Subarachnoid Hemorrhage and Endothelial L-Arginine Pathway in Small Brain Stem Arteries in Dogs

Zvonimir S. Katušić, MD, PhD; James H. Milde; Francesco Cosentino, MD; and Bora S. Mitrović, MD

Background and Purpose: Experiments were designed to determine the effect of subarachnoid hemorrhage on endothelium-dependent relaxations in small arteries of the brain stem. A “double-hemorrhage” canine model of the disease was used, and the presence of vasospasm in the basilar artery was confirmed by angiography.

Methods: Secondary branches of both untreated basilar arteries (inner diameter, 324±11 μm; n=12) and arteries exposed to subarachnoid hemorrhage for 7 days (inner diameter, 328±12 μm; n=12) were dissected and mounted on glass microcannulas in organ chambers. Changes in the intraluminal diameter of pressurized arteries were measured using a video dimension analyzer.

Results: In untreated arteries, 10⁻¹¹ to 10⁻⁷ M vasopressin, 10⁻¹⁰ to 10⁻⁶ M bradykinin, and 10⁻⁸ to 10⁻⁴ M calcium ionophore A23187 caused endothelium-dependent relaxations. At 10⁻⁶ and 3×10⁻⁴ M the nitric oxide synthase inhibitor N⁶-nitro-L-arginine methyl ester (L-NAME) abolished relaxations to vasopressin and produced small but significant rightward shifts of the concentration–response curves to bradykinin and A23187. At 10⁻³ M L-arginine prevented the inhibitory effect of L-NAME. Subarachnoid hemorrhage abolished relaxations to vasopressin but did not affect relaxations to bradykinin or A23187.

Conclusions: These studies suggest that in small arteries of the brain stem vasopressin causes relaxations by activation of the endothelial l-arginine pathway. This mechanism of relaxation is selectively inhibited by subarachnoid hemorrhage. Preservation of endothelium-dependent relaxations to bradykinin and A23187 is consistent with the concept that small arteries are resistant to vasospasm after subarachnoid hemorrhage. (Stroke 1993;24:392–399)

Key Words • brain stem • nitric oxide • vasospasm • dogs

Nitric oxide production in endothelial cells via the l-arginine pathway plays a key role in the regulation of cerebral arterial tone.¹ Activation of this pathway mediates basal and stimulated production of nitric oxide and endothelium-dependent relaxations in small as well as large cerebral arteries.²⁻⁶

Subarachnoid hemorrhage impairs endothelium-dependent relaxations in cerebral arteries.⁷⁻¹² This may contribute to the development of cerebral vasospasm in large arteries. By contrast, it has been suggested that vasospasm does not occur in small arteries.¹³ The reason for this differential effect of autologous blood on large versus small cerebral arteries is unknown but may depend on differences in the endothelial regulation of smooth muscle tone. The effect of subarachnoid hemorrhage on relaxations mediated by the activation of endothelial cells in small arteries of the brain stem has not been studied. Thus, the present study was designed to determine the role of the endothelial l-arginine pathway in the reactivity of small brain stem arteries to vasopressin, bradykinin, and A23187 and to examine the effect of subarachnoid hemorrhage on endothelium-dependent relaxations to these agonists.

Materials and Methods

Animal Model of Subarachnoid Hemorrhage

Mongrel dogs of either sex weighing 14–18 kg were used. During general anesthesia with 15 mg/kg thiopental and 15–25 mg/kg i.v. pentobarbital and controlled ventilation, a transfemoral angiogram of the basilar artery was obtained. Subsequently, the cisterna magna was aseptically punctured with a No. 22 spinal needle, and 5 ml cerebrospinal fluid was removed. With the animal in a 30° head-down position, 5 ml autologous venous blood was injected through the spinal needle over 2 minutes. After 15 minutes in the head-down position, the animal was returned to its cage. Two days later (on day 2), the injection of venous blood into the cisterna magna was repeated under general anesthesia. On day 7, angiography was performed, with the animals
under anesthesia and controlled ventilation, to confirm the presence of vasospasm. Figure 1. During the angiography procedures, arterial blood gases were monitored. The diameters of the basilar arteries were measured on the angiograms under optical magnification. The diameters before and after the intracisternal injections of blood were compared, and the data are expressed as a percentage of the value before the injections. The procedures and handling of the animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Mayo Foundation.

**In Vitro Studies**

The brain was removed from dogs (untreated animals or those exposed to subarachnoid hemorrhage) anesthetized with 30 mg/kg i.v. sodium pentobarbital and placed into cold modified Krebs-Ringer bicarbonate solution of the following millimolar composition (control solution): 118.3 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 MgSO₄, 2.50 NaHCO₃, 0.026 calcium-ethylenediaminetetraacetic acid, and 11.1 glucose. Segments 2–3 mm long of a secondary branch of the basilar artery (Figure 2) were carefully dissected using a dissection microscope. The arteries were transferred to an arteriograph filled with oxygenated (94% O₂ and 6% CO₂) control solution and then mounted onto microcannulas (Living System Instrumentation, Burlington, Vt.). Control solution circulated from a 250 ml oxygenated reservoir through the arteriograph chamber at a flow rate of 12 ml/min. Temperature was continuously monitored (model 7000 H, Jenco Electronics) to maintain the vessel environment at 37±0.5°C. All experiments were performed in the presence of 10⁻⁵ M indomethacin to prevent the activity of cyclooxygenase.

The arteriograph was placed on the stage of an inverted microscope (Diaphot-TMD, Nikon) that had a video camera attached to the viewing tube. The signal derived from the video image of the vessel was processed by an electronic system (Living System Instrumentation) for the continuous measurement and recording of both inner diameter and wall thickness.

**Figure 1. Angiograms of canine basilar artery before (left panel) and 1 week after (right panel) injections of autologous blood into cisterna magna. Note vasospasm after intracisternal injections.**

**Figure 2. Schematic representation of anatomy of canine basilar artery and its secondary branches used in present study. a., artery.**

**Table 1. Inner Diameters of Canine Brain Stem Arteries With and Without Endothelium at 50 mm Hg**

<table>
<thead>
<tr>
<th>Artery</th>
<th>Endothelium</th>
<th>Untreated</th>
<th>Without</th>
<th>Subarachnoid hemorrhage</th>
<th>With</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basilar a.</td>
<td>Control</td>
<td>324±11</td>
<td>268±10*</td>
<td>328±12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indomethacin</td>
<td>316±11</td>
<td>232±7*</td>
<td>308±12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>U46619</td>
<td>223±13†</td>
<td>162±12†</td>
<td>194±10†</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SEM μm; n=5–12 dogs.

*tp<0.05 different from untreated with endothelium.

†tp<0.05 different from control or indomethacin.
TABLE 2. Inner Diameters of Canine Brain Stem Arteries in Absence and Presence of L-NAME and L-Arginine Plus L-NAME at 50 mm Hg

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Absence</th>
<th>Presence</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-NAME</td>
<td>395±17</td>
<td>363±17</td>
</tr>
<tr>
<td>10⁻⁴ M</td>
<td>346±11</td>
<td>324±14*</td>
</tr>
<tr>
<td>L-NAME (10⁻³ M)+</td>
<td>378±28</td>
<td>377±32</td>
</tr>
<tr>
<td>L-NAME (10⁻³ M)</td>
<td>378±28</td>
<td>377±32</td>
</tr>
<tr>
<td>L-NAME, N⁰-nitro-L-arginine methyl ester. Values are mean±SEM μm; n=4 or 5 dogs. *p&lt;0.05 different from absence.</td>
<td></td>
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</tr>
</tbody>
</table>

In some experiments the endothelium was removed by intraluminal perfusion with 0.5% 3-[(3-cholamidopropyl)-dimethylammonio]-1-propanesulfonate (CHAPS) for 30 seconds.6,16,17 Removal of the endothelium was confirmed by the absence of relaxations to 10⁻⁶ M bradykinin.

Responses of the pressurized arteries (in the absence of intraluminal flow) were measured at a transmural pressure of 50 mm Hg. This pressure was found to be optimal for contractions of the small brain stem arteries as assessed by repeated exposures to 3x10⁻⁸ M U46619 at various transmural pressures.

After equilibration, the vessels were contracted with 3x10⁻⁸ to 10⁻⁷ M U46619 (Table 1). When a steady tone was established vasopressin, bradykinin, or A23187 was added extraluminally in a cumulative fashion. Only one concentration–response curve was made per preparation with endothelium or without endothelium. The relaxations were expressed as a percentage of the maximal increase in intraluminal diameter obtained in response to 3x10⁻⁴ M papaverine.

Drugs

The following drugs were used: [Arg⁸]-vasopressin (Sigma Chemical Co., St. Louis, Mo.), calcium ionophore A23187 (Sigma), L-arginine hydrochloride (Sigma), bradykinin (Sigma), CHAPS (Sigma), 9,11-dideoxy-9α,11α-methanooxyprostaglandin F₂α (U46619; Cayman Chemical Co., Ann Arbor, Mich.), indomethacin (Sigma), molsidomine (SIN-1; Cassela AG, Frankfurt, FRG), N⁰-nitro-L-arginine methyl ester (L-NAME; Sigma), and papaverine hydrochloride (Sigma).

Stock solutions of the drugs were prepared fresh every day. The stock solution of indomethacin was prepared in an equal molar concentration of Na₂CO₃. The stock solution of 10⁻⁹ M A23187 was prepared in 1.5x10⁻⁴ M dimethyl sulfoxide. The drugs were dissolved in distilled water. Concentrations of the drugs are expressed as the final molar concentration in the bath solution. The incubation periods were 30 minutes for indomethacin and 15 minutes for L-NAME or L-arginine plus L-NAME. Indomethacin did not significantly affect resting diameter (Table 1); 3x10⁻⁵ M L-NAME caused a significant reduction of resting diameter (Table 2).

Calculations and Statistics

Data are given as mean±SEM. In each set of experiments n equals the number of animals studied. Statis-
Table 3. Effect of SIN-1 in Canine Brain Stem Arteries With and Without Endothelium Contracted With U46619

<table>
<thead>
<tr>
<th>Sin-1 (−log M)</th>
<th>Endothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9</td>
</tr>
<tr>
<td>With</td>
<td>2±10</td>
</tr>
<tr>
<td>Without</td>
<td>3±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM % increase in diameter; n=6 dogs. U46619 concentration, 10−8 to 10−7 M.

Results

Effect of Endothelial Removal on Relaxations to Vasopressin, Bradykinin, A23187, and SIN-1

During contractions induced with 3×10−8 to 10−7 M U46619, 10−11 to 10−7 M vasopressin, 10−10 to 10−6 M bradykinin, and 10−9 to 10−6 M A23187 caused concentration-dependent relaxations. Chemical removal of the endothelium abolished these relaxations (Figures 3–5). In arteries without endothelium, A23187 caused concentration-dependent contractions (Figure 5). Removal of endothelial cells did not affect relaxations to SIN-1 (Table 3).

Effect of L-NAME on Relaxations to Vasopressin, Bradykinin, and A23187

Endothelium-dependent relaxations to vasopressin were abolished in the presence of 10−4 and 3×10−4 M L-NAME (Figure 6). In contrast, L-NAME reduced relaxations to bradykinin and A23187 but did not affect the maximal relaxation to these agonists (Figures 7 and 8). In the presence of 10−3 M L-arginine the inhibitory effects of L-NAME on relaxations to vasopressin and bradykinin were reversed (Figures 6 and 7). In rings with endothelium, L-NAME (3×10−4 M) did not affect relaxations to papaverine (3×10−4 M; 99±1%, n=5, and 98±1%, n=5, in the absence and in the presence of L-NAME, respectively).

Angiography

Dogs with subarachnoid hemorrhage developed cerebral vasospasm (diameter of basilar artery 57±7% of diameter before intracisternal injections of blood, n=6; Figure 1).

Effect of Subarachnoid Hemorrhage on Endothelium-Dependent Relaxations to Vasopressin, Bradykinin, and A23187

In small arteries of the brain stem with endothelium obtained from animals with developed vasospasm of the basilar artery, relaxations to vasopressin were abolished (Figure 9). The relaxations to bradykinin and A23187 were not affected except for those at 10−9 M bradykinin (Figures 10 and 11).

Effect of Subarachnoid Hemorrhage on Relaxations to SIN-1

During contractions induced with 3×10−8 to 10−7 M U46619, 10−9 to 10−4 M SIN-1 caused concentration-dependent relaxations in arteries with endothelium. Subarachnoid hemorrhage did not affect the relaxations to SIN-1 (Figure 12).

Effect of Subarachnoid Hemorrhage on Arterial Wall Thickness

At an intra-arterial pressure of 50 mm Hg, wall thickness of the small brain stem arteries was not affected by subarachnoid hemorrhage (28±2 μm, n=12 and 33±3 μm, n=12 for untreated dogs and animals receiving intracisternal blood, respectively).

Discussion

This is the first study to examine the effect of subarachnoid hemorrhage on endothelium-dependent relaxations in small brain stem arteries. The major new finding is that subarachnoid hemorrhage selectively inhibits relaxations to vasopressin mediated by activation of the endothelial L-arginine pathway.

The relaxations to vasopressin, bradykinin, and A23187 were abolished by chemical removal of endothelial cells, demonstrating that the relaxations to these agonists are mediated by the production and release of...
endothelium-derived relaxing factor(s). Our results also demonstrate that in arteries without endothelium the resting diameter was significantly reduced, suggesting that continuous production of endothelium-derived relaxing factor(s) exerts an inhibitory effect on smooth muscle cells under basal conditions. This explanation is consistent with a significant reduction of the inner diameter induced by the nitric oxide synthase inhibitor L-NAME in arteries with endothelium.

The reactivity of smooth muscle cells to a prostaglandin H2/thromboxane A2 receptor agonist (U46619), a nitric oxide donor (SIN-1), or a phosphodiesterase inhibitor (papaverine) appears to be preserved after removal of endothelial cells. Furthermore, in preparations without endothelium, A23187 caused a concentration-dependent decrease in diameter, demonstrating that nonreceptor-mediated mechanisms of smooth muscle contraction are intact.

The results of the present study confirm our previous reports suggesting that the relaxations to vasopressin in canine basilar artery as well as in small arteries of the brain stem are mediated by increased activity of nitric oxide synthase and production of nitric oxide from l-arginine.3,6,18 In contrast, L-NAME produced only small rightward shifts of the concentration–response curves to bradykinin and A23187 and did not affect maximal relaxations to these agonists. Thus, it appears that the inhibitory effects of bradykinin and A23187 are primarily due to increased production of relaxing factor(s) other than nitric oxide. This conclusion is consistent with results reported from several different laboratories. In isolated porcine coronary artery, endothelium-dependent relaxations to bradykinin are not inhibited by the nitric oxide synthase inhibitor N0-monomethyl-l-arginine (L-NMMA).19,20 Similarly, L-NMMA does not prevent endothelium-dependent relaxations to acetylcholine or substance P in rabbit hind limb resistance arteries,21 suggesting that the l-arginine/nitric oxide pathway is not involved. Our experiments were performed in the presence of the cyclooxygenase inhibitor.

**FIGURE 7.** Concentration–response curves to bradykinin in canine brain stem arteries with endothelium in the absence (control) and presence of N0-nitro-l-arginine methyl ester (L-NAME) (left panel) and in the absence (control) and presence of l-arginine (L-ARG) plus L-NAME (right panel). Relaxations were obtained during contractions to 3x10^-8 to 10^-7 M U46619. Data are mean±SEM percentage of maximal relaxation induced by papaverine. *p<0.05 difference between preparations.

**FIGURE 8.** Concentration–response curves to A23187 in canine brain stem arteries with endothelium in the absence (control) and presence of N0-nitro-l-arginine methyl ester (L-NAME). Relaxations were obtained during contractions to 3x10^-8 to 10^-7 M U46619. Data are mean±SEM percentage of maximal relaxation induced by papaverine. *p<0.05 difference between control and L-NAME-treated arteries.

**FIGURE 9.** Concentration–response curves to vasopressin in brain stem arteries from untreated dogs (control) and animals exposed to subarachnoid hemorrhage (SAH). Relaxations were obtained during contractions to 3x10^-8 to 10^-7 M U46619. Data are mean±SEM percentage of maximal relaxation induced by papaverine. *p<0.05 difference between preparations.
indomethacin, indicating that prostacyclin or oxygen-derived free radicals as possible mediators can be ruled out.\textsuperscript{22,23} The precise mechanism of the relaxations to bradykinin and A23187 in small canine brain stem arteries is unknown, but it is likely that the component resistant to inhibition by L-arginine analogues is mediated by a hyperpolarizing factor or some other unknown substance released from the endothelium.\textsuperscript{24}

Angiographically we detected a significant decrease in the diameter of the basilar artery after injections of autologous blood into the cisterna magna. However, we studied the effect of subarachnoid hemorrhage on endothelium-dependent relaxations in secondary branches of the basilar artery that are below the limits of resolution of angiography. Vasospasm of the basilar artery may reduce dye entry into the more distal vessels, making questionable the value of angiography in quantifying narrowing in smaller arteries.\textsuperscript{25} Therefore, we quantified only changes in diameter of the basilar artery.

The role of small arteries in the pathophysiology of cerebral vasospasm during subarachnoid hemorrhage has been studied in monkeys.\textsuperscript{26} The authors were able to detect spontaneous irregular increase in tone. However, since diameters of small arteries could not be estimated from angiography, it remains unknown whether this increased contractility detected in vitro was translated into narrowing of these vessels in vivo.\textsuperscript{26} We have not detected spontaneous increase in tone in isolated canine small arteries exposed to SAH. This may be due to species differences, regional heterogeneity (cerebral versus brain stem arteries), or methodologies used to induce SAH. Nevertheless, the results of the present study are consistent with the concept that in small arteries subarachnoid hemorrhage may lead to alterations in vascular reactivity without affecting the mechanical properties of the tissue.\textsuperscript{25} This is supported by the fact that optimal pressures for the reactivity of untreated and vasospastic arteries were identical. In addition, we did not detect any differences in wall thickness between the two preparations.

Subarachnoid hemorrhage abolished the endothelium-dependent relaxations to vasopressin, whereas the relaxations to bradykinin and A23187 were not affected (except for those at 10\textsuperscript{−6} M bradykinin). In contrast to small arteries, in the basilar artery the endothelium-dependent relaxations to bradykinin are abolished by subarachnoid hemorrhage.\textsuperscript{27} Furthermore, the relaxations to bradykinin in the basilar artery are mediated by activation of endothelial nitric oxide synthase and are abolished by L-arginine analogues\textsuperscript{5,28} (F. Cosentino and Z.S. Katusic, unpublished observation). The inhibitory effects of nitric oxide synthase inhibitors and subarachnoid hemorrhage on endothelium-dependent relaxations strongly suggests that the development of cerebral vasospasm is associated with inactivation of the relaxations mediated by the endothelial L-arginine pathway. However, the exact cellular mechanism of the subarachnoid hemorrhage–induced inhibition of the relaxations to vasopressin remains unknown. Relaxations to the nitric oxide donor SIN-1 were not inhibited in arteries obtained from dogs with developed vaso-

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure10.png}
\caption{Concentration–response curves to bradykinin in brain stem arteries from untreated dogs (control) and animals exposed to subarachnoid hemorrhage (SAH). Relaxations were obtained during contractions to 3\times10\textsuperscript{−8} to 10\textsuperscript{−7} M U46619. Data are mean±SEM percentage of maximal relaxation induced by papaverine. \textsuperscript{*}p<0.05 difference between preparations.}
\end{figure}
spasms, suggesting that, unlike in basilar artery,29 vascular smooth muscle cells have preserved reactivity to nitric oxide. This finding also suggests that the production, release, or transfer of nitric oxide rather than the reactivity of smooth muscle cells to nitric oxide may be impaired by subarachnoid hemorrhage. We do not have an explanation for the differential effect of subarachnoid hemorrhage on reactivity of smooth muscle cells to nitric oxide in large versus small cerebral arteries.

It has been reported that 25% of a series of 42 patients with subarachnoid hemorrhage had increased concentrations of vasopressin in either the plasma or cerebrospinal fluid.30 We did not measure circulating levels of vasopressin, and it is impossible to rule out that prolonged exposure to high concentrations of vasopressin may contribute to alterations of V$_1$-vasopressinergic receptors present on endothelial cells.

All experiments on arteries exposed to subarachnoid hemorrhage were performed in the presence of the cyclooxygenase inhibitor indomethacin. In our previous studies we demonstrated that 10$^{-5}$ M indomethacin inhibits the production of prostanooids and prevents the formation of endothelium-derived contracting factor(s) generated by the cyclooxygenase pathway in the metabolism of arachidonic acid.31 Thus, the inhibition of endothelium-dependent relaxations to vasopressin by subarachnoid hemorrhage cannot be explained by increased metabolism of arachidonic acid and release of contracting factor(s) from endothelial cells. On the other hand, the presence of indomethacin in our experiments imposes a limitation concerning the role of cyclooxygenase in the mediation of endothelium-dependent responses. Further studies are needed to characterize the importance of endothelial arachidonic acid metabolism in the regulation of smooth muscle tone in small brain stem arteries.

The results of the present study demonstrate that in small canine brain stem arteries endothelium-dependent relaxations to vasopressin are mediated by activation of the L-arginine pathway. This mechanism of relaxation appears to be selectively inhibited by subarachnoid hemorrhage. Unlike in large cerebral arteries, the endothelium-dependent relaxations to bradykinin and A23187 are not abolished by L-NNAME or subarachnoid hemorrhage. The selective preservation of endothelial function may help to explain the observation that cerebral vasospasm does not occur in small arteries.13

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Endothelium plays an important role in regulation of cerebral vascular tone through the production and release of endothelium-derived relaxing factor (EDRF), which has been identified as nitric oxide (NO) or an NO-containing compound.\(^1\)–\(^4\) Impaired endothelium-dependent relaxation of large cerebral arteries after subarachnoid hemorrhage has been described in humans and experimental animal models and may contribute to vasospasm.\(^5\)–\(^10\)

The present study by Katusič et al examined endothelium-dependent relaxation of small arteries of the brain stem in a canine model of subarachnoid hemorrhage. Subarachnoid hemorrhage selectively impaired endothelium-dependent relaxation in response to vasoressin but not in response to bradykinin or the calcium ionophore A23187. Because an inhibitor of NO-synthase and subarachnoid hemorrhage produced similar reductions in responses to vasoressin, these findings suggest that subarachnoid hemorrhage selectively impairs the l-arginine/NO (EDRF) pathway in endothelium. In contrast to large cerebral arteries and small arteries taken from the surface of the brain, a recent study suggests that endothelium-dependent responses are not impaired in penetrating arterioles after subarachnoid hemorrhage.\(^11\)

The mechanism that accounts for impairment of endothelium-dependent relaxation in response to specific agonists after subarachnoid hemorrhage is not clear. Impaired endothelium-dependent relaxation may be due to abnormal receptor function, impaired production of EDRF, or simultaneous production of an endothelium-derived contracting factor. Impaired endothelial function was observed in the present experiments in the presence of indomethacin, suggesting that formation of a cyclooxygenase-derived contracting factor did not contribute to abnormal responses. The finding that relaxation of arteries in response to an NO donor was normal suggests that impaired endothelium-dependent responses were not due to reduced activity of soluble guanylate cyclase and formation of cyclic GMP in response to EDRF.\(^10\)

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