Effects of subarachnoid hemorrhage on cerebral blood volume, blood flow, and oxygen utilization in humans

ROBERT L. GRUBB, JR., M.D., MARCUS E. RAICHLE, M.D., JOHN O. EICHLING, PH.D., AND MOKHTAR H. GADO, M.B., B.CH., F.F.R.

Department of Neurology and Neurological Surgery, and Division of Radiation Sciences and Neuroradiology, The Edward Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri

Forty-five studies of regional cerebral blood volume (rCBV), regional cerebral blood flow (rCBF), and regional cerebral oxygen utilization (rCMRO₂) were performed in 30 patients undergoing diagnostic cerebral angiography for evaluation of a subarachnoid hemorrhage due to a ruptured intracranial aneurysm. Tracer methods employing radioactive oxygen-15 were used to measure rCBV, rCBF, and rCMRO₂. The patient studies were divided into groups based on their neurological status and the presence or absence of cerebral vasospasm. Subarachnoid hemorrhage, with and without vasospasm, produced significant decreases in CBF and CMRO₂. In general, patients with more severe neurological deficits, and patients with more severe degrees of vasospasm, had a more marked depression of CBF and CMRO₂. The most striking finding was a significant (p < 0.001) increase in CBV (to 58% above normal) in patients with severe neurological deficits associated with severe cerebral vasospasm. This large increase suggests that cerebral vasospasm consists of constriction of the large, radiographically visible extraparenchymal vessels accompanied by a massive dilation of intraparenchymal vessels.

KEY WORDS • subarachnoid hemorrhage • cerebral vasospasm • cerebral blood volume • cerebral blood flow • cerebral oxygen utilization

SUBARACHNOID hemorrhage (SAH) from the rupture of an intracranial artery aneurysm is known to produce severe focal as well as generalized disturbances in brain function. A combination of factors is thought to contribute to these disturbances. First, direct exposure of brain tissue to blood appears to disrupt normal brain metabolism. Second, brain tissue may be injured by the marked rise in intracranial pressure (ICP) and mechanical distortion of intracranial structures resulting from the sudden injection of blood into the subarachnoid space. Finally, it has been suggested, although by no means proven, that brain tissue may be rendered ischemic by spasm of the cerebrovasculature that frequently accompanies SAH. The extent to which each of these factors actually contributes to the morbidity and mortality associated with SAH is unclear.
Cerebral metabolism in subarachnoid hemorrhage

This is the result of two deficiencies. First, we have only limited quantitative information on the effect of SAH and vasospasm on the cerebral circulation, and no information on cerebral metabolism in humans. Second, we have no model of this condition in animals that satisfactorily duplicates the clinical situation of vasospasm plus neurological deterioration. To provide this information, we have measured not only regional cerebral blood flow (rCBF), but also regional cerebral blood volume (rCBV), and regional cerebral oxygen utilization (rCMRO₂) in patients with SAH.

Clinical Material and Methods

We conducted 45 studies of rCBV, rCBF, and rCMRO₂ in 30 unselected, but not formally randomized, patients undergoing diagnostic cerebral angiography for evaluation of an SAH due to a ruptured intracranial aneurysm. Eighteen patients had either a preoperative or a postoperative study, nine patients had both a preoperative and a postoperative study, two patients had one preoperative and two postoperative studies, one patient had two preoperative studies only, and one patient had two postoperative studies only.

A short Teflon catheter was placed in the internal carotid artery for injection of the isotopes and angiographic contrast material. The isotope studies were always performed at least 15 minutes after the angiographic studies to avoid the effects of the contrast agents on cerebral hemodynamics and metabolism. Each patient study consisted of an injection of ¹⁵⁰-oxyhemoglobin followed 6 minutes later by an injection of C¹⁵⁰, and then 2 minutes later by an injection of H₂¹⁶⁰. Radioactive oxygen-15 was prepared in the Washington University Medical School Cyclotron by the irradiation of nitrogen gas containing oxygen carrier with 7 MeV deuterons. Several measurements of arterial pH, pCO₂, and O₂ content were made during the data collection period. The mean arterial blood pressure (MABP) was monitored in all patients during the study and the ICP was determined in most patients by a lumbar puncture. Cerebral perfusion pressure (CPP) was calculated as MABP minus ICP.

The washout of these isotopes was monitored by a multiprobe radiation detection system consisting of 5 × 5 cm NaI(TI) scintillation probes fitted with converging collimators and held in a lead shield conforming to the shape of the head. Three to 13 separate regions of the injected hemisphere were monitored in this group of patients. The signal from the detector was processed by a pulse height analyzer† with an energy window of acceptance adjusted symmetrically around the 511 keV photopeak (481–541 keV) to eliminate scattered radiation. There would, of course, be no difference in the responses arising from the use of the three different radiopharmaceuticals C¹⁵⁰-hemoglobin, H₂¹⁴⁰, and O₂-oxyhemoglobin, since all are positron emitters and are counted with identical detection efficiencies for the same counting geometry.

The accepted events (counts) per time frame were stored in the memory of an Interdata 70 minicomputer. Appropriate data processing, including corrections of the count rate for electronic dead time loss, physical decay, background, and conversion to count rate (ct/sec) as a function of time were performed by the computer. Routine data retrieval was in the form of processed count rate as a function of time plotted by a graphical line printer. Optimal temporal resolution was achieved in the initial portion of each recording by using sampling integration times of 0.1 second. Statistically smooth recordings were insured by injection of sufficient C¹⁴⁰-hemoglobin, O₂-oxyhemoglobin, and H₂¹⁶⁰ to achieve a peak counting rate of 1000 to 3000 ct/sec for the first two tracers and 5000 to 10,000 ct/sec for the third.

Cerebral blood flow was determined by residue detection of the injected bolus of labeled water. A 75-second index from the clearance curve was used to calculate CBF. This index has been shown to have an excellent correlation with compartmental analysis of the clearance curve.

The fractional extraction of oxygen by brain was determined from the analysis of the

---

*Scintillation probe system constructed at the Mallinckrodt Institute of Radiology, St. Louis, Missouri. Sodium iodide crystals manufactured by Harshaw Chemical Company, 6801 Cochran Road, Solon, Ohio 44139.
†Pulse height analyzers manufactured by Ortec Inc., 100 Midland Road, Oak Ridge, Tennessee 37830.
TABLE 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>asymptomatic or minimal headache</td>
</tr>
<tr>
<td>Grade II</td>
<td>moderate to severe headache, no neurological deficit other than cranial nerve palsy</td>
</tr>
<tr>
<td>Grade III</td>
<td>drowsiness, confusion, or mild focal deficit</td>
</tr>
<tr>
<td>Grade IV</td>
<td>stupor, moderate to severe hemiparesis, possibly early decerebrate rigidity and vegetative disturbances</td>
</tr>
<tr>
<td>Grade V</td>
<td>deep coma, decerebrate rigidity, moribund appearance</td>
</tr>
</tbody>
</table>

was performed by injection of $^{18}$O-oxyhemoglobin for each probe. The CBFO$_2$ was then computed by combining CBF and the corresponding oxygen fractional extraction for each probe with the arterial content of oxygen.

Cerebral blood volume was calculated employing the equation:

$$ CBV = \lambda \cdot \bar{t}_{co}/f \cdot \bar{t}_{h_{2}o} $$

where CBV is the vascular volume of distribution per gram of monitored tissue, $\lambda$ is the mean tissue-blood partition coefficient for water, $\bar{t}_{co}$ and $\bar{t}_{h_{2}o}$ are the mean transit times for $^{18}$O-hemoglobin and H$_2$O, respectively, and $f$ is the ratio of the mean cerebral hematocrit to the large vessel hematocrit. A value of 0.95 was used for $\lambda$. An average value of the ratio of cerebral small vessel hematocrit (Hct$_{sr}$) of 85% of the large vessel hematocrit was used in these studies. The mean transit time of the diffusible tracer H$_2$O was determined from the residue curve used to calculate CBF. The mean transit time for the vascular tracer $^{18}$O-hemoglobin was determined by analysis of the clearance curve using a modification of the technique of Zierler.

Average values of CBF of 54 ml/100 gm/min and of CMRO$_2$ of 3.6 ml/100 gm/min have been obtained with $^{18}$O-isotope methods in patients without brain pathology. With the x-ray fluorescence method our laboratory previously reported an average value of CBV in humans without brain pathology of 3.2 ml/100 gm. Further experience with this method has changed our average value of CBV for normal humans to 3.6 ml/100 gm.

The measurements of cerebral blood flow, volume, and metabolism were evaluated in two ways. First, the regional studies were averaged for each patient to obtain mean hemispheric values for CBF, CBV, and CMRO$_2$. This was done for two reasons: 1) the number of regions studied in each hemisphere varied from three in our earliest studies to 13 in our latest studies, thus precluding systematic regional comparison, and 2) despite the focal nature of the vascular lesion, the resultant changes in flow, volume, and metabolism often occurred diffusely over the homolateral and occasionally the contralateral hemisphere. The patient studies were then divided into groups based on their neurological status and the presence or absence of cerebral vasospasm. The neurological condition of the patients was graded according to the Hunt and Hess modification of the classification of Botterell (Table 1). Each grouping included both preoperative and postoperative patients, as they showed similar degrees of changes in CBF, CBV, and CMRO$_2$. T-tests were used to test the significance of observed changes from normal values in CBF, CBV, and CMRO$_2$ in each group. Differences in observed values of CBF, CBV, and CMRO$_2$ in all patients without vasospasm as compared to observed values of CBF, CBV, and CMRO$_2$ in patients with vasospasm were also tested for significance by t-tests. Twelve patients had aneurysms of the internal carotid artery at the posterior communicating artery origin, nine had anterior communicating artery aneurysms, seven had middle cerebral artery aneurysms, and two had aneurysms of the vertebral artery at the posterior inferior cerebellar artery origin.

Serial angiograms made in conjunction with the cerebral hemodynamic and metabolic studies were reviewed independently by a neuroradiologist, with no knowledge of the patients' clinical status or the results of the isotopic studies, to determine the presence or absence of cerebral vasospasm. Evaluation of the degree of vasospasm was made on the basis of careful visual estimation. If vasospasm was present, it was classified both to its degree and extent. Focal vasospasm was defined as vasospasm involving less than 4 cm of an arterial seg-
Cerebral metabolism in subarachnoid hemorrhage

Fig. 1. Mean values of CBV, CBF, and CMRO₂ in patients following a subarachnoid hemorrhage with and without cerebral vasospasm. Standard deviation of mean values is shown by vertical bars. Mean values significantly different from normal values are indicated by stars.

Results

Mean values of CBV, CBF, CMRO₂, PaCO₂, MABP, ICP and CPP for all four groups of patients are depicted in Fig. 1 and Table 2. Subarachnoid hemorrhage, with and without vasospasm, produced significant decreases in CBF and CMRO₂ (Fig. 1, Table 2). Patients with more severe neurological deficits and patients with more severe degrees of vasospasm in general had a more marked depression of CBF and CMRO₂. The most striking finding was the significant increase (p < 0.001) in CBV seen in Grade III and IV patients with cerebral vasospasm (Fig. 1, Table 2). More moderate but not significant increases in CBV were seen in Grade I and II patients with vasospasm. In general, patients with more severe degrees of vasospasm demonstrated the largest elevations in CBV (Table 3). In patients with SAH, but without vasospasm, CBV was not significantly elevated (Fig. 1, Table 2). Significant increases in CBV (p < 0.001), decreases in CBF (p < 0.01), and decreases in CMRO₂ (p < 0.001) were seen in all patients with vasospasm in comparison to all patients without vasospasm.

Table 4 lists the percentage of patients in each group with focal changes in CBF,
### TABLE 2
**Hemodynamic and metabolic effects of subarachnoid hemorrhage in humans**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Without Vasospasm</th>
<th>With Vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade I-II</td>
<td>Grade III-IV</td>
</tr>
<tr>
<td></td>
<td>(NS)</td>
<td>(p &lt; .001)</td>
</tr>
<tr>
<td>CBV (ml/100 gm)</td>
<td>3.6 ± 0.8</td>
<td>4.0 ± 0.5</td>
</tr>
<tr>
<td>CBF (ml/100 gm/min)</td>
<td>54 ± 9</td>
<td>42 ± 6</td>
</tr>
<tr>
<td>CMRO₂ (ml/100 gm/min)</td>
<td>3.6 ± 0.5</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>PaCO₂ (mm Hg)</td>
<td>35 ± 2</td>
<td>36 ± 5</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>100 ± 10</td>
<td>105 ± 20</td>
</tr>
<tr>
<td>ICP (mm Hg)</td>
<td>19 ± 9</td>
<td>16 ± 11</td>
</tr>
<tr>
<td>CPP (mm Hg)</td>
<td>83 ± 12</td>
<td>88 ± 25</td>
</tr>
<tr>
<td>total patients</td>
<td>17</td>
<td>10</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation.
†CBV = cerebral blood volume; CBF = cerebral blood flow; CMRO₂ = cerebral oxygen utilization; PaCO₂ = arterial carbon dioxide pressure; MABP = mean arterial blood pressure; ICP = intracranial pressure; CPP = cerebral perfusion pressure.
†Degrees of significance of changes in CBV, CBF, and CMRO₂ from normal values are below the mean values.

### TABLE 3
**Cerebral blood volume (CBV) in patients with cerebral vasospasm**

<table>
<thead>
<tr>
<th>No. of Cases</th>
<th>Vasospasm</th>
<th>CBV* (ml/100 gm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Degree</td>
<td>Extent</td>
</tr>
<tr>
<td>10</td>
<td>severe</td>
<td>diffuse</td>
</tr>
<tr>
<td>4</td>
<td>severe</td>
<td>focal</td>
</tr>
<tr>
<td>2</td>
<td>mild</td>
<td>diffuse</td>
</tr>
<tr>
<td>2</td>
<td>mild</td>
<td>focal</td>
</tr>
</tbody>
</table>

*Values are means ± standard deviation.

CMRO₂, and CBV as compared to normal values, that both correlated and failed to correlate with focal neurological deficits. More than half the Grade III and IV patients with vasospasm had focal decreases in CBF and CMRO₂ that correlated with focal neurological deficits. Of these same Grade III and IV patients with vasospasm, only 23% had focal increases in CBV that correlated with focal neurological deficits, while 47% of these patients demonstrated a diffuse elevation of CBV. A large number of patients without

### TABLE 4
**Regional hemodynamic and metabolic changes in subarachnoid hemorrhage correlated with focal neurological deficits**

<table>
<thead>
<tr>
<th>Category</th>
<th>No. Cases</th>
<th>Focal Neurological Deficits</th>
<th>rCBF Decreases</th>
<th>rCMRO₂ Decreases</th>
<th>rCBV Increases</th>
<th>rCBV Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I-II without vasospasm</td>
<td>17</td>
<td>0</td>
<td>0</td>
<td>65%</td>
<td>0</td>
<td>56%</td>
</tr>
<tr>
<td>Grade III-IV without vasospasm</td>
<td>10</td>
<td>0</td>
<td>10%</td>
<td>40%</td>
<td>0</td>
<td>70%</td>
</tr>
<tr>
<td>Grade I-II with vasospasm</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>100%</td>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>Grade III-IV with vasospasm</td>
<td>14</td>
<td>93%</td>
<td>57%</td>
<td>14%</td>
<td>62%</td>
<td>14%</td>
</tr>
</tbody>
</table>

*rCBF = regional cerebral blood flow; rCMRO₂ = regional cerebral oxygen utilization; rCBV = regional cerebral blood volume; A = correlated with a focal neurological deficit; B = failed to correlate with any focal neurological deficit.*
Cerebral metabolism in subarachnoid hemorrhage

vasospasm had focal decreases in CBF and CMRO₂ and both focal increases and decreases in CBV that did not correspond to any focal neurological deficit.

Discussion

Our data are in accord with the observations of others⁰,⁵,⁵,⁴,¹⁰,⁵⁰ that SAH causes a significant decrease in CBF. In addition, we observed a significant decrease in CMRO₂. The reduction in CBF and CMRO₂ occurred even in the patients in the best clinical condition (Grade I and II) without vasospasm. Although all groups of patients had a modest increase in ICP (Table 2), several experimental observations suggest that this degree of intracranial hypertension alone was not likely to be responsible for the observed changes in flow and oxidative metabolism. Elevation of ICP by the intracisternal infusion of saline or mock cerebrospinal fluid does not cause a reduction in blood flow or metabolism until pressures of greater than 60 mm Hg are reached.⁴,⁵,⁵⁰ Furthermore, Fein⁶ reports that the intracisternal injection of whole blood under experimental conditions designed to maintain normal ICP results in a significant reduction in CBF and alterations in cerebral energy metabolism. Elevation of ICP by the intracisternal infusion of saline or mock cerebrospinal fluid does not cause a reduction in blood flow or metabolism until pressures of greater than 60 mm Hg are reached.⁴,⁵,⁵⁰ We must conclude that SAH, by some as yet unspecified mechanism, has a direct effect on CBF and metabolism in humans, as well as experimental animals.

Our most striking and unexpected finding was the increase in CBV in Grade III and IV patients with severe, diffuse vasospasm. This finding suggests that cerebral vasospasm, associated with SAH, consists of constriction of the large, radiographically visible, extraparenchymal vessels accompanied by massive dilation of intraparenchymal vessels as manifested by an increased blood volume. This massive increase in CBV is a unique finding not seen in other patients we have studied with a variety of diseases such as dementia,¹⁹ pseudotumor,⁰⁰ cerebral infarction (unpublished), and diffuse injury to the brain (unpublished).

Increases in CBV have been observed under a variety of experimental conditions. Acutely increasing the arterial carbon dioxide tension produces not only the expected increase in CBF, but also an increase in CBV presumably due to a relaxation and dilation of cerebral resistance vessels.⁴,¹⁰ Cerebral blood volume is also observed to increase when the CPP is acutely reduced, either by reducing systemic arterial pressure⁴,¹¹ or increasing ICP.¹¹ These latter changes in CBV form the basis for the concept that the normally observed constancy of CBF over a wide range of perfusion pressures, so-called cerebral autoregulation,²² is accomplished by changes in the diameter and, therefore, the volume of cerebral resistance vessels. The mild elevation in CBV seen in our patients without vasospasm is probably explained by a reduction in CPP caused by the observed increase in ICP. The very large increase in CBV seen in patients with vasospasm is probably the result of a profound reduction in perfusion pressure distal to the constricted segments of the arterial tree.

The large increase in CBV in patients with cerebral vasospasm, especially severe, diffuse vasospasm, suggests a differential susceptibility of the cerebral vascular tree to this particular insult, with the small resistance vessels opposing or compensating for the abnormal action of the large resistance vessels. The cerebral vasculature can be viewed as a series of resistance vessels with factors affecting the resistance in large extraparenchymal blood vessels differing from those affecting intraparenchymal blood vessels. Specifically, it has been suggested that the large extraparenchymal vessels are under the influence of the sympathetic nervous system, whereas the small intraparenchymal vessels are primarily under the influence of the products of cellular metabolism.¹²,¹₆ Because the large extraparenchymal arteries are the vessels constricted in vasospasm, it is attractive to suggest that vasospasm may represent a malfunction of the sympathetic innervation of these vessels induced by the SAH. However, two alternative hypotheses cannot be excluded at this time. First, vasospasm of the larger extraparenchymal vessels may simply reflect the fact that the factor(s) released into the subarachnoid space which is responsible for the vasospasm simply does not diffuse into brain and, therefore, never comes into direct contact with the intraparenchymal vasculature. Second, although the intra-
parenchymal vasculature may be sensitive and exposed to the factor(s) responsible for vasospasm, the products of cellular metabolism exert the dominant influence on this part of the vascular bed. Further information will be necessary to resolve these issues.

The exact role of vasospasm in the morbidity and mortality associated with SAH remains unclear. We submit that it is not necessary to postulate that vasospasm is the only factor contributing to this morbidity and mortality of SAH, but rather that it can set the stage for events which either further decrease brain perfusion or lead to clotting in the parenchymal microvasculature. In the presence of vasospasm the brain becomes more vulnerable to increased metabolism or decreased CBF because of the exhaustion of reserve capacity of the vasculature to respond to tissue metabolic needs. A further decrease in perfusion pressure due to increased ICP may be the final event leading to tissue ischemia and infarction. In addition, stagnation of blood within the parenchymal vasculature may predispose to clotting and infarction.

Acknowledgments

The authors wish to thank Mr. Mark Selikson, Mrs. Christa Cooper, and the staff of the Washington University School of Medicine cyclotron for their invaluable technical assistance in these experiments. The authors would also like to thank Mr. Philip Miller of the Division of Biostatistics, Washington University School of Medicine, for performing the statistical analysis of the data in these experiments. We are grateful to Dr. Michel Ter-Pogossian for his generous support and helpful suggestions during the course of this work.

References

Cerebral metabolism in subarachnoid hemorrhage


This work was supported by U.S. Public Health Service Grants 5 PO1 HL13851 and PO1 NSO 6833 (NINDS); and by Teacher-Investigator Award 1-F11-NS11059 from NINDS to Dr. Raichle.

Address reprint requests to: Robert L. Grubb, Jr., M.D., Department of Neurology and Neurological Surgery, Washington University School of Medicine, Barnes Hospital Plaza, St. Louis, Missouri 63110.