Cerebrovascular Reactivity and Metabolism After Subarachnoid Hemorrhage in Baboons

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SUMMARY Subarachnoid hemorrhage (SAH) was induced in baboons by puncturing the middle cerebral artery. Four to seven days later cerebral blood flow (CBF) responses to changing Paco₂ and to intracarotid infusion of 1.0, 2.5 and 5.0 μg of 5-hydroxytryptamine (5-HT)/kg/min were studied using the intracarotid °Xe clearance technique. Indices of cerebral metabolism were determined by measuring arterio-venous differences for oxygen, pyruvate, lactate and glucose. The results were compared with those from sham-operated baboons. In the sham-operated group normal CO₂ reactivity was seen, and 5-HT infusion did not produce any significant change in CBF or cerebral metabolism. By contrast, the group in which SAH was induced showed a significant decrease in CBF and cerebral oxygen utilization, and attenuated CO₂ reactivity.

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Ever since Crompton1 reported a 75% incidence of cerebral infarction in patients who die from ruptured intracranial aneurysms, there has been an intensified search for its etiology. In the 119 patients with infarction which he reported, only 2 had documented arterial thrombosis, and 5 had venous thrombosis. The cause of the infarction appeared not to be thromboembolic in the vast majority, and the cause was assigned to cerebral vasospasm. The definition of vasospasm remains controversial, and may be taken to mean either angiographic narrowing of the large cerebral arteries in the region of the aneurysm or diminished cerebral blood flow (CBF) which may not correlate in time with angiographic spasm, and may not always be related to the general clinical state of the patient.

There is also controversy as to whether “acute” or “early” vasospasm is as important as “chronic” or “delayed” vasospasm. That there is a difference between acute and chronic spasm has been stressed by several authors.8 It is likely that chronic spasm is of “delayed” vasospasm. That there is a difference between acute and chronic spasm has been stressed by several authors.8 It is likely that chronic spasm is of greater importance in the clinical situation, although a recent report has suggested that angiographic spasm may in fact be detectable at an early stage, but only becomes clinically evident later.9 We have chosen a primate model of chronic vasospasm after subarachnoid hemorrhage (SAH) to study cerebrovascular reactivity and metabolism.

Materials and Methods

Two groups of adult baboons (Papio ursinus) weighing 13 to 20 kg were used. In the experimental group (SAH group) we induced a subarachnoid hemorrhage in 10 animals under anesthesia by piercing the right middle cerebral artery, via a small cranietomy. In the control group of 5 animals the middle cerebral artery was exposed in the same way, but no holes were made. In both groups CBF and cerebral metabolism were studied 4–7 days later.

Surgical Technique

All animals were anesthetized with phenylcyclidine (Sernylan, Bioceutic), intubated and ventilated. Anesthesia was maintained with intravenous thiopentone (Intraval Sodium, May Baker). The right middle cerebral artery was exposed in all animals through a small fronto-temporal craniectomy. With the aid of a dissecting microscope the main trunk of the middle cerebral artery was pierced with a 26-gauge needle without opening the overlying arachnoid membrane. If one hole did not produce an adequate hemorrhage, further holes were made. In the control group the same operative approach was used, but the middle cerebral artery was not damaged. Operative procedures were carried out in an operating theater with careful attention to sterile techniques. Intravenous fluid was given until the animals had recovered from anesthesia. In 2 animals, which did not recover consciousness, nasogastric tubes were passed and artificial feeding maintained until the day of experimentation. All other animals recovered sufficiently well to feed normally.

General Procedures

On the day of experimentation (4 to 7 days after surgery) animals were again anesthetized with phenylcyclidine, intubated and ventilated. Anesthesia was maintained with thiopentone by a continuous low-dose intravenous infusion at a rate sufficient to maintain light sedation with a 7–14 Hz rhythm on the electroencephalograph. A femoral arterial catheter was inserted for measurement of pulsatile and mean blood pressure (MBP) and for withdrawal of arterial blood for measurements of pH, Paco₂, Pao₂, hematocrit, hemoglobin and percentage oxygen saturations, as well as lactate, pyruvate and glucose. A double lumen catheter was inserted via the lingual artery to permit independent injection of °Xe and drugs. All other branches of the external carotid artery were ligated.
Cerebral venous blood samples were withdrawn via a radio-opaque catheter which was inserted into the internal jugular vein, and passed into the sigmoid sinus. Lumbar cerebrospinal fluid (CSF) pressure, rectal temperature and endotracheal CO₂ percentage were also measured and the bladder was catheterized and allowed to drain freely throughout the experiment.

Measurement of CBF

CBF was measured by the intracarotid ¹³³Xe clearance method. A bolus of 50–100 µCi of ¹³³Xe was injected via one lumen of a double lumen lingual artery catheter into the internal carotid artery. The subsequent clearance of ¹³³Xe from the parieto-temporal region was measured with a highly collimated 50 mm diameter sodium iodide scintillation detector connected to a digital ratemeter. The skin and temporalis muscle were reflected from the area under the scintillation detector to minimize contamination from extracerebral sources. The ¹³³Xe clearance curve was analysed compartmentally into fast and slow clearing components representing flow through cerebral grey (fg) and white matter (fw) respectively. The weighted average flow (f) was calculated from the values for fg and fw assuming a ratio of 52:48.¹⁰

Measurement of Cerebral Metabolism

The cerebral metabolic rates (CMR) of oxygen, lactate, pyruvate and glucose were calculated from the arteriovenous differences for these substances using the Fick equation. Plasma levels of lactate, pyruvate and glucose were determined with Biochemica Test Combination Kits (Boehringer Mannheim) using a Beckman Acta III spectrophotometer. Percentage oxygen saturation was measured on an I.L. 182 Co-Oximeter, CMRO₂ was measured in both groups of animals, and CMR lactate, CMR pyruvate and CMR glucose were measured in the group with SAH.

Experimental Procedures

In both groups of animals an identical protocol was followed. After insertion of catheters, the animals were allowed to stabilize for 30 minutes and during this period normocapnia was maintained. Two baseline measurements of CBF and CMR were then made, at a PACO₂ of 35 mm Hg. Hypercapnia was then produced by adding CO₂ to the inlet valve of the ventilator at a fixed rate until the arterial PCO₂ had stabilized at 45 mm Hg. CBF and CMR were again measured. This procedure was repeated at 55 mm Hg. Hypocapnia (PCO₂ 25 mm Hg) was produced by hyperventilation with room air. Between each of the above measurements, a period of normocapnia was allowed for animals to stabilize. A third baseline measurement at normocapnia was made after the 2 periods of hypercapnia. After the period of hyperventilation was completed, normocapnia was maintained for the remainder of the experiment.

After a further period of stabilization, the response to intracarotid infusions of 1.0, 2.5 and 5.0 µg of 5-hydroxytryptamine (5-HT)/kg/min were separately determined in both groups of animals. The 5-HT was dissolved in saline, and the solution was infused at a slow rate (0.1 to 0.5 ml/min) into the internal carotid artery via one lumen of the double-lumen catheter in the lingual artery. In both groups Paco₂, PaO₂, pH and MBP were maintained within normal physiological limits for at least 10 minutes before and during the measurement of CBF and CMR at each infusion rate of 5-HT.

Statistics

1) CO₂ Responsiveness

Mean CBF values at each level of PACO₂ in the SAH group were compared with corresponding mean values in the control group using Student’s t-test, unless variances differed significantly, in which case a modified t-test was used.1⁴ Also, slopes of the linear regression lines for the CO₂ response in each group were compared.¹⁸

2) 5-HT Response

Mean values with administration of each dosage of 5-HT were compared with the mean baseline values (Student’s paired t-test) as well as the corresponding mean values for the same dose in the other group (Student’s t-test).

Results

A total of 15 baboons were used in this study. Subarachnoid hemorrhage was induced surgically in 10 animals, and a sham-operation was performed in 5. All 5 of these control animals remained fully conscious with no neurological deficits during the postoperative period, and had clear CSF at the start of the day on which CBF was measured. These 5 animals showed no evidence of SAH at postmortem. Of the 10 animals in which SAH was induced, 2 were excluded from the study, one because the SAH was inadequate when examined at postmortem and the other because of infection. The former had remained conscious with no neurological deficit, and had clear CSF on lumbar puncture. The latter had recovered consciousness, but had a hemiparesis, turbid CSF and pus was discovered in the neck on the day of the experiment. Of the remaining 8 animals, all were proven to have had SAH at postmortem (fig. 1), and all had xanthochromic, but sterile CSF on the day of the experiment. Two animals failed to recover consciousness following the SAH and one of these had a hemiparesis. Two others recovered consciousness, but were unusually docile, and one of these also had a hemiparesis. The remaining 4 were alert and mobile; one was thought to have a hemianopia because of failure to notice any approach from the left side, and one had a mild hemiparesis. Using the Botterell scale,¹⁰ there were 2 animals in each grade from I to IV.
Figure 1. Base of baboon brain removed at postmortem, 7 days after subarachnoid hemorrhage induced by puncture of the right middle cerebral artery.

The cerebrovascular reactivity and CMR in both groups of animals was measured. The response to intracarotid infusion of 5-HT as well as the effect of changing Paco2 were measured using the protocol outlined, and the results are considered separately.

(a) The Effect of 5-HT

Baseline flow measurements, PaCO2 and MBP were similar in both groups (Table 1). In the control group infusion of 5-HT produced a non-significant rise in f g and T, a significant rise in MBP (which remained within the limits of autoregulation), and a significant fall in f w, while PaCO2 remained constant (Fig. 2). In the SAH group there was a significant decrease in fg, fw and T at all doses of 5-HT infused when compared with the baseline values. The mean flow values for fg and T differed from those in the control group at the 2 higher dosages of 5-HT. There was no significant change in MBP or PaCO2 with infusion of 5-HT in this group.

CMRO2 decreased with the infusion of the highest dose of 5-HT in the SAH group, and CMR pyruvate decreased at the intermediate 5-HT dose, but there

Table 1. Mean Grey Matter (fg), White Matter (fw), Mean Weighted Average Flow (f), and Mean PaCO2 and MBP Before (baseline) and During Infusion of 1.0, 2.5 and 5.0 μg 5-HT/kg/min

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
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<th>5.0</th>
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<tr>
<td>fg (ml/min/100g)</td>
<td>SAH</td>
<td>48.4 ± 2.9</td>
<td>39.3 ± 5.0*</td>
<td>40.9 ± 5.3*</td>
</tr>
<tr>
<td></td>
<td>SHAM</td>
<td>46.9 ± 4.0</td>
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<td>57.6 ± 5.2</td>
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<tr>
<td>fw (ml/min/100g)</td>
<td>SAH</td>
<td>15.7 ± 1.0</td>
<td>9.3 ± 0.4*†</td>
<td>8.5 ± 0.9*</td>
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<tr>
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<td>SHAM</td>
<td>14.4 ± 1.0</td>
<td>13.4 ± 1.0</td>
<td>10.8 ± 1.1*</td>
</tr>
<tr>
<td>T (ml/min/100g)</td>
<td>SAH</td>
<td>33.0 ± 2.0</td>
<td>24.9 ± 2.6*</td>
<td>25.3 ± 3.1*†</td>
</tr>
<tr>
<td></td>
<td>SHAM</td>
<td>31.3 ± 2.0</td>
<td>29.2 ± 1.3</td>
<td>35.1 ± 2.6</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>SAH</td>
<td>35.0 ± 0.3</td>
<td>34.3 ± 0.4</td>
<td>34.3 ± 0.5</td>
</tr>
<tr>
<td></td>
<td>SHAM</td>
<td>35.4 ± 0.1</td>
<td>34.5 ± 0.8</td>
<td>35.1 ± 0.2</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>SAH</td>
<td>111 ± 5.9</td>
<td>116 ± 5.2</td>
<td>114 ± 5.5</td>
</tr>
<tr>
<td></td>
<td>SHAM</td>
<td>109 ± 9.3</td>
<td>119 ± 5.5</td>
<td>118 ± 6.5</td>
</tr>
</tbody>
</table>

All values means ± SEM. *Indicates a significant difference (p < 0.05) from the mean baseline value. (Student's paired t-test). † Indicates a significant difference (p < 0.05) from the corresponding value in the SHAM group (Student's t-test). SAH indicates subarachnoid hemorrhage group, SHAM indicates sham-operated group.
REACTIVITY, METABOLISM, AFTER SAH IN BABOONS/A. Mendelow et al.

TABLE 2. Mean Cerebral Metabolic Rates of Oxygen (CMRO$_2$), Lactate (CMR lact), Pyruvate (CMR pyr) and Glucose (CMR glu) Before (baseline) and During Infusion of 1.0, 2.5 and 5.0 µg 5-HT/kg/min in the Baboons after Subarachnoid Hemorrhage.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1.0</th>
<th>2.5</th>
<th>5.0</th>
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<tr>
<td>CMRO$_2$ (ml/min/100 g)</td>
<td>2.07 ± 0.19</td>
<td>1.75 ± 0.14</td>
<td>1.64 ± 0.18</td>
<td>1.58 ± 0.15*</td>
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<tr>
<td>CMR lact (mg/min/100 g)</td>
<td>0.52 ± 0.15</td>
<td>0.43 ± 0.12</td>
<td>0.58 ± 0.14</td>
<td>0.33 ± 0.07</td>
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<tr>
<td>CMR pyr (mg/min/100 g)</td>
<td>0.06 ± 0.01</td>
<td>0.06 ± 0.02</td>
<td>0.03 ± 0.01*</td>
<td>0.05 ± 0.01</td>
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<tr>
<td>CMR glu (mg/min/100 g)</td>
<td>9.56 ± 2.96</td>
<td>5.66 ± 2.55</td>
<td>6.94 ± 1.84</td>
<td>6.45 ± 3.55</td>
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</table>

All values means ± SEM. *Indicates a significant difference (p < 0.05) from the mean baseline value (Student's paired T test).

was no significant change in CMR glucose and CMR lactate (table 2 and fig. 3). CMRO$_2$ in the control group tended to rise with infusion of 5-HT (table 5). Other indices of cerebral metabolism were not measured in this group of animals.

5-HT tended to produce a non-significant increase in blood flow and oxygen utilization in the control group, while animals with SAH responded with a decrease in flow and oxygen utilization which was significant when compared to the baseline values and when compared with the corresponding values in the control group.

b) CO$_2$ Reactivity

Cerebral blood flow and metabolism were measured in both groups of animals at 4 different levels of Paco$_2$. The mean values for Paco$_2$ in the 2 groups were similar. In the control group these values were 26.7, 35.4, 45.0 and 56.2 mm Hg. In the SAH group the values were 24.1, 35.0, 45.3 and 56.1 mm Hg. (table 3). These levels have been designated 25, 35, 45 and 55 mm Hg in the tables and figures and will be referred to as such in the remainder of the text. MBP remained within the limits of autoregulation in both groups at all levels of Paco$_2$. In the control group the usual vasoconstriction with hypocapnia (Paco$_2$ of 25 mm Hg) and vasodilatation with hypercapnia (45 and 55 mm Hg) was seen (table 3 and fig. 4). Comparison of the slopes of the regression lines for fg/Paco$_2$ in the control group (0.88) and the SAH group (0.35) revealed a significant difference. Similar analysis of the values of T revealed a slope of 0.55 in the control group and 0.21 in the SAH group. These slopes also differed significantly from each other. This indicates that there was a diminished response to changing Paco$_2$ in the SAH group when compared with controls. In addition, the mean values for fg and T at 55 mm Hg in each group differed significantly from each other. In the control group CMRO$_2$ increased with hypocapnia and decreased with hypercapnia. This decrease in CMRO$_2$ was significant at both 45 and 55 mm Hg when compared with the mean value at 35 mm Hg (table 5, fig. 5). A similar increase in CMRO$_2$ with hypocapnia and decrease with hypercapnia was recorded in the SAH group (table 4). There was no significant change in CMR lactate with changing Paco$_2$, but CMR pyruvate decreased significantly with hypercapnia. CMR glucose decreased with both hypocapnia and hypercapnia when compared with normocapnia (table 4, fig. 5).

This indicates that there was a diminished CO$_2$ response in the SAH group of animals when compared with controls. In both groups, CMRO$_2$ increased with

![Figure 3. Cerebral metabolic rates (CMR) of oxygen, lactate, pyruvate and glucose before and during infusion of 5-HT in baboons after subarachnoid hemorrhage. Values means ± SEM. *Indicates a significant difference (p < 0.05) from the mean baseline value.](image-url)
TABLE 3. Mean Grey Matter (fg), White Matter (fw) and Mean Weighted Average Flow (f) and Mean PaCO2 and MBP at Each Interval of PaCO2 From 25 to 55 mm Hg

<table>
<thead>
<tr>
<th>Arterial Carbon Dioxide Tension (PaCO2) (mm Hg)</th>
<th>25</th>
<th>35</th>
<th>40</th>
<th>55</th>
</tr>
</thead>
<tbody>
<tr>
<td>fg (ml/min/100g)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>SAH</td>
<td>42.0 ± 1.7</td>
<td>48.4 ± 2.9</td>
<td>47.2 ± 3.7</td>
<td>53.9 ± 5.5</td>
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<td>SHAM</td>
<td>39.6 ± 4.3</td>
<td>46.9 ± 4.0</td>
<td>47.8 ± 3.9</td>
<td>68.7 ± 5.7*</td>
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<td>fw (ml/min/100g)</td>
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<tr>
<td>SAH</td>
<td>12.8 ± 1.1</td>
<td>15.7 ± 1.0</td>
<td>16.0 ± 1.6</td>
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<tr>
<td>SHAM</td>
<td>10.9 ± 1.7</td>
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<td>f (ml/min/100g)</td>
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</tr>
<tr>
<td>SAH</td>
<td>28.0 ± 1.3</td>
<td>33.0 ± 2.0</td>
<td>32.2 ± 1.9</td>
<td>35.2 ± 3.0</td>
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<tr>
<td>SHAM</td>
<td>25.8 ± 2.6</td>
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<td>PaCO2 (mm Hg)</td>
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<tr>
<td>SAH</td>
<td>24.1 ± 0.3</td>
<td>35.0 ± 0.3</td>
<td>45.3 ± 0.6</td>
<td>56.1 ± 0.5</td>
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<tr>
<td>SHAM</td>
<td>26.7 ± 0.5</td>
<td>35.4 ± 0.1</td>
<td>45.0 ± 1.0</td>
<td>56.2 ± 0.8</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>SAH</td>
<td>103 ± 6.0</td>
<td>112 ± 5.7</td>
<td>113 ± 6.8</td>
<td>111 ± 5.8</td>
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<tr>
<td>SHAM</td>
<td>113 ± 7.9</td>
<td>110 ± 9.3</td>
<td>112 ± 9.9</td>
<td>113 ± 8.6</td>
</tr>
</tbody>
</table>

All values means ± SEM. *Indicates a significant difference (p < 0.05) from the corresponding value in the other group at the same PaCO2 level (Student's t-test). SAH indicates subarachnoid hemorrhage group. SHAM indicates sham-operated group.

hypocapnia and decreased with hypercapnia. The fact that flow decreased with infusion of 5-HT in the SAH group indicates that the attenuated CO2 response was not entirely the result of vasoparalysis. In general, these results indicate that this model of chronic SAH produces hypersensitivity to 5-HT and diminished CO2 reactivity.

Discussion

The increased sensitivity of the cerebral vasculature to 5-HT after SAH suggests that the mechanisms which normally prevent cerebrovascular constriction and diminished flow in vivo when 5-HT is administered intravascularly have become disordered.

![Figure 4](http://stroke.ahajournals.org/)  
**Figure 4.** Mean blood flow at different levels of PaCO2 in animals after subarachnoid hemorrhage (open circles) and in sham-operated animals (closed circles). Values means ± SEM. *Indicates a significant difference from the corresponding value in the sham-operated group.

![Figure 5](http://stroke.ahajournals.org/)  
**Figure 5.** Cerebral metabolic rates (CMR) of oxygen, lactate, pyruvate and glucose at different levels of PaCO2 in animals after subarachnoid hemorrhage (open circles) and in sham-operated animals (closed circles). Values means ± SEM. *Indicates a significant difference from the mean value at normocapnia (35 mm Hg).
The effect was seen at the lowest dose of 5-HT infused and this effect appeared to be maximal at this low dose. It is possible that lower dosages may have produced a dose-response relationship. However, even at the concentrations used in these experiments, several previous reports have indicated that intracarotid 5-HT does not alter CBF in vivo, although in vitro work has shown that 5-HT is a potent cerebrovascular vasoconstrictor. The lack of effect of 5-HT in vivo may be accounted for by a differential effect on large extraparenchymal arteries, and the smaller intraparenchymal resistance arteries. The larger vessels may constrict, but the smaller resistance vessels, which may be protected by the BBB, undergo compensatory dilatation which maintains constant flow. If these larger arteries are in a state of constriction after SAH, then the intraparenchymal resistance arteries may be maximally dilated, so that further dilatation is impossible. It is conceivable that in the model used in this study the 5-HT constricted the larger extraparenchymal vessels, and the smaller resistance arteries were unable to undergo further dilatation, so that 5-HT produced a fall in CBF.

An alternative, or perhaps even complimentary, mechanism is that the perivascular adrenergic denervation which follows SAH may lead to denervation hypersensitivity. In vitro studies have demonstrated increased sensitivity of cerebral arteries to noradrenaline and 5-HT following SAH, but previous studies from our laboratory have indicated that chemical adrenergic denervation with 6-hydroxydopamine did not produce hypersensitivity to intravascular 5-HT in vivo. Thus, although the adrenergic nerve fibers on cerebral arteries degenerate after SAH, this may not be the reason for the increased sensitivity to amines in the present model.

The choice of anesthetic agents in studies of vasospasm is difficult and in these experiments thiopentone was used in a constant low-dose intravenous infusion with EEG monitoring to maintain a light level of anesthesia. Thiopentone has been recommended because it is reported to have no direct effect on vasospasm and is commonly used in experiments concerned with this phenomenon. The low flow rates reported in the present study may be accounted for, at least in part, by the thiopentone infusion, although every care was taken to maintain a similar light level of anesthesia in both the groups studied.

The diminished CO₂ reactivity in the SAH group contrasts with the lack of a significant difference in CMRO₂ between the 2 groups. This would suggest that the loss of CO₂ reactivity was not caused by a different metabolic response in the SAH group. In both groups the CMRO₂ fell with hypercapnia. This phenomenon has been noted previously. The CMR pyruvate also fell with hypercapnia in the SAH group. The significance of this is uncertain, but if anything it would suggest that there was not a shift to anaerobic metabolism with hypercapnia. Under similar experimental conditions, we have previously reported diminished CO₂ reactivity in animals after chemical sympathectomy with intracisternal 6-hydroxydopamine. In the SAH group the main difference was seen at a PaCO₂ of 55 mm Hg suggesting that the loss of CO₂ reactivity occurs mainly with pathological hypercapnia, although the slopes of the regression lines plotted from individual flow values at each level of PaCO₂ differed significantly from one another.

There seems to be general agreement that diminished CBF in patients with SAH may be associated with focal neurological deficit and clouding of consciousness. Similarly, many of the animal models of SAH have shown a fall in CBF after SAH, irrespective of the method of production of the hemorrhage. Others have reported angiographic spasm with the SAH. Many of these models mimic the moment of rupture of an aneurysm, and are associated with an immediate and variable rise in intracranial pressure. In our model, the middle cerebral artery was punctured 4–7 days before testing.

### Table 4. Mean Cerebral Metabolic Rates of Oxygen (CMRO₂), Lactate (CMR lact), Pyruvate (CMR pyr) and Glucose (CMR gluc) at each interval of PaCO₂ from 25 to 55 mm Hg in the Baboons after Subarachnoid Hemorrhage.

<table>
<thead>
<tr>
<th>Arterial Carbon Dioxide Tension (PaCO₂) (mm Hg)</th>
<th>CMRO₂ (ml/min/100g)</th>
<th>CMR lact (mg/min/100g)</th>
<th>CMR pyr (mg/min/100g)</th>
<th>CMR gluc (mg/min/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>2.59 ± 0.23*</td>
<td>0.99 ± 0.15</td>
<td>0.07 ± 0.03</td>
<td>3.64 ± 1.03*</td>
</tr>
<tr>
<td>35</td>
<td>2.07 ± 0.19</td>
<td>0.52 ± 0.15</td>
<td>0.06 ± 0.01</td>
<td>2.95 ± 2.25</td>
</tr>
<tr>
<td>45</td>
<td>1.43 ± 0.14*</td>
<td>0.35 ± 0.10</td>
<td>0.02 ± 0.01</td>
<td>5.01 ± 1.61</td>
</tr>
<tr>
<td>55</td>
<td>0.97 ± 0.11*</td>
<td>0.24 ± 0.09</td>
<td>0.03 ± 0.01*</td>
<td>4.75 ± 1.74*</td>
</tr>
</tbody>
</table>

All values means ± SEM. *Indicates a significant difference from the mean at normocapnia.
cerebrovascular reactivity to 5-HT, and no active hemorrhage was produced on the day of the experiment. Clearly, different models are testing different aspects of SAH, but vasospasm is often delayed and unassociated with a massive rupture. The model used here was designed to measure whether there was any change in sensitivity to 5-HT several days after SAH and this was the case. It would, therefore, seem reasonable to postulate that a change in cerebral arteries takes place after SAH, and that this change sensitizes the vascular bed to 5-HT, so that if a second hemorrhage occurs, the 5-HT released from platelets will cause profound vasoconstriction, and, if sufficiently severe, cerebral infarction. This correlates well with the clinical finding that many patients with a significant hemorrhage have had a minor episode of headache in the recent past which has come to be regarded as the "warning leak." Such patients may already have become sensitized at the time of their second hemorrhage and they may, therefore, have greater ischemic problems. This clinical observation also correlates with the reports that chronic or delayed hemorrhage occurs, the 5-HT released from platelets sensitizes the vascular bed to 5-HT, so that if a second hemorrhage and they may, therefore, have greater ischemic problems. This clinical observation also correlates with the reports that chronic or delayed spasm differs from acute or immediate spasm.1-11

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