Changes in Cerebral Blood Flow and Metabolism Following Intraarterial or Local Administration of Nimodipine, Before and After Experimental Subarachnoid Hemorrhage in Baboons

CHRISTINA SAHLIN, M.D., TIA DELGADO, M.D., CHRISTER OWMAN, PH.D., M.D., and NIELS-AAGE SVENGAARD, M.D., PH.D.

SUMMARY Experimental subarachnoid hemorrhage (SAH) was induced in baboons by repeated injections of autologous blood into cisterna chiasmatis and cisterna magna, a total of 14–33 ml being injected over 3–4 days. Cerebral blood flow (CBF; 133Xenon clearance) and cerebral metabolic rate of oxygen (CMRO2) were measured before, and 7 days after, the first blood injection. The effect of the calcium channel blocker, nimodipine, used in a commercially available form for clinical application, was studied following continuous i.a. infusion (0.1 \( \mu \)g x kg\(^{-1} \) x min\(^{-1} \)) for an interval of 45 min, and also 20 and 60 min after intrathecal administration of 1 \( \mu \)g x kg\(^{-1} \). During the infusion experiments, CBF was increased by 25–30% both before and after the cisternal blood injection. CMRO2 was also enhanced, but much less. Nimodipine in doses given did not alter systemic blood pressure. Following intrathecal application, CBF and CMRO2 slightly increased at 20 min only before experimental SAH.

**Material and Methods**

**Animals**

The experiments were performed on 11 baboons (Papio cynocephalus) of either sex, weighing 9.2–21.8 kg. The animals were housed in individual cages 4–8 weeks before (and during) the experiments. They were fed with standard monkey pellets, supplemented with fruit and vegetables, and tap water *ad lib.*
Anesthesia

Anesthesia was initiated with phencyclidine hydrochloride (Sernylan, BioCeutic; 1 mg × kg⁻¹ i.m.) followed by thiopental sodium (Abbott; 7.5 mg × kg⁻¹ i.v.). The animals were intubated endotracheally and respiration was controlled in a semi-open circuit. The anesthesia was maintained with a continuous infusion of phencyclidine (0.2-0.5 mg × kg⁻¹ × hr⁻¹), supplemented with 70% nitrous oxide and 30% oxygen. EEG was monitored continuously in order to allow for adjustment of the phencyclidine dose. Muscular relaxation was achieved initially with suxamethonium chloride (Celoeurin-klorid, Vitrum; 25 mg i.v.) and then continued with 50 mg suxamethonium chloride i.m. every half hour. During all surgical procedures, 0.5% fluothane (Halothane, ICI) was added to the gas mixture.

Blood Flow Measurements

CBF was determined by an intra-arterial injection and cerebral clearance method. 26-27 The tracer, ¹³¹sXe, was dissolved in 0.9% saline to a final volume of 0.5 ml, which was injected manually into the right internal carotid artery via a catheter placed in the linguo-facial artery. The injection time was close to 1.5 sec. Ipsilateral extracerebral contamination of ¹³¹sXe was minimized by clamping the external carotid artery and by extirpation of the temporal muscle. The clearance rate for ¹³¹sXe was measured from the temporoparietal area of the brain during a 10-min period with a single, collimated sodium iodide scintillation crystal of 25 mm diameter and 15 mm in collimator depth. The stochastic (height-over-area) method was used for calculating CBF. 27

Physiological Parameters

The P₇CO₂ was measured during the second and seventh min, respectively, of the 10 min ¹³¹Xe clearance period. The average value was maintained near 40 mm Hg and not allowed to exceed the range of 38-42 mm Hg. The P₇O₂ was kept between 100 and 160 mm Hg. The CMRO₂ was obtained by multiplying the arterio-venous difference of oxygen content with CBF. Venous blood was drawn from a catheter inserted immediately above the confluens sinuum. Superior sagittal sinus pressure (SSP) was monitored continuously during the experiment. EEG was recorded via permanently inserted extradural electrodes.

Intracisternal Blood Injections

The blood injections were started 3-5 days after the baseline CBF measurements had been obtained. The animals were sedated with phencyclidine (1 mg × kg⁻¹ i.m.) and the anesthesia was maintained with fluothane using a face mask.

Blood injections were usually carried out three times with two-day intervals. Fresh autologous blood was obtained from a femoral artery puncture. The first and second injections were given into the cisterna magna and the third through the orbit into the cisterna chiasmatis. A short-beveled needle (1.5 mm o.d.) with a stylet was passed percutaneously into the cisterna magna, and 5-10 ml cerebrospinal fluid (CSF) were withdrawn and replaced with blood until the respiratory rhythm became depressed. This usually occurred when 1-4 ml more than the amount of CSF aspirated had been administered. For the intrachiasmatic injections, the same type of needle was passed through the conjunctiva and the optic foramen. Three to 6 ml blood was injected; it was seldom possible to aspirate more than 1-2 ml CSF prior to the injection. The animals thus received a total amount of 14-33 ml blood intracisternally.

Further technical details have been described elsewhere. 28

Nimodipine Solution

The commercially available nimodipine preparation for clinical application (Bayer AG) was used in the present experiments. The concentration of the calcium uptake blocker is 0.1 mg/ml in a solution of distilled water containing 150 mg × ml⁻¹ each of ethanol and polyethylene glycol. Nimodipine was omitted from the solution given in the control experiments. Both solutions were diluted with 0.9% saline to a suitable volume (approximately 0.5 ml × min⁻¹) for the infusion experiments carried out at room temperature (20°C), and to a 2-ml volume with fresh (37°C) CSF immediately before cisternal administration. Syringes and catheters were wrapped in aluminum foil in order to avoid photodecomposition of nimodipine.

Experimental Design

Animals received the calcium uptake blocker, nimodipine, either intrathecally (i.th.) or intra-arterially (i.a.) before and after experimental SAH. The same amount of solvent was given in control experiments. In the i.th. experiments, cisterna magna was punctured percutaneously, and 1.8 ml CSF was aspirated, the drug (1 μg × kg⁻¹ body weight) or solvent was added, giving a total of 2 ml, which was injected into the cistern rapidly to secure an efficient distribution in the subarachnoid space. The i.a. infusion (0.1 μg × kg⁻¹ × min⁻¹) was performed via a catheter placed in the linguo-facial artery, the infusion being discontinued only for the bolus injection of tracer in the CBF measurements.

CBF, metabolism, and other parameters were measured 20 and 60 min after the i.th. administration, after 45 min of continuous i.a. infusion. In the SAH animals, the nimodipine treatment (or administration of solvent) was performed on the seventh day after the first intracisternal blood injection (i.e. 3 days following the last injection).

Results

Intracisternal blood injection resulted in a statistically significant, 16.3% reduction in CBF and a 12.6% fall in CMRO₂, as shown in table 1. It can also be seen from table 1 that experimental SAH did not cause any significant changes in P₇CO₂, MABP, or blood hemo-
TABLE 1 Effect of Experimental Subarachnoid Hemorrhage (SAH) on Cerebral Blood Flow (CBF) and Cerebral Metabolic Rate of Oxygen (CMRO2). Arterial Carbon Dioxide Tension (P CO2). Mean Arterial Blood Pressure (MABP). Pulse Rate, Sagittal Sinus Pressure (SSP), and Hemoglobin Concentration in 11 Anesthetized Baboons Before and 1 Week After Cisternal Blood Injections

<table>
<thead>
<tr>
<th>Physiological parameter</th>
<th>Before SAH</th>
<th>After SAH</th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF (ml x 100 g−1 x min−1)</td>
<td>58.2 ± 10.7</td>
<td>48.7 ± 1.9</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>CMRO2 (ml x 100 g−1 x min−1)</td>
<td>3.26 ± 0.14</td>
<td>2.85 ± 0.13</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>P CO2 (mm Hg)</td>
<td>39.1 ± 0.3</td>
<td>39.8 ± 0.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>113 ± 5.2</td>
<td>110 ± 3.3</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pulse rate (per min)</td>
<td>90 ± 4.6</td>
<td>113 ± 7.0</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>SSP (mm Hg)</td>
<td>3.2 ± 1.2*</td>
<td>10.4 ± 3.7†</td>
<td>n.s.</td>
</tr>
<tr>
<td>Hemoglobin (g%)</td>
<td>114.9 ± 4.0*</td>
<td>101.1 ± 5.9*</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Mean values ± SEM, n.s. = non-significant.

* For technical reasons only 10 animals included.
† For technical reasons only 8 animals included.

globin concentration; it increased the pulse rate and SSP (though not statistically significant).

Cisternal administration of the calcium uptake blocker, nimodipine, before the blood injections caused a slight, though not significant (compared to baseline values), increase in CBF at 20 min after the injection, the effect being normalized within 60 min (fig. 1). There was no effect on CMRO2. Since the ethanol-containing solvent tended to reduce both CBF and CMRO2, particularly at the 20 min interval, the corrected effect of nimodipine itself at 20 min was a significantly higher flow and metabolism in comparison to the control injections with solvent (fig. 1). Following experimental SAH, the cisternal drug administrations no longer had any effect on either CBF or CMRO2. The MABP remained constant in all the experiments. Nimodipine did not significantly affect SSP, either before or after SAH.

Continuous i.a. infusion of the calcium uptake blocker at a rate of 0.1 µg x kg−1 x min−1 before experimental SAH significantly elevated both CBF and CMRO2 (in comparison with baseline values), as measured 45 min after starting the treatment (fig. 2). This effect was emphasized when comparing with the controls receiving the ethanol-containing solvent, which tended to lower both flow and metabolism. Following SAH, nimodipine increased CBF to the same extent as before the blood injections, though the enhancement in CMRO2, was no longer statistically significant. The mean level of MABP remained unchanged in the experiments, and there was no statistically significant effect of nimodipine on SSP.

**Discussion**

Attempts were made in baboons to simulate the late phase of cerebral vasospasm following SAH in patients by repeated cisternal injections of autologous blood according to a model described in detail elsewhere.28 The blood injections give rise to angiographically visible constriction of the major brain vessels, associated with a decrease in CBF. Also the oxygen consumption of the brain is reduced to a corresponding degree.28

The use of agents blocking the uptake of extracellular calcium into the vascular smooth musculature has been suggested as a means to overcome the circulatory disturbance following SAH.9-10-11 Thus, blockade of the calcium channels counteracts the experimentally induced constriction of pial vessels from cat,14-dog,9 and man.12 Nimodipine prevents depression of CBF following brief total ischemia within the brain of...
EFFECTS OF NIMODIPINE FOLLOWING SAH/Sahlin et al

Nimodipine infusion i.a. 45 min

<table>
<thead>
<tr>
<th>Per cent of baseline level</th>
<th>Before SAH</th>
<th>After SAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMRO₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MABP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Per cent changes in cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMRO₂), and mean arterial blood pressure (MABP) induced by continuous i.a. infusion of 0.1 μg x kg⁻¹ x min⁻¹ nimodipine during 45 min, before and after experimental subarachnoid hemorrhage (SAH). Values are mean ± SEM, number of animals within parenthesis. Differences between mean values from experiments with nimodipine (hatched bars) and the ethanol-containing solvent (filled bars) according to Student’s t-test are indicated, together with differences between absolute baseline values and experimental values according to the paired t-test (*0.01 < p < 0.05, **0.001 < p < 0.01); n.s. = non-significant.
References


Handa J: Cerebral vascular effects of a new derivate of 1,4-dihydropyridine (YC-93), with special reference to its effect on the experimental basilar artery spasm in cats. Arch Jap Chir 44: 343-351, 1975

References

Changes in cerebral blood flow and metabolism following intraarterial or local administration of nimodipine, before and after experimental subarachnoid hemorrhage in baboons.

C Sahlin, T Delgado, C Owman and N A Svendgaard

Stroke. 1986;17:220-224
doi: 10.1161/01.STR.17.2.220

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/17/2/220

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/