Effects of Ischemia on Cerebral Arteriolar Dilation to Arterial Hypoxia in Piglets

Ferenc Bari, PhD; Thomas M. Louis, PhD; David W. Busija, PhD

Background and Purpose—Arterial hypoxia mediates cerebral arteriolar dilation primarily via mechanisms involving activation of ATP-sensitive K⁺ channels (KATP), which we have shown to be sensitive to ischemic stress. In this study, we determined whether ischemia/reperfusion alters cerebral arteriolar responses to arterial hypoxia in anesthetized piglets. Since adenosine plays an important role in cerebrovascular responses to hypoxia, we also determined whether adenosine-induced arteriolar dilation is affected by ischemic stress. We tested the hypothesis that reductions in cerebral arteriolar dilator responses after ischemia would be proportional to the contribution of KATP to hypoxia and adenosine.

Methods—Pial arteriolar diameters were measured using a cranial window and intravital microscopy. We examined arteriolar responses to arterial hypoxia (inhalation of 8.5% and 7.5% O₂), to topical adenosine (10⁻⁵ and 10⁻⁴ mol/L) and to arterial hypercapnia (inhalation of 5% and 10% CO₂ in air) before and after 10 minutes of global ischemia. Ischemia was achieved by increasing intracranial pressure. Arterial hypercapnia was used as a positive control for the effectiveness of the ischemic insult. In addition, we evaluated cerebral arteriolar responses to 10⁻⁵ and 10⁻⁴ mol/L adenosine applied topically with or without glibenclamide, a selective inhibitor of KATP (10⁻⁵ and 10⁻⁶ mol/L). Finally, we administered theophylline (20 mg/kg, IV) to assess the contribution of adenosine to cerebral arteriolar dilation to arterial hypoxia.

Results—Before ischemia, cerebral arterioles dilated by 19±3% to moderate and 29±4% to severe hypoxia (n=7; P<.05); 13±2% to 10⁻⁵ and 20±1% to 10⁻⁴ mol/L adenosine (n=9; P<.05); and by 17±2% to moderate and 28±3% to severe hypercapnia (n=6; P<.05). After ischemia, cerebral arteriolar responses to hypoxia and adenosine were unchanged. In contrast, cerebral arteriolar dilation to hypercapnia was impaired by ischemia (1±1% and 2±1% at 1 hour; n=6). Glibenclamide reduced cerebral arteriolar dilation to adenosine by approximately one half (n=7). In addition, blockade of adenosine receptors by theophylline (20 mg/kg, IV) almost totally suppressed cerebral arteriolar dilation to arterial hypoxia (n=6).

Conclusions—Cerebrovascular responsiveness is selectively affected by anoxic stress. In addition, cerebral arteriolar dilation to hypoxia and adenosine is maintained after ischemia despite the expected impairment in KATP function. (Stroke. 1998;29:222-228.)

Key Words: cerebral arteries ■ cerebral circulation ■ vasodilation ■ adenosine ■ calcium channels ■ hypercapnia

Arterial hypoxia is a potent dilator stimulus in the cerebral circulation. Previous studies have provided evidence that adenosine, nitric oxide, prostanooids, opioids, and/or vasopressin promote cerebrovascular dilation to arterial hypoxia.1–12 The relative contribution of these substances to hypoxia-induced cerebrovascular dilation probably reflects differences in the species studied, the experimental approaches, and the variability of the severity and duration of hypoxic challenge.10 However, several lines of evidence indicate that an elevation of interstitial adenosine concentration is critical to eliciting hypoxic dilation of pial arterioles in newborn pigs.4,7,9 Furthermore, activation of KATP may mediate a substantial part of the cerebrovascular dilation to arterial hypoxia.4,12,11 This conclusion is based on the finding that application of selective KATP blockers attenuates cerebral arteriolar dilation to arterial hypoxia4,13,14 as well as to adenosine.4 In general, inhibition of KATP reduces cerebral arteriolar dilation to arterial hypoxia or adenosine by approximately 50%.

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In recent studies, we showed that KATP function in cerebral arterioles is impaired after ischemia. Thus, pial arteriolar dilations in piglets to aprikalim, CGRP, and iloprost, pharmacological and physiological activators of KATP, are largely absent 1 to 2 hours after 10 minutes of total global ischemia.15,16 In contrast, ischemia fails to alter cerebrovascular dilation to several stimuli that are not dependent on activation of KATP.15,17 The purpose of this study was to examine the effects of ischemia on cerebral arteriolar dilation to arterial hypoxia in
piglets. This is an important issue because derangements of arterial blood gases and local ischemia often occur after successful resuscitation of babies that follows anoxic stress. In addition, we examined the effects of ischemia on cerebral arteriolar dilation to adenosine. Topical adenosine allows assessment of effects of ischemia on a major component of the arteriolar dilator response to arterial hypoxia, without the presence of other, possibly complicating features, of hypoxia. We tested the hypothesis that ischemia-induced reductions in cerebral arteriolar dilation to arterial hypoxia and adenosine would be in proportion to dependence of these dilator responses to \( K_{ATP} \). In addition, we also examined the effects of ischemia on arteriolar dilation to arterial hypercapnia to validate the potency of the ischemic stress.\(^1\)

### Materials and Methods

#### Surgical Preparation

Experiments were carried out on newborn pigs (1 to 7 days old) of either sex weighing 1 to 2 kg. The procedures used in this study were approved by the Institutional Animal Care and Use Committee. The piglets were anesthetized with sodium thiopental (30 mg/kg, IP) and then \( \alpha \)-chlordone was given as needed to maintain a stable level of anesthesia. The piglets were intubated and artificially ventilated. A femoral artery and vein were cannulated with PE-90 tubing. Arterial blood pressure, blood gas values, and \( \mathrm{Pb} \) were maintained within the normal physiological range. Each piglet’s head was fixed in a stereotaxic apparatus, the scalp was cut, and the connective tissue over the parietal bone was removed. A cranietomy (19 mm in diameter) was made in the parietal bone. The dura was cut and reflected over the skull. A stainless steel and glass cranial window with three ports was put into the opening, sealed with bone wax, and cemented with cyanoacrylate ester and dental acrylic. After implantation of the window and the bolt, aCSF was allowed to equilibrate with the periarachnoid CSF under the window for 20 minutes. To induce ischemia, aCSF was infused to maintain intracranial pressure above mean arterial pressure so that blood flow through pial vessels was stopped. Venous blood was withdrawn as necessary to maintain mean arterial blood pressure near normal values. At the end of the 10-minute period of ischemia, the infusion tube was clamped, and the intracranial pressure was allowed to return to preischemia values.

### Experimental Design

#### Interaction Between Global Ischemia and Arterial Hypoxia

At the beginning of each experiment, the cranial window was flushed with aCSF several times. Then, cerebral arteriolar responses were determined to two levels of arterial hypoxia (administration of 7.5% and 8.5% \( \mathrm{O}_2 \) in nitrogen). The exposure to each level of gas was limited to 3 to 4 minutes for two reasons. First, a 3- to 4-minute period of arterial hypoxia is sufficient to achieve maximal arteriolar dilation in piglets, as described by Leffler et al.\(^1\) And, second, repeated exposure to longer periods of arterial hypoxia might compromise the cerebral circulation when combined with ischemia. Animals were subsequently divided into either sham (\( n=6 \)) or ischemia (\( n=7 \)) groups. Animals in the sham group were exposed to two levels of hypoxia 1 hour after the first exposure. In the ischemia group, after recovery, animals were exposed to cerebral ischemia for 10 minutes. At 1, 2, and 4 hours after ischemia, cerebral arteriolar responses were again examined at both levels of arterial hypoxia.

#### Interaction of Ischemia with the Vasodilation to Adenosine

We examined pial arteriolar diameter changes after topical application of adenosine (at \( 10^{-5} \) and \( 10^{-4} \) mol/L). In one group of animals, we determined whether arteriolar responses to adenosine are reproducible over time (\( n=6 \)). Each dose of adenosine in aCSF was introduced into the window, the infusion was stopped, and pial arteriolar diameters were recorded over the next 5 to 10 minutes. In a separate group, cerebral arteriolar responses to topical adenosine (\( n=9 \)) were determined before and 1 hour after ischemia.

### Table 1. Arteriolar Responses to Hypoxia

<table>
<thead>
<tr>
<th>Diameter, ( \mu m )</th>
<th>8.5% ( \mathrm{O}_2 )</th>
<th>7.5% ( \mathrm{O}_2 )</th>
<th>8.5% ( \mathrm{O}_2 )</th>
<th>7.5% ( \mathrm{O}_2 )</th>
<th>8.5% ( \mathrm{O}_2 )</th>
<th>7.5% ( \mathrm{O}_2 )</th>
<th>8.5% ( \mathrm{O}_2 )</th>
<th>7.5% ( \mathrm{O}_2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Diameter, ( \mu m )</td>
<td>102±2</td>
<td>159±2</td>
<td>130±3*</td>
<td>98±3</td>
<td>118±3*</td>
<td>130±4*</td>
<td>101±3</td>
<td>118±4*</td>
</tr>
<tr>
<td>( \Delta )Diameter, ( \mu m )</td>
<td>19±1</td>
<td>30±4*</td>
<td>20±4</td>
<td>32±4*</td>
<td>27±1</td>
<td>32±4*</td>
<td>20±4</td>
<td>32±4*</td>
</tr>
<tr>
<td>( \Delta )pH</td>
<td>7.42±0.02</td>
<td>7.40±0.03</td>
<td>7.41±0.03</td>
<td>7.38±0.03</td>
<td>7.38±0.04</td>
<td>7.38±0.04</td>
<td>7.40±0.03</td>
<td>7.38±0.04</td>
</tr>
<tr>
<td>P(( \mathrm{O}_2 ))</td>
<td>32±3</td>
<td>33±2</td>
<td>33±3</td>
<td>31±2</td>
<td>32±2</td>
<td>31±3</td>
<td>32±2</td>
<td>31±3</td>
</tr>
<tr>
<td>P(( \mathrm{O}_2 ))</td>
<td>91±4</td>
<td>32±2*</td>
<td>25±2*</td>
<td>91±4</td>
<td>31±2*</td>
<td>24±2*</td>
<td>91±4</td>
<td>31±2*</td>
</tr>
</tbody>
</table>
| *Values are mean±SEM; \( n=4 \) for sham group and \( n=7 \) for ischemia group. \( *P<0.05 \) compared with corresponding control; \( \dagger P<0.05 \), compared with 8.5% \( \mathrm{O}_2 \) inhalation.
**Contribution of K<sub>ATP</sub> to Adenosine-Evoked Arteriolar Dilation**

In two separate groups of animals, we monitored the effect of glibenclamide on adenosine-evoked cerebral arteriolar responses. We performed these experiments because the contribution of K<sub>ATP</sub> in mediating adenosine-induced dilation is controversial. We and others have shown previously that these doses of glibenclamide given in this way are effective and specific in blocking cerebral arteriolar dilation to aprikalim, a selective activator of K<sub>ATP</sub>.

**Blade of Adenosine Receptors During Hypoxia**

We determined cerebral arteriolar dilator responses during arterial hypoxia before and 15 minutes after intravenous administration of theophylline (20 mg/kg) (n=6). We did these experiments because the contribution of adenosine to cerebral arteriolar dilation in piglets is controversial. To document effectiveness of blockade, we also determined dilator responses to topical adenosine (10<sup>-5</sup> and 10<sup>-4</sup> mol/L) before and after administration of theophylline (n=4).

**Interaction between Ischemia and Arterial Hypercapnia**

As a positive control, effects of ischemia on arteriolar responses to arterial hypercapnia were examined. In the ischemia group (n=6), pial arteriolar responses to arterial hypercapnia (5% and 10% CO<sub>2</sub> in air) were examined before and 1 and 2, and 4 hours after ischemia. Piglets were exposed to each level of gas for at least 10 minutes. In the sham group (n=4), the hypercapnic challenge was repeated at 1, 2, and 4 hours after the first hypercapnic episode.

**Statistical Analysis**

All values are expressed as mean±SEM. When appropriate, data were analyzed using the paired t test or repeated measures ANOVA, or one way ANOVA. When the F value was significant, pair-wise comparisons were made using the Student-Newman-Keuls test. A value of P<.05 was considered statistically significant.

**Results**

Arterial hypoxia dilated pial arterioles in a dose-dependent fashion (Table 1; Fig 1). Repeated hypoxia resulted in reproducible cerebral arteriolar dilation over time without altering baseline diameters (Table 1). Baseline arteriolar diameters were not different at 1, 2, or 4 hours after ischemia (Table 1). Cerebral arteriolar dilation to hypoxia was not significantly reduced at 1, 2, or 4 hours after ischemia (Table 1; Fig 1).

**TABLE 2. Arteriolar Responses to Adenosine**

<table>
<thead>
<tr>
<th>Group</th>
<th>First Application</th>
<th>Second Application</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
</tr>
<tr>
<td>Group 1, n=6</td>
<td>Baseline</td>
<td>113±2*</td>
</tr>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>99±2</td>
</tr>
<tr>
<td>Group 2, n=9</td>
<td>Baseline</td>
<td>118±4*</td>
</tr>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>104±3</td>
</tr>
<tr>
<td>Group 3, n=6</td>
<td>Baseline</td>
<td>116±1*</td>
</tr>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>103±2</td>
</tr>
<tr>
<td>Group 4, n=7</td>
<td>Baseline</td>
<td>113±5*</td>
</tr>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>100±4</td>
</tr>
<tr>
<td>Group 5, n=4</td>
<td>Baseline</td>
<td>112±3*</td>
</tr>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>101±2</td>
</tr>
</tbody>
</table>

*P<.05 compared with baseline; †P<.05 compared with the lower dose; **P<.05 compared with corresponding control.

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**Figure 1.** Percent change from control arteriolar diameter during two different levels of hypoxic hypoxia (inhaltion of 8.5% or 7.5% O<sub>2</sub>, balance in N<sub>2</sub>; hatched and solid bars, respectively) before (control) and 1, 2, and 4 hours after 10 minutes of global cerebral ischemia. Values are mean±SEM for 7 animals. 

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**TABLE 1. Arteriolar Responses to Adenosine**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</th>
<th>10&lt;sup&gt;-4&lt;/sup&gt; mol/L</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diameter, μm</td>
<td>Diameter, μm</td>
<td>Diameter, μm</td>
</tr>
<tr>
<td>Group 1, n=6</td>
<td>Baseline</td>
<td>113±2*</td>
<td>120±2†</td>
</tr>
<tr>
<td></td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
<td>14±1</td>
<td>21±1*</td>
</tr>
<tr>
<td>Group 2, n=9</td>
<td>Baseline</td>
<td>118±4*</td>
<td>125±5†</td>
</tr>
<tr>
<td></td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
<td>14±2</td>
<td>21±2*</td>
</tr>
<tr>
<td>Group 3, n=6</td>
<td>Baseline</td>
<td>116±1*</td>
<td>124±1†</td>
</tr>
<tr>
<td></td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
<td>13±1</td>
<td>21±2*</td>
</tr>
<tr>
<td>Group 4, n=7</td>
<td>Baseline</td>
<td>113±5*</td>
<td>125±6†</td>
</tr>
<tr>
<td></td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
<td>13±2*</td>
<td>25±3†</td>
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<tr>
<td>Group 5, n=4</td>
<td>Baseline</td>
<td>112±3*</td>
<td>121±2†</td>
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<tr>
<td></td>
<td>10&lt;sup&gt;-5&lt;/sup&gt; mol/L</td>
<td>11±1*</td>
<td>20±1†</td>
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</table>
Adenosine caused dose-dependent pial arteriolar dilation (Table 2; Fig 2). Repeated application of adenosine resulted in reproducible cerebral arteriolar dilation over time without altering baseline diameters (Table 2). As shown in Fig 2, pial arteriolar dilation to adenosine was unaffected by ischemia.

Topical application of glibenclamide in concentrations of 10^{-6} or 10^{-5} mol/L did not change baseline pial arteriolar diameters (Table 2). In the two groups, before application of the K_{ATP} antagonist, baseline diameters were 104.2 ± 2 and 101.3 ± 3 μm, and diameters were 106.2 ± 2 and 100.4 ± 4 μm 5 minutes later, respectively, for the two concentrations. Cerebral arteriolar dilation to adenosine was reduced by approximately one half at either dose of glibenclamide (Table 2).

Pial arteriolar dilator responses to hypoxia were reduced after intravenous administration of theophylline. At 15 minutes after administration of theophylline, cerebral arteriolar diameters were not different from baseline values (103.3 ± 3 versus 101.2 ± 3 μm). Before theophylline, inhalation of 8.5% O_{2} resulted in pial arteriolar dilation of 25.4%. Theophylline administration resulted in an attenuated cerebral arteriolar dilation to hypoxia (7.2% above baseline level; P<.05).

Arterial hypercapnia caused repeatable, dose-dependent pial arteriolar dilation (Table 3). However, ischemia reduced cerebral arteriolar responses to hypercapnia for up to 4 hours.

### Table 3. Arteriolar Responses to Hypercapnia

<table>
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<tr>
<th></th>
<th>Control</th>
<th>5% CO_{2}</th>
<th>10% CO_{2}</th>
<th>Control</th>
<th>5% CO_{2}</th>
<th>10% CO_{2}</th>
<th>Control</th>
<th>5% CO_{2}</th>
<th>10% CO_{2}</th>
<th>Control</th>
<th>5% CO_{2}</th>
<th>10% CO_{2}</th>
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<tbody>
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<td></td>
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</tr>
<tr>
<td>Diameter, μm</td>
<td>104.2 ± 2</td>
<td>121.4 ± 4</td>
<td>140.3 ± 4†</td>
<td>102.2 ± 2</td>
<td>126.3 ± 5</td>
<td>138.6 ± 4†</td>
<td>108.8 ± 4</td>
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<td>139.5 ± 4†</td>
<td>195.7 ± 4</td>
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<td>ΔDiameter, μm</td>
<td>17.1 ± 3</td>
<td>36.5 ± 1†</td>
<td></td>
<td>24.4 ± 4</td>
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<td>28.8 ± 1†</td>
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<tr>
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<td>7.24 ± 0.05</td>
<td>7.12 ± 0.07†</td>
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<td>7.22 ± 0.05</td>
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<tr>
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<tr>
<td>Diameter, μm</td>
<td>98.4 ± 4</td>
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<td>126 ± 7†</td>
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<td>107.4 ± 4</td>
<td>108 ± 5</td>
<td>107.5 ± 5</td>
<td>117 ± 5†</td>
<td>122 ± 6†</td>
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<td>ΔDiameter, μm</td>
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<tr>
<td>pH</td>
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<td>7.29 ± 0.05†</td>
<td>7.13 ± 0.06†</td>
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<td>7.14 ± 0.04</td>
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<tr>
<td>PO_{2}</td>
<td>33 ± 2</td>
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<td>93 ± 5</td>
<td>103 ± 4</td>
<td>100 ± 3</td>
<td>105 ± 4</td>
<td>96 ± 3</td>
</tr>
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</table>

Values are mean±SEM; n=4 for sham group and n=6 for ischemia group.

*P<.05 compared with corresponding control; †P<.05 compared with inhalation of 5% CO_{2}; ‡P<.05 compared with preischemia values.

**Discussion**

The major new finding is that ischemia does not alter cerebral arteriolar dilation to arterial hypoxia and to adenosine in piglets. Thus, despite a substantial contribution of K_{ATP} to arteriolar dilation to hypoxia and adenosine, normal responsiveness is intact. In contrast to arterial hypoxia and adenosine, cerebral arteriolar dilation to arterial hypercapnia is reduced by ischemia. Thus, cerebrovascular responses to arterial hypoxia and arterial hypercapnia, two stimuli commonly used to elicit cerebral arteriolar dilation as well as individual components of asphyxia, are differentially sensitive to anoxic stress.

As shown in numerous studies, arterial hypoxia activates multiple mechanisms that influence cerebrovascular tone. The relative contribution of various mechanisms of hypoxic vasorelaxation vary over time and depend on the severity of hypoxia. There is now a consensus that the release and effects of adenosine determine the majority of the cerebral vasodilator response to hypoxia in piglets. For example, adenosine concentrations in brain interstitial and cerebrospinal fluids increase to the vasodilator range within the first minutes of hypoxia. In addition, adenosine receptor antagonists and adenosine deaminase attenuate the hypoxic, hyperemic response in the cerebral circulation. Our present results also support the view that adenosine plays a significant role in hypoxia-induced cerebral vasodilation in newborn pigs. The relative contribution of adenosine to hypoxia-induced vascular changes may vary during the postnatal period and species-dependent variables may also exist.

The mechanism by which endogenous adenosine causes cerebral vasodilation has been intensively studied. Several studies on isolated arteries have shown that adenosine activates K_{ATP} and that this effect was inhibited by glibenclamide. In addition, our data confirm recent results by and indicate that K_{ATP} contribute to adenosine-induced arteriolar dilation in the in vivo cerebral circulation of piglets. The
precise mechanism of $K_{ATP}$ activation remains unknown, but probably involves elevation of intracellular cAMP and stimulation of protein kinase A.22,29

In a previous study, we showed that arteriolar dilator responses to aprikalim, iloprost, and CGRP, selective activators of $K_{ATP}$, are greatly reduced after ischemia.15,16 Aprikalim is a widely used pharmacological activator of $K_{ATP}$,22,29 iloprost, a stable analogue of prostacyclin, and CGRP may be entirely dependent on activation of $K_{ATP}$ in promoting dilation of cerebral arterioles. Thus, coadministration of glibenclamide, a selective inhibitor of $K_{ATP}$, blocked arteriolar dilator responses to all three substances. In contrast to these three activators of $K_{ATP}$, adenosine and arterial hypoxia do not dilate cerebral arterioles exclusively via the opening of $K_{ATP}$. Thus, approximately one half of the arteriolar dilation to adenosine and arterial hypoxia is intact with coapplication of glibenclamide, which implies that other mechanisms independent from activation of $K_{ATP}$ are also involved. Nonetheless, based on the relative importance of $K_{ATP}$ in promoting dilation to these stimuli,14,15 it was an unexpected finding that normal arteriolar responsiveness remained after ischemia. Our results with adenosine confirm an earlier report by Mayhan et al.21

We considered several possible explanations to account for the retained cerebral arteriolar responses to arterial hypoxia and adenosine. First, alternative dilator mechanisms, including actions of arachidonic acid18 and other as yet undefined factors may have compensated for decreased function of $K_{ATP}$. Although activation of calcium-activated potassium channels has been shown to participate in dilator responses of rat isolated cerebral arterioles,20 recent evidence indicates that their contribution to cerebral arteriolar dilation in piglets is doubtful. Second, the limited $K_{ATP}$ function remaining after ischemia may be sufficient to allow normal arteriolar responsiveness. In our previous study, modest arteriolar dilation to aprikalim was present after ischemia, while glibenclamide coapplication completely abolished aprikalim-induced dilation.15 Thus, low levels of $K_{ATP}$ function may allow normal arteriolar responsiveness to be present for arterial hypoxia and adenosine, perhaps via a “permissive” role as has been suggested for nitric oxide17 and prostaglandins.21,22 Third, the effects of ischemia on arteriolar responses to aprikalim, iloprost, and CGRP may involve inactivation of sites distinct from the $K_{ATP}$ or of sites that are not essential for channel functioning.27 For example, ischemia may impair the function of prostacyclin and CGRP receptors or coupling between receptors and $K_{ATP}$. In addition, ischemia-induced alterations in binding sites for aprikalim may not interfere with adenosine– or hypoxia-stimulated increases in $K_{ATP}$ function. Also, changes in $K_{ATP}$ channel function could be different depending on whether activation is from extra- or intracellular directions. And fourth, preadministration of exogenous adenosine or release of endogenous adenosine by hypoxia could attenuate ischemic damage17 and preserve normal vascular responsiveness.

In contrast to arterial hypoxia, arteriolar dilation to arterial hypercapnia was abolished at 1 hour after ischemia, and normal dilator responses returned to normal 4 hours after ischemia. In piglets, cerebral arteriolar dilation to arterial hypercapnia is not due to activation of $K_{ATP}$.19 Recovery of arteriolar responsiveness to arterial hypercapnia over 2 to 4 hours after ischemia is similar to those observed previously in response to aprikalim and iloprost,15 and may represent general recovery of cerebral blood vessels. It is interesting that cerebral arteriolar responses to arterial hypoxia are extremely stable during this period when dilator responses to other stimuli are attenuated.

Babies are frequently exposed to hypoxic/anoxic stress during the perinatal period, and cerebrovascular dysfunction may contribute to or potentiate development of neurological sequelae. Results from the present study and other studies show that cerebrovascular responsiveness is affected selectively by anoxic stress. Thus, cerebral arteriolar dilation to CGRP,16 prostacyclin,15 N-methyl-d-aspartate,17 and arterial hypercapnia is largely abolished by 1 hour after ischemia, while responsiveness to arterial hypoxia, adenosine, sodium nitroprusside,17 and prostaglandin E117 is intact. Proper management of babies after hypoxic/ischemic stress should take into consideration these relatively selective changes in responsiveness of the cerebral circulation.

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References
Cerebral ischemia can activate any of a multitude of complex mechanisms, depending on the duration, location, and intensity of the insult. Some of these mechanisms, such as the release of nitric oxide and excitatory amino acids, contribute directly to the immediate neuronal death characteristic of cerebral ischemic damage. Other mechanisms target the cerebral vasculature and alter its reactivity, resulting in both immediate and long-term consequences for posts ischemic recovery. Among the cerebrovascular responses long known to be particularly vulnerable to ischemia is the ability of the cerebral circulation to autoregulate its blood flow. In addition, cerebral ischemia can attenuate hypercapnic reactivity, although this effect appears more variably than loss of autoregulation. Reactivity to hypoxia can also be attenuated by potassium channels are clearly implicated in hypoxic cerebral vasodilation and thus the results may not exactly predict hypercapnic reactivity as previously reported, but had no effect on cerebral vasodilatation to either hypoxia or adenosine. Together, these findings reinforce the view that ischemia selectively alters essential cerebrovascular responses and further suggest that mechanisms independent of ATP-sensitive potassium channels can fully mediate posts ischemic hypoxic cerebral vasodilatation in the neonate.

Certainly, careful judgment must be exercised when extrapolating these results to other preparations and situations. The pattern and distribution of ischemia produced in these studies by artificially elevating intracranial pressure is quite different from that produced by vessel occlusion or cardiac arrest. In addition, the duration of hypoxia tested was relatively brief (3 to 4 minutes) and of moderate intensity (PaO$_2$ 25 mm Hg) and therefore may not accurately predict responses to hypoxia of greater duration or intensity. Typically, more severe hypoxia produces greater decreases in the cellular ATP-to-ADP ratio and therefore may more vigorously activate ATP-sensitive potassium channels and heighten any apparent effects of channel dysfunction. Finally, the effects of ischemia are dramatically different in mature and immature brains, as is the functional capacity of cerebrovascular ATP-sensitive potassium channels, and thus the results may not exactly predict the effects of ischemia on hypoxic cerebral vasodilatation in the adult. Nonetheless, the study by Bari et al advances the important concept that in neonates, as previously shown in adults, cerebrovascular responses to hypoxia are more robust than are responses to changes in arterial carbon dioxide tension. This strongly implies that cerebrovascular
reactivity to hypoxia may be expected to survive a moderate ischemic insult but loss of this reactivity is a reliable indicator of poor outcome after a major cerebrovascular ischemic insult, regardless of age.

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