Background and Purpose—Disturbances in cerebral arteriolar function, in addition to large vessel vasospasm, may be responsible for ischemia after subarachnoid hemorrhage. The purpose of this study was to test the hypothesis that subarachnoid hemorrhage alters cerebral microvascular reactivity.

Methods—An endovascular filament model was used to induce subarachnoid hemorrhage in halothane-anesthetized male Sprague-Dawley rats. We evaluated pial arteriolar responses to sciatic nerve stimulation, topically applied vasoactive agents (adenosine or sodium nitroprusside), and CO$_2$ inhalation in rats subjected to subarachnoid hemorrhage at 1 to 5 days after insult.

Results—In sham-operated rats, sciatic nerve stimulation evoked a 23.5±1.8% increase in arteriolar diameter, which was significantly attenuated to 13.7±0.9%, 12.8±2.5%, and 18.8±2.9% at 24, 48, and 72 hours after subarachnoid hemorrhage, respectively (P<0.05; n=7). At 96 and 120 hours after subarachnoid hemorrhage, sciatic nerve stimulation-induced dilation recovered to sham levels. Somatosensory-evoked potentials were unaltered by subarachnoid hemorrhage. Pial vasodilatation to adenosine (10 µmol/L) and sodium nitroprusside (1 µmol/L) were significantly impaired, by 47% and 41%, respectively, at 48 hours after subarachnoid hemorrhage (P<0.05; n=7). In contrast, CO$_2$ reactivity was unaffected by subarachnoid hemorrhage.

Conclusions—Pial arteriolar responses to cortical activation may be decreased in the initial 2 to 3 days after experimental subarachnoid hemorrhage. (Stroke. 2007;38:1329-1335.)

Key Words: cerebral arterioles • somatosensory stimulation • subarachnoid hemorrhage

Outcome after rupture of a cerebral aneurysm remains poor and is associated with 30-day mortality rates between 45% and 80%, with half of all survivors sustaining irreversible brain damage.¹ One significant cause of morbidity and mortality after subarachnoid hemorrhage (SAH) is cerebral ischemia,² believed to be the result of vasospasm affecting the larger vessels in the brain. Consequently, previous research has focused on mechanisms involved in cerebral vasospasm of larger vessels in the brain.³⁻⁵ In contrast, Geraud et al demonstrated ischemic deficits in the absence of vasospasm on angiography.⁶ Other investigators have also reported microvasospasm in humans using MRI⁷ and orthogonal polarization spectral imaging.⁸ Thus, in addition to large vessel vasospasm, disturbances in cerebral arterioles may be responsible for ischemia after SAH.

The small arteries and arterioles of the brain are a major site of vascular resistance and, consequently, play a significant role in the regulation of cerebral blood flow (CBF).⁹,¹⁰ As in clinical studies, experimental SAH data are mainly derived from studies of large cerebral arteries. However, several recent studies have examined the changes in the microcirculation after SAH. For example, Ishiguro et al evaluated pressure-induced constriction in small diameter cerebral arteries using a rabbit model of SAH. Their results suggest that increased constrictive reactivity in small diameter cerebral arteries may play a role in the pathogenesis of decreased CBF associated with SAH.¹¹ Another study by Park et al showed early endothelial dysfunction in vitro in cortical arterioles in a rat SAH model. Vasomotor responses were abnormal in arterioles from animals subjected to SAH, such that dilation to the endothelium dependent dilator adenosine diphosphate was attenuated while constriction to endothelin-1 was accentuated.

The purpose of the present study was to test the hypothesis that SAH alters cerebral microvascular reactivity. We determined pial arteriolar responses to cortical activation during sciatic nerve stimulation, vasoactive agents (adenosine, nitric oxide [NO]), and systemic hypercapnia at 1 to 5 days after SAH.
Methods

Approval from the University of Washington Animal Welfare Committee was obtained before any experimentation. A total of 76 animals were used in this study. The animals were obtained from Charles River Laboratories, Wilmington, Mass. Success rates for the SAH procedure and cranial window experiments were ~80% and 75%, respectively. Taking into account our procedural and experimental success rates, 47 animals were used for data analysis, 35 of which were subjected to SAH and 12 assigned to the naïve and sham groups.

Endovascular Filament Model of SAH

We used the endovascular filament technique for inducing SAH in male Sprague-Dawley rats weighing 350 to 450 grams. The rats were intubated, ventilated, and maintained under halothane anesthesia (1.5% to 2.0%). The tail artery was cannulated for monitoring blood pressure and for blood gas determination. Body temperature was maintained at 37°C. The atlanto-occipital membrane was fitted with a PE-50 catheter for monitoring intracranial pressure (ICP) and maintained at 37°C. The tail artery was cannulated for monitoring blood pressure, blood gas determination, and intravenous administration. A recording electrode, secured over the cortex, allowed simultaneous measurement of somatosensory-evoked potentials (SEPs) and arteriolar diameter. The exposed contralateral sciatic nerve was placed on stimulating electrodes and halothane anesthesia was replaced with α-chloralose and urethane (50 and 500 mg/kg, respectively, intraperitoneal). Stimulation parameters consisted of 0.2-V, 0.5-ms rectangular pulses at 5 Hz for 20 seconds. The rats were allowed to survive for 1 to 5 days after SAH. Naïve animals were not subjected to any of the SAH procedural operations; shams underwent exposure of the ICA and introduction of the prolene filament, but no SAH was induced.

Cranial Window Preparation

A closed cranial window preparation and the sciatic nerve stimulation (SNS) paradigm in the rat has been published previously. Briefly, rats subjected to SAH were anesthetized with 1.5 to 2.0% halothane. The right femoral artery and vein were cannulated for monitoring blood pressure, blood gas determination, and intravenous drug administration. The rats were tracheostomized, immobilized with D-tubocurarine chloride (1 mg/kg, intravenous), and mechanically ventilated. Body temperature was maintained at 37°C. A cranial window (4×6 mm) was created over the right hemisphere, fully exposing the dorsal surface branches of the middle cerebral artery in the hindlimb sensory cortex. The pial arterioles were quantified online using a video microscope system and an automated dimension analyzer. A recording electrode, secured over the cortex, allowed simultaneous measurement of somatosensory-evoked potentials (SEPs) and arteriolar diameter. The exposed contralateral sciatic nerve was placed on stimulating electrodes and halothane anesthesia was replaced with α-chloralose and urethane (50 and 500 mg/kg, respectively, intraperitoneal). Stimulation parameters consisted of 0.2-V, 0.5-ms rectangular pulses at 5 Hz for 20 seconds. Arteriolar responses to SNS were calculated as percent increase over resting diameter. SEPs were recorded and evaluated as previously described.

Experimental Protocol

Cortical Activation by SNS

In all experiments, arterial blood pressure and blood gases were maintained within physiological range. During SNS, changes in pial arteriolar diameter and SEPs were observed and recorded. A minimum of 3 consistent responses to SNS was obtained.

Microcirculatory Response to Adenosine and SNP

We then evaluated dose-dependent arteriolar reactivity to topical application of either adenosine (ADO) or SNP. Each concentration of ADO or SNP was applied for 5 minutes, followed by a 2-minute equilibration period and vessel diameter measurement before proceeding to the next higher concentration. A 5-minute washout period with artificial cerebrospinal fluid was performed to return pial arteriolar diameter to baseline and then the same procedure was repeated with topical application of SNP. Mean arterial blood pressure (MABP) and arterial blood gases were maintained stable throughout the entire duration of the experiment.

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SAH Procedural Data: Physiological Parameters

SAH resulted in an increase in ICP from a baseline of 61.1±0.4 mm Hg to 63.9±5.3 mm Hg (Figure 1; n=35, P<0.01, comparable to previous studies using this technique). MABP was kept stable within physiological range throughout the SAH procedure. Before induction of SAH, MABP was 92.3±6.1 mm Hg. Advancement of a 4-0 prolene filament caused a transient decrease in MABP to 85.5±2.6 mm Hg, which returned to pre-SAH values within 5 to 10 minutes after SAH induction (Figure 1). Before SAH, arterial pH, PCO₂, and PO₂ were 7.38±0.02, 33.5±1.2 mm Hg, and 116.1±8.0 mm Hg, respectively, and not significantly different compared with post-SAH values. Core temperature was maintained at 37°C with an isothermal heat pad.

Effect of SAH on Pial Arteriolar Response to SNS

Physiological parameters were monitored and maintained within physiological range throughout the experiments. MABP was stable before and during cortical activation by SNS (Table 1). In sham-treated animals (n=7), pial arterioles dilated 23.6±1.8% in response to contralateral SNS (P<0.001 compared with resting diameter). This response

Figure 1. MABP and intracranial pressure before, during, and after subarachnoid hemorrhage induced by the endovascular filament model. All values are expressed as means±standard deviation (SD); n=35. *P<0.01 compared with pre-SAH.

Microcirculatory Response to Alteration in PaCO₂

We evaluated reactivity of pial arterioles to CO₂ inhalation as previously described. The respirator was switched to a special gas mixture containing 6% CO₂, 34% O₂, and 60% N₂ for 2 minutes. Changes in pial arteriolar diameter and PaCO₂ were quantified for calculation of CO₂ reactivity. CO₂ reactivity is expressed as percent increase in diameter per mm Hg increase in PaCO₂.

Statistical Analysis

Data and statistical analyses were performed as previously described. All values are expressed as means±standard deviation. Changes in pial arteriolar diameter were calculated as percent of control diameter. Intergroup differences were determined using a 1-way ANOVA. Bonferroni test was then applied for post-hoc comparisons. P<0.05 was used to indicate statistically significant differences.

Results

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was similar to the reactivity observed in the naive group of animals (27.03 ± 3.0%, n=5).

In the rats subjected to SAH, cerebral arteriolar reactivity to SNS was significantly impaired at 24, 48, and 72 hours after SAH (Figure 2; n=6; *P<0.01 compared with sham). However, by 96 hours after SAH, SNS-induced vasodilation to cortical activation was no longer significantly different from sham. In contrast, simultaneously recorded SEPs were not significantly different among any of the experimental groups (data not shown).

Effect of SAH on Pial Arteriolar Response to Topically Applied Adenosine or SNP

We also evaluated dose-dependent responses of pial arterioles, in vivo, to the vasodilators, ADO and SNP (NO donor). Physiological parameters were not different among all the groups (Table 1). The effects of SAH on vasodilation to topical application of ADO are depicted in Figure 3. Pial vasodilation to ADO (1, 10, and 100 μmol/L) was significantly (P<0.01) attenuated at 48 hours as compared with sham-treated animals. At 72 hours after SAH and thereafter, the response to topical ADO remained decreased but did not differ significantly from baseline responses.

The effects of SAH on vasodilation induced by topical SNP are shown in Figure 4. Arteriolar dilation to topical application of SNP was significantly depressed at 48 and 72 hours after SAH. The magnitude of attenuation was similar at both doses and at both time periods after SAH. The effects of SAH were transient, such that by 96 hours after SAH, arteriolar reactivity to SNP returned to baseline values.

Effect of SAH on Pial Arteriolar Reactivity to CO2 Inhalation

Data summarizing the effect of SAH on pial arteriolar reactivity to CO2 inhalation is presented in Table 2. Physiological parameters were stable and maintained within normal physiological range before and during CO2 inhalation. During hypercarbia, PacO2 increased ≈15 mm Hg and was comparable in each of the experimental groups. MABP was stable before and during CO2 inhalation. Moreover, our data revealed that SAH did not significantly affect pial arteriolar response to hypercarbia.

<p>| TABLE 1. Resting Pial Arteriolar Diameter and Physiological Data Before and During SNS |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Naive</th>
<th>Sham</th>
<th>24 Hours</th>
<th>48 Hours</th>
<th>72 Hours</th>
<th>96 Hours</th>
<th>120 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting diameter</td>
<td>39.1±7.1</td>
<td>36.6±3.0</td>
<td>37.1±3.9</td>
<td>33.6±6.3</td>
<td>33.5±4.8</td>
<td>36.1±7.5</td>
<td>37.4±5.4</td>
</tr>
<tr>
<td>Peak diameter</td>
<td>48.7±10.7</td>
<td>44.7±5.4</td>
<td>43.1±6.9</td>
<td>37.4±7.2</td>
<td>43.7±12.8</td>
<td>43.3±9.1</td>
<td>47.0±8.9</td>
</tr>
<tr>
<td>MABP1</td>
<td>103.2±11.4</td>
<td>102.5±13.5</td>
<td>106.0±11.1</td>
<td>97.7±12.9</td>
<td>98.5±14.2</td>
<td>96.3±8.6</td>
<td>93.8±17.8</td>
</tr>
<tr>
<td>MABP2</td>
<td>106.7±13.4</td>
<td>103.2±16.8</td>
<td>106.5±12.1</td>
<td>101.5±17.4</td>
<td>100.1±17.2</td>
<td>97.8±9.0</td>
<td>94.8±16.7</td>
</tr>
<tr>
<td>ABG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.35±0.06</td>
<td>7.36±0.06</td>
<td>7.39±0.03</td>
<td>7.38±0.03</td>
<td>7.38±0.05</td>
<td>7.34±0.03</td>
<td>7.39±0.06</td>
</tr>
<tr>
<td>PacO2</td>
<td>35.0±2.8</td>
<td>34.9±3.8</td>
<td>32.6±14.1</td>
<td>31.5±3.1</td>
<td>31.7±6.0</td>
<td>34.1±2.9</td>
<td>30.7±4.8</td>
</tr>
<tr>
<td>PacO2</td>
<td>110.7±8.7</td>
<td>123.1±19.5</td>
<td>117.7±5.8</td>
<td>114.3±22.2</td>
<td>115.1±23.8</td>
<td>117.9±15.5</td>
<td>117.8±11.9</td>
</tr>
<tr>
<td>n</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

Resting and Peak Diameters are expressed as μm. MABP1 indicates mean arterial blood pressure prior to sciatic nerve stimulation (SNS); MABP2, mean arterial blood pressure during SNS; ABG, arterial blood gases prior to SNS. PacO2 and PacO2 are expressed as mm Hg. All values are expressed as means±SD.

Figure 2. Effect of subarachnoid hemorrhage on pial arteriolar dilation to contralateral SNS. Values are expressed as means±SD. *P<0.01 and n=6.

Figure 3. Dose-response of pial arterioles, in vivo, to topically applied ADO before and after subarachnoid hemorrhage. Values are expressed as means±SD. *P<0.01 vs sham; n=6.
microvascular reactivity, few studies have addressed the effects of SAH on the cerebral microvascular reactivity.\(^{19–21}\) In the present study, SAH resulted in a significant (\(\approx 45\%), P<0.01\)) reduction of pial arteriolar response to SNS at 24, 48, and 72 hours after insult. In contrast to the vascular response, SAH in the present study had no effect on SEPs. Thus, the diminished microcirculatory response between 24 and 72 hours after SAH cannot be attributed to alterations in evoked neuronal or metabolic activity. Our observations in the rat is consistent with clinical studies in which evoked potentials remain constant after moderate SAH.\(^{22}\)

At the time of SAH, a sharp increase in ICP coupled with a decrease in CBF has commonly been reported.\(^{23}\) The decrease in CBF in the early time periods after SAH may represent an ischemic episode as a result of elevated ICP.\(^{23}\) Thus, it is possible that elevated ICP after SAH may be a primary factor in predicting SAH-induced alterations in cerebrovascular physiology. However, several previous studies provide evidence that elevated ICP alone cannot account for alterations in CBF patterns or the onset of vasospasm after SAH.\(^{23}\) Nevertheless, the present study cannot rule out the possibility that the spike in ICP associated with the induction of SAH may contribute to compromised arteriolar reactivity during somatosensory stimulation.

In our model of cortical activation, pial arterioles supplying the hindlimb somatosensory cortex dilate in response to contralateral SNS.\(^{14}\) The precise mechanism of this dilation response remains unclear, but likely involves initiation of the dilator signal in the brain parenchyma subsequent to synaptic activity, and upstream travel of a dilator signal to pial arterioles. Various vasoactive metabolites and chemicals, including ADO and NO, have been proposed to contribute to the initial intraparenchymal vasodilator response. In the present study, the loss in SNS-induced dilation paralleled the impairment in the reactivity of pial arterioles to ADO or a NO donor, suggesting that reduced arteriolar reactivity to mediators of neurovascular coupling contributes to the attenuation of pial arteriolar response to SNS after SAH. However, SAH may also impair SNS-induced pial vascular responses by

### Table 2. Effect of CO\(_2\) Inhalation on Pial Arteriolar Diameter Before and After Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>After SAH</th>
<th>24 Hours</th>
<th>48 Hours</th>
<th>72 Hours</th>
<th>96 Hours</th>
<th>120 Hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paco(_2)-1</td>
<td>34.2±4.1</td>
<td>32.9±3.7</td>
<td>31.5±2.5</td>
<td>31.9±5.9</td>
<td>31.8±3.1</td>
</tr>
<tr>
<td>Paco(_2)-2</td>
<td>48.3±5.7</td>
<td>46.2±6.1</td>
<td>45.6±5.3</td>
<td>46.4±5.7</td>
<td>42.6±4.8</td>
</tr>
<tr>
<td>% Dilation</td>
<td>23.5±7.5</td>
<td>17.8±5.7</td>
<td>20.8±8.6</td>
<td>19.8±8.5</td>
<td>20.4±11.3</td>
</tr>
<tr>
<td>ΔCO(_2)</td>
<td>14.1±5.7</td>
<td>13.3±5.5</td>
<td>14.1±4.2</td>
<td>14.5±5.9</td>
<td>10.8±6.2</td>
</tr>
<tr>
<td>CO(_2)-R</td>
<td>1.76±0.50</td>
<td>1.47±0.60</td>
<td>1.50±0.57</td>
<td>1.61±0.67</td>
<td>1.96±0.31</td>
</tr>
<tr>
<td>MABP(_1)</td>
<td>103.6±10.1</td>
<td>105.4±8.4</td>
<td>97.7±5.0</td>
<td>105.7±9.0</td>
<td>97.6±10.5</td>
</tr>
<tr>
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<td>103.9±9.7</td>
<td>102.8±9.9</td>
<td>99.7±5.5</td>
<td>106.6±12.0</td>
<td>100.4±9.5</td>
</tr>
</tbody>
</table>

Paco\(_2\) is expressed as mm Hg.

Paco\(_2\)-1 indicates arterial Paco\(_2\) before CO\(_2\) inhalation; Paco\(_2\)-2, arterial Paco\(_2\) during CO\(_2\) inhalation; MABP\(_1\), mean arterial blood pressure before CO\(_2\) inhalation; MABP\(_2\), mean arterial blood pressure during CO\(_2\) inhalation; CO\(_2\)-R, CO\(_2\) reactivity and is expressed a percent increase in arteriolar diameter per ΔCO\(_2\). All values are expressed as means±SD.
disrupting upstream vasomotor conduction, which likely involves the spread of membrane current via gap junctions of endothelial and smooth muscle cells. Consistent with such a hypothesis, oxyhemoglobin treatment markedly impaired vascular conductin in isolated intracerebral arterioles.

**Time Course**

The time course for alterations described in the present study parallel previous reports on histology and vascular reactivity in larger cerebral arteries after experimental SAH in rats. Delgado et al evaluated vertebral-basilar arteries after SAH and reported biphasic development of vasospasm. Maximal acute spasm occurred at 10 minutes after SAH and delayed maximal spasm developed at 48 hours after SAH. Another study by Barry et al reported basilar artery vasospasm that peaks at 2 days after SAH. Interestingly, the time course for alterations in arteriolar reactivity reported in the present study, along with previous descriptions of the onset of vasospasm after experimental SAH in rats, differs from the onset of vasospasm in humans. Whereas the time course of SAH-induced events in rats occurs 1 to 3 days after insult, SAH-induced vasospasm in humans develops 5 to 14 days after aneurysm rupture. We speculate that the difference in time course between humans and rats relates to species differences (including cerebrospinal fluid turnover rates, metabolic rates, etc).

ADO

ADO is a potent cerebral vasodilator and is thought to play an important role in CBF regulation. The actions of adenosine are mediated by 4 receptor subtypes (A<sub>1</sub>, A<sub>2A</sub>, A<sub>2B</sub>, and A<sub>3</sub>). Although activation of adenosine<sub>A<sub>1</sub></sub> receptors has been shown to stimulate adenylate cyclase activity, leading to increased cAMP levels in brain tissue, recent evidence suggests that adenosines effects may also involve a cGMP-dependent pathway, similar to NO. Despite evidence supporting the importance of adenosine in CBF regulation, relatively little is known regarding the potential effects of SAH on the physiological and pathophysiological actions of adenosine. In the present study, ADO-induced vasodilatation of pial arterioles was significantly attenuated beginning at 48 hours after SAH. Our observations are consistent with a recent study demonstrating that ADO-induced vasodilatation of intracerebral arterioles, in vitro, is significantly attenuated by oxyhemoglobin. Our findings, however, contrast with other studies in which ADO-induced vasodilatation of rat basilar artery was unaffected by SAH. Moreover, SAH had no effect on 3',5' cAMP formation in dog basilar arteries. The different models of SAH used (autologous blood injection versus endovascular filament model) and analysis of different cerebral vascular beds (basilar artery versus pial arteriole) may account for the disparate reports, and emphasizes the need for more studies on cerebral arterioles if meaningful comparisons are to be made.

NO

Like adenosine, NO is an important regulator of cerebral vascular tone and a purported mediator of neurovascular coupling. The specific role of NO in cerebrovascular physiology after SAH remains unclear. The results of the present study demonstrate that dose-dependent dilations to the NO donor SNP were significantly attenuated after SAH. Our observations are in agreement with several previous studies demonstrating that cerebral vasodilatation to NO donor compounds is significantly impaired after SAH. In contrast to the present study, other studies have reported a lack of effect of SAH on vasodilatation to NO donor compounds. The reason for the discrepancy in findings is unclear, but may be related to the different methods for inducing SAH, the different post-SAH time period analysis, and the different vascular beds within the cerebral circulation (arteries versus arterioles).

**Mechanism for Impairment of Vascular Reactivity by SAH**

Previous findings, derived mainly from studies on large cerebral arteries, suggest that deleterious agents released during lysis of blood clots, including oxyhemoglobin, bilirubin, and free radicals, may damage both vascular and neuronal tissue. In addition to being a potent NO scavenger, hemoglobin may destroy NO-releasing neurons, and directly inactivate guanylate cyclase by oxidation, thus decreasing production of cGMP. These actions of hemoglobin may explain the attenuation of cerebral dilation responses to NO donors observed in the present and previous studies. Free oxygen radicals released by hemoglobin breakdown also may attack specific membrane-bound receptors, including ADO receptors, thus leading to a reduced response to ADO.

The perivascular presence of large amounts of hemoglobin after SAH has been shown to attenuate conducted dilation responses in intracerebral arterioles to ATP and adenosine. SAH may also cause the release of pathogenic factors, such as endothelin, vascular endothelial growth factor, free radicals, and cytokines that are known to disrupt gap junction communication. The mechanisms whereby these agents attenuate gap junction activity may involve either connexin phosphorylation or alteration of gap junction expression. Because the dilation response of pial arterioles during somatosensory stimulation likely involves intercellular communication, SAH may therefore disrupt neurovascular coupling after SAH.

**CO<sub>2</sub> Reactivity**

Vasodilatation of pial arterioles to hypercapnia is thought to be dependent on the reduction of pH subsequent to an increase in CO<sub>2</sub> partial pressure. In the present study, SAH had no effect on pial arteriolar reactivity to hypercapnia. Previous clinical and experimental studies on the effects of SAH on CO reactivity reported disparate results. For example, CO<sub>2</sub> reactivity was chronically (hours to days) preserved in dogs, rabbits, and rats subjected to SAH. A lack of response to changes in Paco<sub>2</sub> has also been observed during acute time periods (ie, minutes) after SAH. In contrast, SAH attenuated CO<sub>2</sub> reactivity in other studies. However, meaningful comparisons between the various studies can be problematic because of the various models of SAH used and the differences in post-SAH time period evaluations. Although vasodilation to hypercapnia was not
significantly altered after SAH in the present study, it is uncertain whether the phenomenon of reduced vasodilation is restricted to pathways associated with SNS-induced vasodilation. Nevertheless, our observations of attenuated pial arteriolar response to somatosensory stimulation and to pharmacological stimulation coupled with the fact that SAH had no effect on CO2 reactivity leads us to conclude that SAH does not result in nonspecific cerebral arteriolar paralysis. Instead, mechanisms responsible for arteriolar responses during somatosensory stimulation and to pharmacological manipulation appear to be specifically altered by SAH.

Previous reports suggest that CO2 reactivity may involve NO production. However, the role of NO in hypercarbia-induced vasodilation of cerebral arterioles appears to be controversial.47–50 NO may play a permissive role by maintaining the requisite level of cGMP for the manifestation of CO2-induced dilation.

Cerebral vasodilatation in response to CO2 inhalation is well-described,81 likely affecting ion channels directly. The CO2-mediated increase in hydrogen ion concentration and decrease in brain extracellular pH is the initial step leading to changes in vascular tone. Hydrogen ion accumulation can, among other things, lead to alterations in Ca++ channel activity on vascular smooth muscle cells causing vasodilatation.52,53 However, adenosine must first activate a receptor, which then triggers a signal transduction pathway involving intermediaries such as phosphodiesterases, cyclic nucleotides, protein kinases, all of which are upstream from ion channel activity.54,55 Similarly, the effects of NO on vascular tone is influenced by guanylate cyclase activation, accumulation of cGMP, phosphodiesterase activity, and other signal transduction events that are upstream of ion channel activation. Thus, we would surmise that ion channel activation during CO2-induced cerebral vasodilatation is selectively preserved after SAH. In contrast, SAH may be affecting the signal transduction events (upstream of ion channels) involved in adenosine or NO-mediated vasodilation.

In summary, the results of the present study demonstrate time-dependent alterations in arteriolar reactivity after SAH. Cerebral arteriolar response to somatosensory stimulation was significantly attenuated after SAH. The effects of SAH peaked at 48 hours and returned to normal by 96 hours after insult. Because SAH had no effect on SEPs, the attenuated arteriolar response to somatosensory stimulation cannot be attributed to alterations in evoked neuronal or metabolic activity. SAH also significantly attenuated vasodilatation to ADO and NO (SNP), both purported mediators of CBF regulation during somatosensory stimulation. The effects of SAH on ADO and NO-induced pial vasodilatation paralleled the effects of SAH on SNS-induced vasodilatation. SAH, however, had no effect of cerebral arteriolar reactivity to CO2, suggesting that SAH was not evoking nonspecific arteriolar paralysis.

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Disclosures

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References


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