Effects of Nimodipine on Acute Focal Cerebral Ischemia

G. H. Barnett, M.D.,* Bikash Bose, M.D.,* John R. Little, M.D.*, Stephen C. Jones, Ph.D.,†‡ and Harry T. Friel, M.S.*

SUMMARY Nimodipine is a calcium slow channel blocker with several pharmacologic properties suggesting the potential to favorably modify outcome in focal cerebral ischemia. Thirty adult cats underwent unilateral middle cerebral artery (MCA) occlusion for 4 hours. Seventeen cats were treated with an ipsilateral intracarotid infusion of nimodipine (1 μg kg⁻¹ min⁻¹) beginning 15 minutes before MCA occlusion and continuing throughout the occlusion period. Eight nimodipine treated cats maintaining MAP > 90 mmHg were assigned to a Higher Pressure Nimodipine (HPN) group. The remaining nine treated cats with MAP < 90 mmHg were assigned to the Lower Pressure Nimodipine (LPN) group. Thirteen cats were untreated, receiving an isovolumetric amount of vehicle through the ipsilateral carotid artery. Local cerebral blood flow (rCBF) was continuously monitored using thermal diffusion probes. The brains, assessed for colloidal carbon perfusion, fluorescein and Evans blue staining, electroencephalographic activity (EEG), and histological changes, revealed no significant differences by any of these methods between the HPN and control animals with the exceptions of: 1) HPN treated cats exhibited a preservation of EEG activity at 15 minutes post-occlusion compared to the untreated cats, and 2) Post-ischemic surface colloidal carbon perfusion was better preserved in the treated cats than in the untreated cats. Mild hypotension, as demonstrated by the LPN group, negated these two positive effects. Prior to MCA occlusion, ICBF was bilaterally significantly increased after nimodipine infusion in the HPN group as compared to vehicle infusion. Intra-arterially infused nimodipine did not reduce infarct size.

AN EFFECTIVE REGIMEN for the treatment of acute focal cerebral ischemia remains elusive despite testing of a host of theoretically promising compounds. Rational approaches to therapy should ideally be directed toward improvement of tissue perfusion, edema reduction, and preservation of tissue (particularly neuronal) viability. Attention has been directed toward the calcium entry blocking as potential therapeutic agents in acute focal cerebral ischemia¹,² because of several pharmacologic properties these agents possess in keeping with these goals.

The Ca²⁺ entry blocking agent, verapamil, has been evaluated in cats undergoing MCA occlusion.³ Treatment with this drug did not favorably modify rCBF and EEG changes, blood-brain barrier breakdown, or infarct size. Nimodipine, a calcium entry blocking agent with more potent effects upon the cerebral vasculature,⁴ might be more effective in improving collateral circulation during acute focal cerebral ischemia and thereby reducing ischemic damage. An earlier study by Harris et al.,¹ however, failed to show any clear-cut benefit from treatment with nimodipine in baboons undergoing unilateral MCA occlusion. The present study was designed to evaluate the potential utility of nimodipine as an agent to improve collateral circulation and to limit focal cerebral ischemic damage in cats undergoing MCA occlusion.

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From the Departments of Neurological Surgery, * Neurology, † and Cardiovascular Research, ‡ Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.

This study was funded, in part, by a grant from Miles Laboratories. Address correspondence to: John R. Little, M.D., Department of Neurological Surgery, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, Ohio 44106.

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Methods and Materials

Cat Preparation

A detailed account of the surgical model has been previously reported.³ Anesthesia in 30 adult cats was induced with subcutaneous ketamine hydrochloride (35 mg/kg) and atropine (0.6 mg/kg), while maintained with a 75% nitrous oxide and 25% oxygen mixture. The animals underwent tracheostomy and were mechanically ventilated after being paralyzed with tubocurarine chloride or gallamine. Femoral venous and arterial catheters as well as a right lingual artery catheter were placed. Rectal temperature was maintained at 37 degrees Celsius. Electrocardiogram, arterial pressure and end tidal CO₂ were continuously monitored. Arterial blood gases were periodically sampled. PaCO₂ was maintained between 30–35 Torr and PaO₂ ≥ = 100 Torr.

The orbit was exenterated and a small craniectomy performed at the orbital apex. Using microsurgical techniques, the portion of the MCA immediately underlying the optic nerve was dissected free. The scalp and temporalis muscles were removed and 15 mm trephinations made bilaterally for the later placement of the thermal diffusion probes. Bolt electrodes (#2-56) were placed about the trephinations for bipolar electroencephalographic (EEG) recording. An account of the recording techniques has been previously published.³

Cerebral Blood Flow

The dura exposed by the previous trephination was carefully removed. Thermal diffusion flow probes and monitor (Flowtronics, Inc., 10250 No. 19th Ave., Suite B, Phoenix, Arizona, 85021), were calibrated and applied lightly to the cortical surface. Measurements of temperature differences with the Peltier stacks in operation as well as stack current and "flow"
were recorded. Continuous recording of "flow" was carried out on a Gould Mark 220 chart recorder (Gould Inc. Co., Cleveland, OH 44114).

MCA Occlusion and Treatment Groups
The right MCA was occluded for 4 hours with a miniature aneurysm clip directly overlying the right optic nerve. Thirteen cats were randomly assigned to the vehicle-infused group (all of which had Mean Arterial Pressures [MAP] > 90 mmHg) and 17 animals to the nimodipine infusion groups. The nimodipine animals were subdivided into those with MAP > 90 mmHg (Higher Pressure Nimodipine [HPN]) throughout each experiment, and 9 phlebotomized cats with MAP < 90 mmHg (Lower Pressure Nimodipine [LPN]). On the morning of each experiment the nimodipine solution was prepared to provide a dose of 1 μg kg⁻¹ min⁻¹ at an infusion rate of 0.2 ml/min. Each 10 ml of vehicle contained 1.5 g ethanol, 1.5 g polyethylene glycol 400, 0.02 g sodium citrate, 0.003 g citric acid, and 7 g water. The nimodipine was protected from light during both preparation and infusion and was initially dissolved in ethanol. Bioactivity of the nimodipine solution distinct from that of the vehicle had been previously confirmed in our laboratory by the production of dose-dependent hypotension. Beginning fifteen minutes prior to MCA occlusion the 17 treated cats received an infusion of nimodipine, 1 μg kg⁻¹ min⁻¹, via the lingual artery catheter, administered via an IMED 965 microinfusion pediatric pump (IMED Corp., 9925 Carroll Canyon Rd., San Diego, CA 92131) and continued throughout the experiment until time of sacrifice. Similarly, the 13 control animals received the vehicle solution at the same rate. Systemic stability was maintained in the 30 cats undergoing right MCA occlusion. One animal was treated with aramine to control an episode of transient hypotension.

Perfusion and Examination of Brains
Three and one-half hours after MCA occlusion intravenous Evans blue dye and sodium fluorescein were administered. At the end of the ischemic period, the aneurysm clip was removed, and 100 ml of heparinized saline, followed by 100 ml of colloidal carbon and 100 ml of phosphate buffered (7.4 pH) 4% formaldehyde were infused at 120 Torr pressure into the aorta. After a 30 minute period the brain of each animal was removed, and placed in 4% phosphate buffered formaldehyde (7.4 pH) for at least 48 hrs prior to pathologic preparation. The presence or absence of Evans Blue dye and fluorescein extravasation were recorded as indices of blood-brain barrier disruption. The distribution of carbon staining was graded according to Crowell and Olson. Paraffin embedded coronal hemispheric sections, stained with hematoxylin and eosin and periodic acid Schiff, were examined by light microscopy. In coronal sections of each hemisphere 3 mm posterior to the temporal poles, the cross-sectional area of gray area where moderate and severe neuronal alterations (grade II, III) predominated was measured by a blinded observer using a bit pad planimetry device.

Statistical Analysis Methods
Statistical analysis was performed on the following physiological parameters: arterial blood pressure, heart rate, thermister temperature difference on both control and ischemic hemispheres, E EG slow wave activity and EEG fast wave activity. One-way analysis of variance with repeated measures was performed on measurements taken at 5 time periods: 15 min pre-infusion (C), 15 min post-infusion (T1), 15 min post-occlusion (T2), 2 hrs post-occlusion (T3) and 3.75 hrs post-occlusion (T4). If the analysis of variance test showed a significant difference with time (p < 0.05) the following tests were performed: paired-T test for C vs T1 (significance level = p < 0.05) and multiple unpaired-T tests with a Bonferroni correction for T1 vs T2, T3 and T4 using a significance level of p < 0.017. If the analysis of variance showed a significant difference between treatment groups unpaired-T tests with a Bonferroni correction were done at each of the 5 time periods (significance level = p < 0.01).

Comparisons of infarct size were carried out using unpaired-T tests (significance level = p < 0.05). Comparisons of gross exam measurements were performed using Mann-Whitney rank sum tests (significance level = p < 0.05). The above statistical analysis was performed on the following 2 groupings: vehicle vs higher pressure nimodipine (HPN), and HPN vs lower pressure nimodipine (LPN). All results were expressed as mean ± standard error of the mean.

Results
Vital Signs
No significant change in blood pressure occurred after beginning infusion with nimodipine or vehicle, nor during the four hour ischemic period (fig. 1). He-

![Mean Arterial Blood Pressure](https://example.com/meanarterialbloodpressure.png)

**FIGURE 1.** Mean Arterial blood Pressure (MAP) of untreated cats, Higher Pressure Nimodipine (HPN) treated cats, and Lower Pressure Nimodipine (LPN) treated cats. Note stability throughout 4 hour duration of experiments.
TABLE 1 Physiologic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Hemoglobin (Gm/dl)</th>
<th>PaCO₂ (Torr)</th>
<th>pH</th>
<th>PaO₂ (Torr)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle treated cats</td>
<td>15.0 (0.7)</td>
<td>33.9 (0.5)</td>
<td>7.31</td>
<td>144.9 (0.01)</td>
<td>115.5 (3.2)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>15.5 (0.7)</td>
<td>30.8 (0.5)</td>
<td>7.33</td>
<td>145.6 (0.01)</td>
<td>120.4 (5.9)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>12.9 (0.5)</td>
<td>33.4 (0.6)</td>
<td>7.31</td>
<td>141.6 (0.01)</td>
<td>82.8 (2.9)</td>
</tr>
</tbody>
</table>

Mean (± standard error of the mean).

Hemoglobin was 15.1 ± 3.9 Gm/dl in the vehicle group and 15.1 ± 2.7 Gm/dl in the H.P.N. treated group. Arterial pCO₂, pO₂, pH and MAP were not statistically different except for lower blood pressure in the LPN group (table 1).

Cerebral Blood Flow

The reciprocal of the difference in temperature (T.D. −¹) across the Peltier stack/thermister array is plotted vs time in figure 2 for the vehicle infused animals and HPN animals. T.D. −¹ values for all groups are shown in table 2. Previous studies have demonstrated that increasing T.D. −¹ corresponds to increasing ICBF. For HPN cats, an increase in flow compared to preinfusion control (C) was noted bilaterally after infusion (I) of nimodipine (0.307 ± 0.030 °C−¹ vs 0.319 ± 0.032 °C−¹, p = 0.032 contralaterally and 0.313 ± 0.040 °C−¹ vs 0.342 ± 0.059 °C−¹, p =
TABLE 2 Local Cerebral Blood Flow

<table>
<thead>
<tr>
<th>Ischemic hemisphere (°C-1)</th>
<th>Control</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle treated cats</td>
<td>0.330(0.012)</td>
<td>0.336(0.014)</td>
<td>0.235(0.004)</td>
<td>0.228(0.004)</td>
<td>0.237(0.005)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>0.313(0.014)</td>
<td>0.342(0.021)</td>
<td>0.242(0.008)</td>
<td>0.246(0.011)</td>
<td>0.252(0.011)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>0.319(0.011)</td>
<td>0.323(0.011)</td>
<td>0.226(0.005)</td>
<td>0.227(0.004)</td>
<td>0.228(0.003)</td>
</tr>
<tr>
<td>Control hemisphere (°C-1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle treated cats</td>
<td>0.328(0.012)</td>
<td>0.331(0.011)</td>
<td>0.3295(0.011)</td>
<td>0.321(0.010)</td>
<td>0.314(0.013)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>0.307(0.011)</td>
<td>0.319(0.011)</td>
<td>0.315(0.010)</td>
<td>0.315(0.011)</td>
<td>0.328(0.010)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>0.307(0.008)</td>
<td>0.308(0.009)</td>
<td>0.304(0.009)</td>
<td>0.301(0.009)</td>
<td>0.305(0.007)</td>
</tr>
</tbody>
</table>

Temperature difference \( T^1 \) across Peltier stacks. Mean TD \( T^1 \) (± standard error of the mean).

0.017 ipsilaterally). No such increase was observed from vehicle infusion alone (0.328 ± 0.044 °C-1 vs 0.331 ± 0.043 °C, not significant, NS) contralaterally and 0.330 ± 0.045 °C-1 vs 0.336 ± 0.050 °C-1, NS ipsilaterally (fig. 2d)), nor in the LPN animals. A marked decrease in T.D. \( T^1 \), indicative of decreased CBF, occurred coincident with right MCA occlusion in both treated and untreated groups (0.342 ± 0.059 °C-1 vs 0.241 ± 0.022 °C-1, \( p = 0.005 \) for nimodipine animals; 0.336 ± 0.050 °C-1 vs 0.235 ± 0.015, \( p = 0.0001 \) for vehicle animals. No change in T.D. \( T^1 \) compared to post-infusion values was observed in the contralateral side after MCA clipping. This index of CBF remained unchanged throughout the period of occlusion, bilaterally (\( p > 0.05 \)).

EEG Findings

The EEG background consisted of 5–10 Hz activity of up to 50 μV. No significant change of either fast or slow activity expressed as the percentage of left hemisphere control amplitude was encountered after infusion of vehicle or nimodipine were begun. Slow wave activity was assessed as percentages at 15 minutes, 2 hours and 3.75 hours post-occlusion compared to left hemisphere control values. A significant post-occlusion reduction was found irrespective of treatment (\( p = 0.009 \) for nimodipine, \( p = 0.0005 \) for vehicle). Similar assessment of fast activity failed to demonstrate a significant reduction at 15 minutes post-occlusion in normotensive nimodipine treated animals (\( p = 0.118 \)). Significant reduction of this activity was encountered in vehicle treated animals at this interval (\( p = 0.002 \)), and in both groups thereafter (\( p = 0.006 \)). Lower pressure nimodipine treated animals exhibited reduction of both fast and slow activity post-occlusion.

Morphological Studies

Carbon perfusion was technically unsatisfactory in one untreated cat. The right MCA and its branches in the remaining cats were well filled with carbon fixative solution, confirming vessel reperfusion after aneurysm clip removal. The distribution of carbon filling in brains of treated and untreated cats are summarized in table 3. The mean right to left shift of midline structures was 0.3 mm in the vehicle treated group and 0.2 mm for both groups treated with nimodipine. Carbon perfusion defects of the caudate nucleus were present in 3/13 untreated and 0.8 HPN treated animals. One LPN cat did not receive Evans Blue dye and Fluorescein. The presence of fluorescein and Evans Blue dye extravasation is summarized in table 4. Surface colloidal carbon perfusion was significantly better in the HPN treated group as compared to the untreated group.

TABLE 3 Distribution of Carbon Filling in Brains of Untreated and Nimodipine Treated Animals Four Hours After Right MCA Occlusion

<table>
<thead>
<tr>
<th></th>
<th>No pallor</th>
<th>Grade 1 pallor</th>
<th>Grade 2 pallor</th>
<th>Grade 3 pallor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>3 (25)</td>
<td>6 (50)</td>
<td>2 (17)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>4 (50)</td>
<td>0 (0)</td>
<td>4 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>1 (11)</td>
<td>3 (33)</td>
<td>3 (33)</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

Number of animals (percentage).

TABLE 4 Extravasation of Dyes in Brains of Untreated and Nimodipine Treated Animals Four Hours After Right MCA Occlusion

<table>
<thead>
<tr>
<th></th>
<th>None-mild</th>
<th>Moderate-marked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein staining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle treated cats</td>
<td>3 (23)</td>
<td>10 (77)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>2 (25)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>1 (13)</td>
<td>7 (87)</td>
</tr>
<tr>
<td>Evans blue staining</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle treated cats</td>
<td>12 (92)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>HPN treated cats</td>
<td>7 (87)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>LPN treated cats</td>
<td>7 (87)</td>
<td>1 (13)</td>
</tr>
</tbody>
</table>

Number of cats (percentage).
however (p = 0.05). The LPN treated group showed no such improvement.

Microscopically, severe ischemic neuronal alterations were present in the caudate nucleus and/or cortex in all cats. Substantial astrocyte swelling, capillary narrowing and obstruction were invariably seen in areas where neuronal changes were noted. The percentage of ischemic gray matter cross-sectional area was 27.8% ± 4.0% in untreated animals and 23.3% ± 9.0% in HPN treated animals. The difference in size of infarct between untreated and treated animals did not achieve statistical significance as determined by the unpaired t-test (p = 0.11).

Discussion

Compared to currently available calcium antagonists nimodipine has a preferential vasodilatory effect on cerebral vasculature with respect to its systemic vascular effects.11,12 In vitro basilar and pial artery preparations have demonstrated that nimodipine acts as an antagonist toward pharmacologically induced contraction and has a direct dilatory effect.11,12 Auer found a significant dose–dependent pial artery dilatation in cats without decrease in BP until infusion exceeded 1 μg kg⁻¹ min⁻¹. No significant venodilatory effect was noted, however.

This dilatory effect on cerebral vessels, however, has not uniformly resulted in significant increases in cerebral blood flow. Harper et al studied the effects of nimodipine on the rCBF and cerebral metabolism of baboons.13 This agent was found to increase rCBF, the effects being greatest with intracarotid infusion (i.e. 46–57% above control). rCBF was also increased after urea-induced disruption of the blood brain barrier. The administration of nimodipine did not change the cerebral metabolic rate for oxygen. In closed skull preparations, Harris and associates found no increase in basal CBF in baboons given 0.6 μg kg⁻¹ min⁻¹ of nimodipine via lingual artery catheter. In open skull preparations, however, nimodipine was found to markedly increase basal cerebral blood flow15 and also resulted in derangements of cerebral vascular responsiveness to arterial PCO₂ and autoregulation with respect to hypotension.14 Mohamed et al found autoradiographic evidence of increased basal CBF in 9 of 31 cerebral regions in closed skull rat preparations.16 Ott and Lechner found no effect on basal blood flow,1 whereas Craigen et al found an opposite effect. Our results showed a consistent bilateral increase in basal CBF after nimodipine infusion compared to vehicle infused animals. No difference between ipsilateral vs contralateral flow elevations was detected.

Calcium entry blocking agents may have potent effects on the cardiovascular system.18 Nimodipine has been demonstrated to have the potential to impair myocardial performance11,18 and to produce dose–dependent hypotension.9 As these hemodynamic effects may impair cerebral perfusion,19 a population of cats where the MAP was slightly reduced, yet well within the limits of autoregulation, was assessed (the LPN treated cats). The above-noted improvements in basal flow were negated by the mild hypotension of the LPN treated cats.

Nimodipine’s effect on regional cerebral blood flow during focal ischemia remains unclear. In Harris et al’s study of rCBF in baboons undergoing MCA occlusion in both open and closed skull preparation,15 treatment was found to improve rCBF after occlusion in the open skull studies. Rats subjected to 15 minutes of forebrain ischemia, pretreated with 0.1 mg kg⁻¹ of nimodipine, showed patchy areas of increased perfusion admixed with areas of hypoperfusion, yielding a net increase in rCBF.20 No difference in electrical recovery was found between animals given nimodipine vs vehicle.20 Ott and Lechner found that oral nimodipine caused redistribution of blood flow in an infarcted hemisphere. Blood flow in ischemic areas increased, whereas that in hyperemic areas, decreased. This increase in collateral circulation has been suggested as a mechanism underlying the protective effect of Ca⁺⁺ antagonists found by workers investigating myocardial ischemia.21

Our investigation failed to demonstrate a significant increase in ICBF after intracarotid infusion of nimodipine vs vehicle during acute focal cerebral ischemia. Basal flow, however, was increased after the agent was administered, further supporting the potential activity of nimodipine (and the dihydropyridines) as potential cerebral dilators. As the microvasculature surrounding an ischemic zone undergoes spontaneous maximal vasodilatation, it is likely that administration of an agent with vasodilatory properties, such as nimodipine, does not produce further vasodilatation or substantially increase collateral flow to the ischemic zone. Indeed, experience with other cerebrovasodilators such as induced hypercapnea and prostacyclin have not proven encouraging.22 It would seem unlikely that the vasodilatory properties of Ketamine may have augmented the above mechanism as the agent was administered more than 4 hrs before flow measurements were initiated.23 As in all animal and human studies, species and model differences warrant caution in interpretation of results.

Cerebral Protective Effect of Nimodipine

It has been suggested that the therapeutic potential of Ca⁺⁺ antagonists in cerebral ischemia may not rest solely on their effects on cerebral blood flow.24,25 Farber et al24 have suggested that an ischemia-induced loss of Ca⁺⁺ homeostasis causes a substantial increase of cytoplasmic Ca⁺⁺. The influx of Ca⁺⁺ is ordinarily coupled to a preceding efflux of K⁺, occurring 1–2 minutes after the onset of profound ischemia,18 suggesting disruption of normal ATP dependent ionic pumps. A rise in intracellular Ca⁺⁺ may initiate or contribute to numerous processes which may jeopardize neuronal integrity.25,26 This “Ca⁺⁺-overload” hypothesis states that activation of these deleterious mechanisms (including production of arachidonic acid, prostaglandins, thromboxanes, leukotrienes and super-oxide radicals) may substantially contribute to irreversible myocardial, neuronal or vascular injury following ischemia.27 Irreversible loss of mitochon-
drial activity may be an equally important factor in determining cell death. A reduction in myocardial work, however, is an important protective mechanism yielded by Ca++ antagonists in myocardial ischemia. There is evidence for an analogous reduction in neuronal metabolism being affected by nimodipine or other organic Ca++ antagonists, as such, their protective potential may be more limited than for the heart.

Evidence that cerebral tissue is subject to increases in intracellular Ca++ content in ischemia is implied from studies by Harris et al who measured the extracellular Ca++ concentration of the cortex of baboons undergoing MCA occlusion. They reported a decrease in extracellular Ca++ after MCA occlusion which was produced by an rCBF reduction to the 5-10 ml 100 gm^-1 min^-1 range. The decrease in the Ca++ concentration followed an increase in the extracellular K^+ concentration. The decrease in the extracellular Ca++ concentration has been interpreted as an intracellular shift of Ca++. Conflicting evidence exists regarding the protective and restorative benefits of nimodipine in different models of cerebral ischemia. Improved survival and reduction of deficit and/or ischemic damage has been demonstrated in several studies of complete cerebral ischemia. Hofmeister et al demonstrated markedly increased survival rate in cats subjected to complete cerebral ischemia when pretreated with nimodipine 1 mg kg^-1 po 15 min before ischemia. In an allied experiment, improved survival and decreased retrograde amnesia in mice subjected to hypoxia were shown as well. Steen et al reported significantly better neurologic recovery from 10 minutes of aorticaval occlusion in dogs pretreated with a 10 μg kg^-1 bolus of nimodipine followed by a 1 μg kg^-1 min^-1 infusion. Institution of treatment after restitution of flow, however, proved less efficacious.

The effect of Ca++ entry blocking agents upon the pathophysiologic evolution of acute focal cerebral ischemia appears less promising. In a recent report, Harris et al described the effects of nimodipine, in baboons undergoing MCA occlusion for 90 minutes. Nimodipine did not alter K^+ or Ca++ extracellular activity at normal flows. However, when reduced flow states were assessed, K^+ and Ca++ activities were altered in the nimodipine treated animals, while ion homeostasis was still preserved in the control group. This result is compatible with an increased susceptibility to disruption of ionic homeostatic mechanisms with nimodipine. The findings of this study would suggest that rather than inhibit Ca++ influx to cerebral tissue, nimodipine may enhance the process. Further, Hossman et al found increased tissue Ca++ content after complete cerebral ischemia in the cat only in those animals with metabolic recovery and no effect on Ca++ content after administration of Flunarizine, another Ca++ antagonist.

Our study demonstrated a short-lived preservation of EEG in HPN treated cats after onset of acute focal ischemia and improved surface colloidal carbon perfusion; however, all other parameters, in particular, infarct size, were unaffected. Mild hypotension negated any observed beneficial effects. As such, both verapamil and nimodipine have failed to provide a clear-cut benefit in this model of focal cerebral ischemia. There are several reasons why nimodipine and other dihydropyridine-based Ca++ antagonists may not have a significant protective effect on neuronal integrity. First, it is possible that the large supplies of intracellular Ca++ which already exist in various organelles (and not inhibited by these agents) may play a pivotal role in cerebral ischemic injury. Further, Ca++ membrane channels differ between tissues, particularly in their sensitivity to Ca++ blocking agents. Although Heffez has provided evidence that pharmacologic cerebral tissue concentrations are attainable, the ability of the presently available dihydropyridine Ca++ antagonists to have significant binding to neuronal or glial Ca++ membrane channels would appear to be exceedingly region-specific. There is conflicting evidence as to whether these drugs are capable of blocking these neuronal voltage operated Ca++ channels, although more recent work supports their ability to do so. Other agents capable of inhibiting neuronal Ca++ influx exist as well and include several anticonvulsants. It is intriguing that propranolol has had limited efficacy in reducing infarct size in this model and also has certain Ca++ blocking properties. There is evidence to suggest that these dihydropyridine agents may enhance Ca++ influx for cerebral cells during ischemia and that ischemic edema is worsened by their administration. Although not supported by our data, several studies suggest improved flow by these agents during and after ischemia. Overall outcome may well reflect the summation of nimodipine's potential deleterious effect on ischemic cerebral tissue vs its apparent cerebrovascular protective effects. Although treatment with nimodipine has theoretical benefits, the results of this study do not support a profound protective effect. The few beneficial effects were negated by mild hypotension, reinforcing the importance of maintaining normotension when evaluating or using this drug. Substantial gaps in the understanding of the function of Ca++ antagonists are underscored by their apparent deleterious effects on extracellular ion homeostasis and water content in ischemic cerebral tissue. It remains to be established that the benefits of Ca++ antagonists outweigh their liabilities in focal cerebral ischemia.

References
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