oregon), after discarding the initial 40 seconds of clearance to assure an arterial H₂ concentration of zero.

Experimental Procedure

Each experiment consisted of five 30 min experimental periods. At the end of each period, CBF, blood
pressure, and PCO₂ were measured, a manipulation performed (for description see Groups, below) and the next 30 min period begun. In those animals in which CBF was measured using H₂ clearance, H₂ inhalation was started 15 min prior to blood flow measurement. In those animals serving as volume controls (non-hemorrhaged) blood removed during microsphere injection was replaced with blood from a donor animal. To avoid the confounding effects of hemodilution, no volume replacement was undertaken in the animals subjected to blood loss.

Groups

Group I. Normotensive Subjected to Blood Loss

Seven cats were subjected to blood loss, 5 ml/kg for each manipulation. No pressor substances were given. In four cats, CBF was measured with the microsphere technique. In the remaining three, CBF was measured using the H₂ clearance technique.

Group II. Blood Loss With Induced Hypertension

Seven cats were subjected to blood loss, 5 ml/kg, for each manipulation. In addition, their diastolic blood pressure was elevated to and maintained at 110–120 mm Hg with infused phenylephrine (20 μg/ml in 5% dextrose). Phenylephrine was selected because it does not alter CBF.ª

This group included four cats in which CBF was measured with microspheres and three in which CBF was measured using the H₂ clearance method.

Group III. Normotensive Without Blood Loss

This group consisted of four cats in which CBF was measured using microspheres. Blood removed during the microsphere injections was replaced with blood from a donor cat. These cats received no pressor substances.

Group IV. Hypertensive Without Blood Loss

In the four cats in this group, CBF was measured using microspheres. Any blood removed during microsphere injection was replaced with blood from a donor cat. Diastolic blood pressure in these cats was also elevated to 110–120 mm Hg with infused phenylephrine.

Methods Used for Statistical Analysis

CBF results were compared using an analysis of variance, with p < 0.05 considered significant. The significance of differences between the treatment groups and the significance of time-treatment interaction were examined for frontal, parasagittal, temporal, parietal, and occipital cortices in all cats, and in cerebellar and brainstem regions in cats where CBF was measured using the microsphere technique. Where possible, CBF values in cortical regions were also tested for differences between microsphere and H₂ clearance methods.

Results

CBF values in a representative brain region (parietal) are shown for the entire experiment for Groups I and II in table 1. In these groups H₂ clearance blood flows are also shown in table 1. The arterial blood pressure is shown for each group. For all measurements, PCO₂ was between 28 and 32 mm Hg, and temperature was between 37.2° and 38.8°C.

For the entire group of animals, analysis of variance showed:

1) There were significant differences between animals subjected to blood loss compared to controls. This was found in all brain regions except the medulla and appeared by both methods of CBF measurement. There were significant increases in CBF as a response to blood loss.

2) There were significant time-treatment interactions. In the animals not subjected to blood loss, both normotensive and hypertensive, blood flow remained constant throughout the experiment, with no sustained increases or decreases (see table 2). In the normotensive animals subjected to blood loss, however, blood flow increased following withdrawal of 10 ml/kg of blood. In hypertensive animals subjected to blood loss CBF increased following withdrawal of 20 ml/kg of blood.

3) Significant differences were found between the CBF values measured by the two techniques. Despite similarities in mean values using either microsphere or H₂ clearance methods, there were significantly greater variances associated with the H₂ clearance method than with the microsphere meth-

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Table 1

<table>
<thead>
<tr>
<th>Time</th>
<th>Cortical Blood Flow (ml/min/100 g) Microsphere</th>
<th>H₂ Clearance</th>
</tr>
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<tbody>
<tr>
<td>30'</td>
<td>40 ± 4</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>60'</td>
<td>40 ± 4</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>90'</td>
<td>40 ± 4</td>
<td>33 ± 9</td>
</tr>
<tr>
<td>120'</td>
<td>40 ± 4</td>
<td>33 ± 9</td>
</tr>
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</table>

*Vol of blood withdrawn (ml/kg) 0 5 10 15 20

Group I diastolic BP (mm Hg)

<table>
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<th>x</th>
<th>SEM</th>
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<tr>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>84</td>
<td>8</td>
</tr>
<tr>
<td>75</td>
<td>5</td>
</tr>
<tr>
<td>60</td>
<td>3</td>
</tr>
<tr>
<td>51</td>
<td>3</td>
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Group II diastolic BP (mm Hg)

<table>
<thead>
<tr>
<th>x</th>
<th>SEM</th>
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<td>120</td>
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<td>128</td>
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<td>3</td>
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Mean ± standard errors are given.
Discussion

These studies demonstrate that graded, non-hypotensive, blood loss is associated with an increase of CBF. In addition, our findings suggest that hypotension delays the increase in CBF which accompanies graded blood loss.

There are several mechanisms by which moderate blood loss could increase CBF. Decreased cerebrovascular resistance associated with hypercarbia cannot account for it, since PCO₂ was unchanged throughout the duration of the experiment. Systemic blood loss could alter local metabolic factors, resulting in a reactive hyperemia or luxury perfusion such as that accompanying stroke. However, this mechanism should cause a similar or even greater increase in blood flow in the hypertensive animals, because of the greater perfusion pressure. This did not occur in the present experiments. Thus while the influence of metabolic factors cannot be totally excluded, it is unlikely that they are solely responsible for increased CBF following hemorrhage.

The importance of neural influences on the cerebral circulation remains to be clarified. Some studies demonstrate no effect; others indicate a definite role for neural modulation of CBF. Denervation of aortic and carotid chemoreceptors in dogs does not alter the CBF response to systemic hypoxemia. This lack of effect is attributed to the marked direct effects of hypoxemia on cerebrovascular tone. Similarly, denervation of superior or cervical and stellate ganglia in dogs alters neither the distribution of CBF nor its response to hypocapnia and hypotension. Semi-selective elevation of carotid sinus pressure in dogs does not alter CBF in normo-, hypo-, or hypercapnic dogs. In cats, bilateral intracranial division of the 9th and 10th nerves does not alter the CBF responses to hyper- and hypocapnia.

In contrast, alterations in carotid sinus pressure or arterial PCO₂ of the vascularly isolated dog carotid sinus produce reciprocal changes in CBF which are abolished by carotid sinus nerve section. Cervical sympathetic nerve section in baboons enhances vascular responsiveness to PCO₂ and increases tolerance to hypotension. Similarly, acute surgical sympathetomy or alpha blockade with phenoxybenzamine preserves blood flow in baboons during hemorrhagic hypotension. Finally, activation of baroreceptors by severe hypertension produces a decline in CBF in cats.

Activation of some neural mechanism seems the most likely explanation for the observations of increased CBF following moderate blood loss and the retarding effect of hypertension on this increase. Since blood pressure did not fall significantly in the normotensive animals until after CBF had increased (table 1) it is unlikely that the afferent activators of this response arise from the arterial side of the circulation. Since acute volume contraction ordinarily causes decreased central venous or right atrial pressure, afferent information which leads to the observed increases in CBF may arise from these low pressure sources. More exact localization of afferent stimulation is not possible using the present data.

In apparent contrast to the present findings, Davis and Sundt reported decreased cerebral blood flow with blood loss. However there are two important methodological differences between the two studies which may account for such discrepancies. First, Davis and Sundt used pentobarbital anesthesia. The depressant effects of barbiturates on autonomic ganglia are well documented, and may account for their inability to demonstrate a volume dependent reflex increase in cerebral blood flow. Secondly, Davis and Sundt decreased blood volume by only 10 ml/kg over 2 hrs.
This may not have been adequate to evoke the response. Present observations that blood loss evoked increases in CBF are delayed by hypertension is consistent with another report, which demonstrated a restrictive effect of hypertension on CBF.

These findings may be particularly pertinent in head injured patients, where CBF is compromised by increased intracranial pressure. Attendant hypotension may further limit cortical perfusion. Intensive management of cardiopulmonary function is an important determinant of outcome following head injury.

Diuretic induced volume contraction is also cited as an important therapeutic adjunct in brain trauma. Diuresis is thought to improve cerebral perfusion by decreasing intracranial pressure; but the present findings indicate that diuresis may also augment cerebral perfusion by reflexively causing cerebral vasodilation.

In summary, moderate blood loss increases CBF, and this response is delayed by induced systemic hypertension. In the absence of PCO₂ changes or large metabolic alterations, present results are consistent with a neurally evoked cerebral vasodilation and this may be impeded by elevations of arterial blood pressure.

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