Human Pial Vascular Reactions to Intravenous Nimodipine-Infusion During EC-IC Bypass Surgery

LUDWIG M. AUER, M.D., RAINER W. OBERBAUER, M.D. AND HANS V. SCHALK, M.D.

SUMMARY In previous experimental work, the Ca-antagonist Nimodipine had shown a predominantly cerebroarterial dilatory effect. In the present double-blind study of 16 patients, pial arterial and venous reaction was investigated during EC-IC bypass surgery, infusing 1 μg kg⁻¹min⁻¹ of Nimodipine intravenously. In pial arteries with resting diameters between 25 and 70 μm, a significant 18% dilatation was observed. Results are considered promising for future trials in the treatment and prevention of cerebral ischemia caused by vasoconstriction or vasospasm, especially vasospasm following subarachnoid hemorrhage.

PREVIOUS EXPERIMENTAL WORK has shown a longlasting predominantly cerebrovascular dilatory effect of the lipophilic Calcium-antagonist Nimodipine (isopropyl (2-methoxyethyl)-1,4-dihydro-2,6-dimeth­yl-4 (3-nitrophenyl)-3,5 pyridinedicarboxylate). Ca-ions are required for the actin-myosin contraction-mechanism in smooth muscle cells. Ca⁺⁺ can either be mobilised from intracellular stores by receptor stimulation, or provided by influx from the extracellular space during depolarisation. This transport into smooth muscle cells of brain vessels is accomplished by the Receptor Operated Calcium channels ("ROC"). These channels are opened for extracellular calcium by the receptor-action of serotonin and prostaglandins, as well as by K⁺-induced depolarisation. Calcium influx can be prevented by the calcium antagonist Nimodipine which has a special affinity to the ROC's.

Considerations have been made for the treatment of cerebral ischemia and cerebral vasospasm. In patients, intraoperative topical administration of Nimodipine dilated the intracranial portion of the internal carotid artery and its major branches, above all, however, its smaller branches. The present study has been performed in order to observe in vivo reactions of small pial vessels during continuous intravenous administration of Nimodipine in patients.

Selection of Patients and Methods

Investigations were performed in 16 patients, 3 women and 13 men with a mean age of 54 years (ranging between 30 and 69 years). Five patients had suffered transient ischemic attacks. The others had suffered a completed stroke 11 weeks prior to scheduled surgery on the average (ranging between 5 weeks and 6 months); computerized tomography had revealed cerebral infarction. Angiographically, carotid occlusion or high cerebral stenosis had been found according to the neurologically symptomatic side. During extracranial-intracranial arterial (EC-IC) bypass surgery, the cortical surface of the frontal and temporal lobes adjacent to the peripheral portion of the Sylvian fissure was exposed through a small osteoplastic craniotomy. On opening of the dura, special care was taken to preserve the arachnoid membrane and therefore normal CSF circulation in the subarachnoid space around investigated vessels. Before continuing surgery and performing the superficial temporal artery to middle cerebral artery anastomosis, a 10 minutes' delay was used to perform the following investigation: Reactions of pial arteries and veins were observed through a Zeiss operating microscope and photographed in minute-intervals before and during 10 minutes' continuous intravenous infusion of 1 μg/kg/min. Nimodipine, or Placebo, as a randomized blinded study. Before and at the end of the treatment, blood gases were checked.

Mean arterial blood pressure (MAP) was continuously recorded via a catheter to the radial artery, using a Statham P23Db pressure transducer and a Hellige 1214-type electromanometer. Anaesthesia was induced with 5 mg/kg sodium-pentobarbital and continued with N₂O/O₂ and continuous infusion of Fentanyl® (Janssen, Beerse, Belgium). Relaxation was performed with 4 mg Pavulon® (Pancuronium-bromide). Diameter variations of defined pial arterial portions were measured from magnified color slides. Measurements with a millimeter scale were performed by two persons not informed about the aim of the study. Moreover, the slides from each patient were projected for measurements in a randomised order unrelated to the sequence in which they had been made during surgery. The arithmetical mean value of the two measurements by two investigators from each individual vessel portion was used for further evaluation. Statistical calculation was performed using F-Test and t-test.

Results

The mean resting diameter of 132 investigated pial arteries was 87 ± 4 μm (range 25 to 305 μm); 27 pial veins had a mean resting diameter of 153 ± 8 μm (range 73 to 229 μm). 75 pial arteries had resting diameters up to 70 μm, 57 above 70 μm.

Five minutes after beginning of Nimodipine-infusion, mean overall pial arterial dilatation was 8.1 ± 2.4% (mean standard error SEM), significantly different from arteries in the Placebo-treated group (−1.4 ± 1.3%). After 10 minutes, a 6.3 ± 2.4% Nimodipine-induced dilatation was observed, significantly more than the 1.6 ± 1.4% of the Placebo-group (fig. 1a, b).
NIMODIPINE INFUSION DURING EC-IC BYPASS/Auer et al.

![Graph showing percentage dilatation of pial vessels during continuous infusion of Nimodipine (NIMO) or Placebo-treatment.](image)

**Figure 1.** Percentage dilatation of pial vessels during continuous infusion of Nimodipine (NIMO) or Placebo-treatment.

*p < 0.01.  
**a.** Total number of pial arteries (OA) compared to Placebo.  
**b.** Comparison of dilatation of pial arteries smaller than 70 μm vessel diameter (< 70 μm).  
**c.** Reactions of pial veins (OV). N = number of investigated vessel portions.

Pial arteries smaller than 70 μm dilated 18.4 ± 4.9% (SEM) five minutes after beginning of Nimodipine-infusion, again significantly different from vessels in Placebo-treated patients (−0.4 ± 2.1%). After 10 minutes, small arteries' dilatation was 12.9 ± 4.4%, significantly more than the 3.6 ± 2.3% in the Placebo-group.

A 2% and 1%, respectively, dilatation of arteries larger than 70 μm was not significantly different from Placebo-reactions.

As shown in figure 1c, pial venous reaction to Nimodipine did not significantly differ from Placebo-treated patients, though a 5% dilatation was noted at 10 minutes with Nimodipine.

During Nimodipine-administration, mean arterial pressure (MAP) remained stable in 3 patients, decreased in the others; the mean decrease of 10% from 117.8 ± 10 mmHg to 104.8 ± 8 mmHg was statistically insignificant. In the Placebo-group, MAP was 98 ± 6 mmHg before and 95.5 ± 7 mmHg after 10 minutes' treatment (table 3).

In the Nimodipine-group, PaO2 was 107.8 ± 14 mmHg before and 101 ± 10 mmHg at the end of treatment. PaCO2 was 34.8 ± 9.8 mmHg and 34 ± 1.2 mmHg, respectively. In the Placebo-group, PaO2-values were 120 ± 12 mmHg and 131 ± 11 mmHg, respectively; PaCO2 was 29 ± 2 mmHg before and 29 ± 1.5 mmHg at the end of the 10 minutes' period (tables 1 and 2).

No complications were observed attributable to the Nimodipine-treatment.

**Discussion**

The present series showed that a dose of 1 μg/kg/min of Nimodipine dilates small pial resistance-vessels without significantly lowering blood pressure. An autoregulatory response due to blood pressure changes cannot be the explanation for the observed dilatations, since 15% MAP-reduction in a placebo-treated patient induced no marked dilatation; in addition, dilatation of 12.7% and 8.2% was measured in patients with stable MAP. Experimental investigations showed that autoregulatory dilatation of small pial arteries occurs only at mean arterial pressure below 80 mmHg.14 The observation of a more pronounced dilatation of small arteries as compared to larger ones is similar to previous experimental data obtained with Nimodipine.1,13

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**Table 1 PaCO2**

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TABLE 2 PaO₂

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The substance has primarily become interesting for prevention and treatment of cerebral vasospasm from subarachnoid hemorrhage. The dose-response relation from the present series in man (18% dilatation of small arteries) is also comparable with the previous results obtained in cats (25% dilatation). A longlasting effect as observed in the cat study, however, could not be measured in the present investigation for evident ethical reasons. Repeatedly, the relevance of observing pial vessels for conclusions on CBF has been a matter of debate. Such discussion is not necessary if the goal of treatment is dilatation and/or prevention of constriction of pial arteries. It appears, however, of some interest to consider, that intraparenchymal arteries should react to a calcium-antagonist the same way as pial arteries, hence suggesting dilatation of both intra- and extraparenchymal vessels. As a consequence, increasing CBF could be expected. Significant CBF-increase due to Nimodipine was in fact shown both in animal experiments and in patients. In one experimental series, rCBF, measured with the hydrogen clearance technique, rose even significantly despite a significant fall in blood pressure. This effect of Nimodipine in comparison to other so-called 'vasoactive drugs' of the same pharmacological group can be explained with its predominantly cerebrovascular effect: cerebral vasodilatation is achieved before systemic blood pressure falls significantly, as shown by the present data as well as other experimental investigations. The dilatory effect is stronger than other known vasodilators such as papaverine. Moreover, the in vitro effect lasts at least several hours compared to a few minutes with papaverine.

The substance has primarily become interesting for prevention and treatment of cerebral vasospasm from subarachnoid hemorrhage. A second topic of recent investigation has become the effect of nimodipine in the early stage of cerebral ischemia to counteract the deleterious effect of increased intracellular Ca²⁺ and probably serotonin-induced vasoconstriction.

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Transientorial Diaschisis: Reduction of Cerebellar Blood Flow Caused by Supratentorial Local Cerebral Ischemia in the Gerbil

Hiroaki Naritomi, M.D.

SUMMARY To assess the effect of supratentorial cerebral ischemia on infratentorial brain function, changes in regional cerebellar blood flow (rCeBF), after right carotid occlusion for 4 hours, were studied in 30 mongolian gerbils. The regional cerebral blood flow (rCBF) in the occluded cerebral hemisphere and rCeBF in both cerebellar hemispheres were measured simultaneously by hydrogen clearance methods. Before carotid occlusion, rCBF was 0.44 ± 0.07 ml/g brain/min, and rCeBF in the left and right cerebellar hemispheres was 0.37 ± 0.09 and 0.40 ± 0.09 ml/g brain/min, respectively. After carotid occlusion, rCBF decreased in all animals showing levels of above 0.20 ml/g brain/min in 14 (group A), between 0.10 and 0.19 ml/g brain/min in 7 (group B) and below 0.10 ml/g brain/min in 9 (group C). rCeBF exhibited no changes in group A and a mild reduction in group B after carotid occlusion. In group C, rCeBF was significantly reduced 30 min after carotid occlusion in the left cerebellar hemisphere followed subsequently by bilateral reduction. In groups B and C, supratentorial brain edema was observed 4 hours after occlusion, but the degree of edema was moderate. The results of the present study suggest that depression of infratentorial brain function may occur after supratentorial local cerebral ischemia, presumably due to diaschisis.

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IT HAS BEEN REPEATEDLY SHOWN during the last several decades that in acute unilateral cerebral infarction, cerebral blood flow and metabolism may be reduced in both cerebral hemispheres. As first described by Von Monakow who used the term "diaschisis," local cerebral ischemia may cause depression of the function in remote areas of brain presumably by a transneural mechanism. However, little is yet known concerning whether such a remote effect also influences the infratentorial brain reducing the blood flow and metabolism of the brain stem as well as the cerebellum.

In the present study, the regional cerebellar blood flow (rCeBF) was repeatedly measured before and after unilateral carotid occlusion in mongolian gerbils. The purpose of the study was to clarify whether supratentorial cerebral ischemia provides remote depressive effects on the infratentorial brain function.

Methods

Operative Procedure

Thirty-six adult gerbils weighing 55 to 90 g were lightly anesthetized by intraperitoneal injection of pentoobarbital (40 mg/kg). The animals were allowed to breathe spontaneously throughout the experiments. PE-10 polyethylene catheters were introduced into the...
Human pial vascular reactions to intravenous Nimodipine-infusion during EC-IC bypass surgery.

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