Cerebral Vascular Response to Moderate Blood Loss: Modification by Hypertension

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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 radiolabelled 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.

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pressure, and PCO	extsubscript{2} 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 H	extsubscript{2} clearance, H	extsubscript{2} 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 H	extsubscript{2} 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.\(^6\)

This group included four cats in which CBF was measured with microspheres and three in which CBF was measured using the H	extsubscript{2} 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,\(^7\) 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 H	extsubscript{2} 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 H	extsubscript{2} clearance blood flows are also shown in table 1. The arterial blood pressure is shown for each group. For all measurements, PCO	extsubscript{2} 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 H	extsubscript{2} clearance methods, there were significantly greater variances associated with the H	extsubscript{2} clearance method than with the microsphere meth-

### Table 1  Blood Pressure and Parietal CBF Values for Normotensive Blood Loss (Group I) and Hypertensive Blood Loss (Group II)

<table>
<thead>
<tr>
<th>Time</th>
<th>Vol of blood withdrawn (ml/kg)</th>
<th>Group I diastolic BP (mm Hg)</th>
<th>Group II diastolic BP (mm Hg)</th>
<th>Cortical blood flow (ml/min/100g) microsphere</th>
<th>Cortical blood flow (ml/min/100g) H\textsubscript{2} clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30'</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>60'</td>
<td>SEM</td>
<td>SEM</td>
<td>SEM</td>
<td>SEM</td>
</tr>
<tr>
<td></td>
<td>90'</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>120'</td>
<td>SEM</td>
<td>SEM</td>
<td>SEM</td>
<td>SEM</td>
</tr>
<tr>
<td></td>
<td>150'</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

Mean ± standard errors are given.
od. This increased variance did not, however, alter the significance of the results as discussed in 1) and 2) above.

Table 3 summarizes results of the analysis of variance between treatment groups and time-treatment interactions for various brain regions. Note that the only brain region that showed no treatment or time treatment effect was the medulla.

**Discussion**

These studies demonstrate that graded, non-hypotensive, blood loss is associated with an increase of CBF. In addition, our findings suggest that hypertension 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 sympathectomy 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.

**Table 2** Blood Pressures and Parietal CBF Values of Normotensive (Group III) and Hypertensive Normovolemic (Group IV) Cats

<table>
<thead>
<tr>
<th>Time</th>
<th>Vol of blood withdrawn (ml/kg)</th>
<th>Group III diastolic BP (mm Hg)</th>
<th>Group IV diastolic BP (mm Hg)</th>
<th>Cortical blood flow (ml/min/100 g) microsphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30'</td>
<td>60'</td>
<td>90'</td>
<td>120'</td>
</tr>
<tr>
<td>x</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SEM</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Cortical blood flow (ml/min/100 g) microsphere</td>
<td>40</td>
<td>41</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

**Table 3** F Ratios Associated with Variance Estimates from between Treatment and Time-Treatment Sources for Various Brain Regions. All Except Medulla are Significant (p < 0.05)

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Treatment</th>
<th>Time-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>24.15</td>
<td>16.95</td>
</tr>
<tr>
<td>Parasagittal</td>
<td>15.13</td>
<td>19.57</td>
</tr>
<tr>
<td>Temporal</td>
<td>10.08</td>
<td>7.14</td>
</tr>
<tr>
<td>Parietal</td>
<td>21.7</td>
<td>20.28</td>
</tr>
<tr>
<td>Occipital</td>
<td>20.5</td>
<td>15.63</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>17.6</td>
<td>16.2</td>
</tr>
<tr>
<td>Pons</td>
<td>19.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Medulla</td>
<td>1.1</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Mean ± standard errors are given.
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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References

Cerebral vascular response to moderate blood loss: modification by hypertension.
F P Holladay, J R Bean, B Young, E P Todd and M W Roy

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