The Effects of a Calcium Antagonist, Nimodipine, Upon Physiological Responses of the Cerebral Vasculature and Its Possible Influence upon Focal Cerebral Ischaemia


SUMMARY The effects of a calcium antagonist, nimodipine, were tested on the response of the cerebral circulation to arterial pCO₂ and blood pressure changes. The effects of reduced blood flow upon oedema formation and extracellular ion homeostasis under nimodipine preloading were studied. Both open and closed skull primate models were used, with alpha-chloralose anaesthesia. Nimodipine infusion increased basal blood flow in the open skull, but not the closed skull animals. Autoregulation to increased blood pressure was little affected. Responses to arterial pCO₂ changes and autoregulation to reduced blood pressure were severely impaired. Residual blood flow after middle cerebral artery occlusion was significantly higher with nimodipine than in controls. The threshold levels of blood flow for the development of cortical oedema and for disturbance of ion homeostasis were, however, increased, suggesting that nimodipine interferes with cellular energy metabolism and increases the susceptibility of tissue to ischaemic damage.

Stroke, Vol 13, No 6, 1982

THERE HAS BEEN CONSIDERABLE RECENT DISCUSSION on the mechanism of cell injury in ischaemia, much of which has centred on the role of calcium.¹ ² The hypotheses put forward propose that increased intracellular calcium activity exerts its pathological effects not only by the physical effects of mitochondrial calcium accumulation,³ but also through stimulation of membrane phospholipid breakdown.¹ ² A possible basis for the suggestion that calcium plays a major role in the pathophysiology of ischaemia was provided by Schanne,⁴ who showed that a range of membrane-active toxins only caused toxic cell death in the presence of normal extracellular calcium activity. When the extracellular calcium activity was reduced to that of normal intracellular activity, the toxins had little effect.

Calcium antagonists⁵ are supposed to block calcium entry into cells under certain conditions. Their use appeared to be the obvious means to test whether an influx of calcium into the cells is involved in the pathophysiology of ischaemia. Fleckenstein⁶ described the action of calcium antagonists as a selective inhibition of the influx of calcium into the cell, by blockade of the so-called slow channels of the cell membrane. Other workers, using a variety of compounds and preparations, have confirmed Fleckenstein's proposal.⁷⁻¹⁰

Many workers have shown that calcium antagonists protect the myocardium from the effects of ischaemia,¹¹⁻¹⁵ although the mechanisms of this protection are unclear. Nimodipine has been shown¹⁶ to be one of the most potent calcium antagonists with a selective action on the intracranial vessels. Kazda et al.,¹⁶ have shown that nimodipine improves the post-ischaemically impaired flow in cats following 7 minutes total ischaemia, and the same group¹⁷ have shown increased survival rates and functional protection in the same preparation.

The present study was designed to test the effects of nimodipine on cerebrovascular physiological responses and on the pathophysiological effects of acute middle cerebral artery occlusion in primates.

Methods

Surgical preparation

Twelve baboons (Papio cynocephalus) in the weight range 6–8kg were used in 2 groups. In group 1, 7 animals were used to measure blood flow, CO₂ reactivity, extracellular ion homeostasis and oedema formation, and in group 2 the remaining animals were used to measure autoregulation to changing blood pressure.

All animals were anaesthetised with alpha chloralose (60 mg/kg i.v.) and immobilized with gallamine triethiodide (1 mg/kg as necessary). Respiration was maintained using pure oxygen delivered by a Starling pump at the appropriate stroke volume to maintain normocapnia or to alter the arterial pCO₂ for CO₂ reactivity determinations. Systemic pCO₂, pO₂, pH (using an Astrup BMS2 blood gas analyser) and serum electrolytes were frequently monitored. Both end tidal CO₂ and pulsatile blood pressure were continuously recorded. A large Ag/AgCl electrode was placed in the ani-
Area A is most affected and C the least. The distribution of regions of measurement within these areas are described in the text.

The effect of MCA occlusion on blood flow can be divided into 3 areas, A, B, C. Previous work has shown that Area A is most affected and C the least. The distribution of regions of measurement within these areas are described in the text.

The platinum electrodes were inserted in groups of 3 (of which at least 2 were recorded) into predetermined regions of the hemisphere, designated A, B and C in previous work, and were distributed across the exposed cortex as follows: 3 groups in area A, 2 in area B and 1 in area C as shown in figure 1. The effect of MCA occlusion in these areas has been described previously. Extracellular potassium (K) and calcium (Ca) activity were measured using triple-barrelled double ion sensitive microelectrodes (ISMs) described in detail previously. The ISMs were inserted 0.5–1.0 mm into the cortex in the region of 2 platinum electrodes. When all electrodes had been inserted, the cortex was covered by a warmed paraffin pool for protection.

In group 2, ICBF was measured in a closed skull preparation in order to test the effect of nimodipine on cerebral autoregulatory capacity. The middle cerebral artery was not occluded in this group and extracellular ion activities were not measured. Three burr holes were drilled on each side corresponding to areas A, B and C (fig. 1). Up to 16 platinum electrodes were inserted into the burr holes, two or three per hole, and held in place with acrylic which also stopped leakage of cerebrospinal fluid.

In all animals the right lingual artery was cannulated and the right external carotid artery ligated. A continuous slow infusion of warmed heparinised Hartman's solution (pH 7.4 at 0.1 ml/min) was maintained until the start of the nimodipine infusion. After control measurements of blood flow and either CO2 reactivity (group 1) or autoregulation (group 2), nimodipine was continuously infused into the lingual artery for the remainder of the experiment. Continuous infusion of nimodipine was necessary because of its short half-life in blood (about 10 mins.). The nimodipine solution was made up to give a dose of 0.6 μg/kg/min at an infusion rate of 0.2 ml/min. On the morning of each experiment a 0.1% stock solution of nimodipine was made using Lutrol (polyethylene glycol 400) as the solvent, and 0.3 ml of the stock solution per kg body weight was diluted in 100 ml of heparinised phosphate buffer, pH 7.4. The infusate was unstable in light of wavelength less than 450 nm and was therefore appropriately protected by preparing it under light from sodium vapour lamps, covering all infusion catheters in black rubber tubing and the infusing syringe with a Wratten 8 filter, and placing the whole infusion apparatus in a cardboard box. The windows were covered to exclude direct sunlight.

Experimental Protocols

The protocol for group 1 animals was as follows. The animal was allowed to stabilize for 30 minutes following electrode implantation after which a basal blood flow determination was made. The pCO2 was reduced from a normal value of 39–42 torr to a minimum of 34 torr to test the CO2 reactivity. The pCO2 was returned to normal, blood flow checked and the nimodipine infusion was started (and was continued for the rest of the experiment). The effect of nimodipine upon basal flow was tested for the next 45 minutes, CO2 reactivity was then retested and when the blood flow had been checked at normal pCO2, the MCA was occluded for 90 min. After the occlusion graded exsanguination was used to obtain the desired range of blood flows. At the end of the experiment, the brain was removed and immersed in kerosene prior to sampling the cortex for brain water determination.

The protocol for group 2 animals was as follows. After basal blood flow determination the mean arterial blood pressure was raised and held steady for 13 ± 3.8 mins. while blood flow was measured. This procedure was then repeated at a higher blood pressure. The blood pressure was raised by an i.v. infusion of aramine in a solution of 1 mg/ml at a rate of 0.3–1.3 ml/min. After the aramine infusion was turned off, blood pressure and flow were allowed to stabilize for 30–45 minutes, the nimodipine infusion was then started and continued for the rest of the experiment. Two or 3 blood flow measurements were made over the next 45 minutes after which the blood pressure was raised again, flow measured and the preparation again allowed to stabilise as described above. The blood pressure was then dropped stepwise by exsanguination and blood flow was measured at each step. When the blood pressure had been reduced to between 10–50 mm Hg the experiment was ended.
Calculations

CO₂ reactivity was defined²⁶ as the percentage change in flow (relative to the blood flow at higher pCO₂) per torr change in pCO₂ and expressed as % \( \cdot \) torr⁻¹.

Autoregulation was expressed²⁷ as the autoregulatory index, defined as the percentage change in flow per torr change in blood pressure and expressed as % \( \cdot \) torr⁻¹.

Results

Group I (Open skull)

In one animal infusion of the carrier, diluted in the normal way only without the drug, showed no change in blood flow or CO₂ reactivity.

Nimodipine infusion significantly increased blood flow by approximately 25% over the 45 minute test period (table 1). The heart rate was unaffected but there was a significant drop in blood pressure (p < 0.005) from 114 ± 11 to 103 ± 14 torr. These data are shown in table 2.

The CO₂ reactivity was taken as the mean of the reactivity to decreasing and increasing arterial pCO₂. There was no significant difference between the two directions of reactivity (using a paired t-test). CO₂ reactivity was significantly decreased (p < 0.005) after nimodipine infusion from a normal level of 3.51 ± 1.04 % \( \cdot \) torr⁻¹ to 0.87 ± 1.47 (mean ± SD) (table 3). The pretreatment CO₂ reactivity was not significantly different from that found in previous studies.²⁵,²⁶

The residual flow (in ml/100g/min) after MCA occlusion was averaged within each of areas A, B and C, and compared with the corresponding flow measured before occlusion. Treated and untreated animals had equivalent initial flow values in all areas. In area A the blood flow reduction in untreated animals was from 89 ± 37 to 15 ± 8 ml/100g/min and in treated animals from 98 ± 29 to 30 ± 18 ml/100g/min. In area B the flow reduction in untreated animals was from 92 ± 33 to 21 ± 8 ml/100 g/min and in treated animals from 93 ± 35 to 31 ± 12 ml/100g/min. In areas A and B the immediate post-clip flows were significantly higher with nimodipine infusion (p < 0.025 and p < 0.05 respectively), but not so in area C. The immediate post-clip flow was recorded at normocapnia (39–42 torr). This flow was measured before exsanguination at which time the haematocrit was unlikely to have changed from its pre-occlusion value of 45 ± 3.5%. At the time of MCA occlusion the blood pressure of treated and untreated animals was not significantly different (99 ± 38 and 91 ± 12 mmHg respectively).

The group of 15 untreated animals used in the above comparison were prepared similarly to the treated group. Within this untreated group, the lingual artery cannulation (performed in 4 animals) produced no statistically significant change in either pre-clip flow or residual flow.

The water content of the regions of the right hemisphere (ipsilateral to occlusion) were compared with that in the left occipital cortex which was not affected by MCA occlusion.²³,²⁴ The 6 untreated animals used for this comparison were taken from a previous series

Table 1  The Blood Flow Changes with Nimodipine Infusion in Group 1 Animals

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Time from infusion (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

mean ± SD 4 ± 10 26 ± 16 20 ± 25 24 ± 14

p value NS < 0.05 NS < 0.01

The values are expressed as percentage change from preinfusion values. All flows were performed at normocapnia. There was no relationship between the change in blood flow and any other variable measured.

Table 2  Blood Pressure Change Before and 45 Min After the Start of Nimodipine Infusion in Both Groups 1 and 2

<table>
<thead>
<tr>
<th>Experiment number</th>
<th>Group 1 Blood pressure</th>
<th>Group 2 Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-infusion</td>
<td>45 min post infusion</td>
</tr>
<tr>
<td>1</td>
<td>98</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>127</td>
<td>120</td>
</tr>
<tr>
<td>3</td>
<td>110</td>
<td>105</td>
</tr>
<tr>
<td>4</td>
<td>125</td>
<td>112</td>
</tr>
<tr>
<td>5</td>
<td>108</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>115</td>
<td>100</td>
</tr>
</tbody>
</table>

mean ± SD 114 ± 11 103 ± 14 116 ± 17 107 ± 16

p < 0.005 NS< 0.05 NS

The values are expressed in mmHg. The statistical significance of the differences was calculated using a paired t-test. When using all 11 animals the reduction was significant (p < 0.001). The reduction in blood pressure was 8–10%. Heart rate did not change.

There was no correlation between the degree of effect on blood pressure and any other variable measured.

Table 3  Changes in CO₂ Reactivity with Nimodipine Infusion in Group 1 Animals

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Pre-infusion</th>
<th>During infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.8</td>
<td>0.35</td>
</tr>
<tr>
<td>2</td>
<td>4.9</td>
<td>0.58</td>
</tr>
<tr>
<td>3</td>
<td>3.1</td>
<td>1.39</td>
</tr>
<tr>
<td>4</td>
<td>2.1</td>
<td>-1.4</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>6</td>
<td>4.4</td>
<td>3.08</td>
</tr>
</tbody>
</table>

Mean ± SD 3.51 ± 1.0 0.87 ± 1.5

p < 0.005

The significance of the change was calculated using a paired t-test. The values are expressed as %·torr⁻¹ (see methods).
in which the surgical preparation and experimental protocol were the same. The water content of the left occipital cortex in treated and untreated animals was not significantly different, 798.1 ± 5 and 797.9 ± 2.7 mg H₂O/g tissue (mg/g) respectively. The water content of the right occipital cortex (ipsilateral to infusion) of treated animals was not significantly different from that in the left occipital cortex or the mean value of the right occipital cortex of untreated animals. Data from the exposed region of the right hemisphere were grouped into bands of flow as follows; 0–4.9, 5–9.9, 10–14.9, and > 15 ml/100g/min. Over the right hemisphere the treated animals had significantly higher water content than untreated animals at all blood flows greater than 4.9 ml/100 g/min (fig. 2).

The changes in Kₑ and Caₑ associated with reduced blood flow have been reported previously. Nimodipine infusion did not affect the resting level of either Kₑ or Caₑ, or the level of Kₑ at which Caₑ began to change. This level of Kₑ in treated and untreated animals was 13.2 ± 3.2 mM and 13.5 ± 3.8 mM respectively. Figure 3 shows the relationship between Kₑ and Caₑ and blood flow in untreated animals and figure 4 the equivalent relationships in treated animals. A measure of the blood flow threshold of these ion changes is the average level of Kₑ and Caₑ in a given blood flow band. Within the blood flow band 6–16ml/100g/min, Kₑ was 33.7 ± 23 mM in treated and 6.6 ± 3.7 mM in untreated animals. These values are significantly different (p < 0.025). Within the blood flow band 6–10 ml/100 g/min Caₑ was 0.71 ± 0.53 mM in treated and 1.26 ± 0.18 mM in untreated animals. These values are significantly different (p < 0.05). These data indicate that the blood flow at which ion homeostasis was disrupted was higher in treated animals than in untreated ones.

Serum sodium, potassium, calcium, osmolality, glucose and haematocrit were measured before and after the MCA had been clipped. These data are summarised in table 4. Serum potassium, osmolality and glucose tended to increase in all experiments whereas calcium tended to decrease. During the clip phase treated animals showed a significant (p < 0.01) decrease in haematocrit not seen in untreated animals.

Group 2 (Closed skull)

Basal blood flow was not significantly affected by nimodipine infusion averaged over the 5 animals (table 5). Heart rate was unaffected as was blood pressure (table 2).

The autoregulatory index was measured in two untreated as well as 5 treated animals within the blood pressure range 78–157 torr. Neither lingual artery cannulation nor phosphate buffer infusion affected autoregulation. The pre-infusion autoregulatory index to increased blood pressure was 0.93 ± 0.37% • torr⁻¹ and was unchanged by Nimodipine infusion (0.92 ± 0.56% • torr⁻¹). Figure 5 shows the relationship between blood pressure and flow in untreated animals. These data are from a previous study in which the
animals were prepared in a similar way to those in this study, but without lingual artery cannulation.

Table 6 shows the changes in serum electrolytes during the group 2 experiments.

**Discussion**

**Group 1 — Cerebrovascular Effects**

The increase in basal blood flow by nimodipine infusion is consistent with the action of a calcium antagonist. There is however some unexplained variability in the degree of sensitivity of animals to nimodipine, and the response is somewhat less than that found by Craigin et al.

CO₂ reactivity was tested over the range of 34-42 torr in order to minimise any changes in brain volume. The degree of response to arterial pCO₂ was markedly reduced by nimodipine infusion. There was no significant difference between the reactivity of the vessels to either decreased or increased arterial pCO₂. It is difficult to understand the abolition of reactivity to increased pCO₂ in the light of the proposed action of nimodipine, but competitive inhibition of vasodilation by cerebral vasodilators is well known.

The increased residual flow after MCA occlusion with nimodipine preloading does not appear due to any of the factors known previously to affect flow in ischaemic regions. Specifically arterial pCO₂, haematocrit and blood pressure of treated and untreated animals were equivalent and there was no relationship between blood pressure and residual flow.

Our finding that nimodipine decreases the effect of MCA occlusion on residual blood flow in MCA territory is consistent with the demonstration by Ott and Lechner that oral nimodipine causes redistribution of blood flow in an infarcted hemisphere. Ott showed that blood flow increases in ischaemic areas and decreases in hyperaemic areas without affecting hemispheric blood flow. This increase in collateral circulation has been suggested to be the mechanism of the protective effect, found by workers in the field of myocardial ischaemia.

**Pathophysiological Effects**

Infusion of nimodipine did not affect osmoregulation in non-ischaemic tissue, as shown by the similarity of water content values of the left occipital cortex in treated and untreated animals. However, when blood flow was reduced in treated animals, water accumulation was significantly greater than that previously observed in untreated ones. Blood flow thresholds for the disruption of Kₑ and Caₑ homeostasis were also increased by nimodipine treatment. The increase in Kₑ in ischaemia is almost certainly the result of an increase in potassium permeability associated with an impairment and/or overload of potassium clearance mechanisms. Therefore an increase in the level of flow at which Kₑ increases in ischaemia may be the result of an increase in permeability. However, since there was no change in Kₑ or Caₑ when the drug was infused, we think this is unlikely. This suggests, therefore, that there is an increased susceptibility of cellular

**Table 4 Serum Electrolyte Changes of the Group 1 Series and Untreated Animals from a Previous Series**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Na (mM)</th>
<th>K (mM)</th>
<th>Ca (mM)</th>
<th>Osmol. (mOsm/Kg)</th>
<th>Glucose (mM)</th>
<th>HCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated animals (n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td>143 ± 5.4</td>
<td>3.4 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>286 ± 9.0</td>
<td>6.5 ± 2.4</td>
<td>45 ± 3.8</td>
</tr>
<tr>
<td>Post MCA clip 1</td>
<td>144 ± 3.3</td>
<td>4.0 ± 0.7</td>
<td>1.8 ± 0.2†</td>
<td>295 ± 6.3‡</td>
<td>11 ± 4.0‡</td>
<td>44 ± 6.1</td>
</tr>
<tr>
<td>Post MCA clip 2</td>
<td>143 ± 3.4</td>
<td>4.4 ± 0.8†</td>
<td>1.8 ± 0.3‡</td>
<td>296 ± 13</td>
<td>13 ± 5.5‡</td>
<td>43 ± 7.8</td>
</tr>
<tr>
<td>p values of differences between treated and untreated animals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Post MCA clip 1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Post MCA clip 2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Nimodipine treated animals (n = 7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinfusion</td>
<td>146 ± 2.4</td>
<td>3.1 ± 0.3</td>
<td>2.5 ± 0.4</td>
<td>290 ± 6.8</td>
<td>7.0 ± 2.0</td>
<td>46 ± 3.6</td>
</tr>
<tr>
<td>Post MCA clip 1</td>
<td>149 ± 5.1</td>
<td>4.7 ± 1.7</td>
<td>2.1 ± 0.3†</td>
<td>314 ± 17.4‡</td>
<td>11.2 ± 7</td>
<td>38 ± 6.6‡</td>
</tr>
<tr>
<td>Post MCA clip 2</td>
<td>148 ± 3.1</td>
<td>5.0 ± 1.5†</td>
<td>2.2 ± 0.5</td>
<td>305 ± 9.3</td>
<td>14.4 ± 5‡</td>
<td>37 ± 6.3‡</td>
</tr>
</tbody>
</table>

* p < 0.05; †p < 0.025; ‡p < 0.01; §p < 0.001.
All values are quoted as mean ± SD. Post MCA clip samples 1 and 2 were taken at 30 and 90 minutes post-occlusion respectively. The significance of differences between stages of the experiment were calculated using paired t-tests and between treated and untreated groups using unpaired t-tests.

**Figure 4.** The relationship between Kₑ, Caₑ and blood flow in treated animals. The critical level of flow below which ion homeostasis is lost has been significantly increased from that seen in figure 3. See text for details.
energy metabolism to ischaemic damage following nimodipine infusion. There are, however, no biochemical data concerning this proposal.

The relationship between $K_e$ and $Ca_e$ and blood flow have been reported in detail previously. When flow is reduced to a critical level of about 10 ml/100 g/min, there is an increase in $K_e$, while $Ca_e$ is unaffected. When $K_e$ reaches an average value of $2.4 \pm 3.8$ mM $Ca_e$ begins to fall. This is probably a movement of calcium into the cells. This fall in $Ca_e$ may be due either to depolarisation associated with the elevated $K_e$, or to a critical lowering of energy reserves causing a general loss of ion homeostatic mechanism. Our present data show that the value of $K_e$, at which $Ca_e$ falls is not significantly altered by nimodipine infusion, suggesting that mechanisms coupling these ionic changes are unaffected. The fall in $Ca_e$ in ischaemia is also not affected by nimodipine infusion. Unless there has been a massive rise in the binding capacity of the extracellular space, this fall in $Ca_e$ is likely to be the result of a movement of calcium into the cells.

Opinions differ as to the degree of calcium antagonism involved in the protective effect afforded by calcium antagonists. Henry suggested that nifedipine decreased slow channel uptake of calcium in myocardial low flow perfusion and that this was correlated with mechanical recovery. However, Poole-Wilson showed a difference in the effect of pre- and post-insult verapamil and suggested that the accumulation of calcium in myocardial ischaemia was via routes other than the slow channel. Poole-Wilson also concluded that the protection afforded by pre-insult verapamil was by a mechanism other than stopping calcium accumulation. Church and Zsoter have shown that the effect of some calcium antagonists on the uptake and efflux of $^{45}Ca$ was not consistent with an inhibition of transmembrane calcium flow. They suggested that an intracellular action of calcium antagonists was a more likely explanation. Our results show that nimodipine preloading does not stop the movement of calcium into ischaemic cells, which suggests that either nimodipine does not affect the membranes of neurons and glia or, as suggested by Poole-Wilson, the route of calcium movement is not the slow channels.

Treated animals showed a significant ($p < 0.01$) decrease in haematocrit during the period of occlusion.

### Table 5: The Blood Flow Changes with Nimodipine Infusion in Group 2 Animals

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Time from infusion (min)</th>
<th>Mean ± sd</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>15</td>
<td>1 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>5 ± 18</td>
<td>NS</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>5 ± 16</td>
<td>NS</td>
</tr>
</tbody>
</table>

The values are expressed as percentage change from preinfusion values. All flows were measured at normocapnia. There was no relationship between the change in blood flow and any other variable measured.

### Table 6: Serum Electrolyte Changes of the Group 2 Series

<table>
<thead>
<tr>
<th>Sample</th>
<th>Na (mM)</th>
<th>K (mM)</th>
<th>Ca (mM)</th>
<th>Osmol. (mOsm/Kg)</th>
<th>Glucose (mM)</th>
<th>HCT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated animals (n = 6)</td>
<td>Preinfusion</td>
<td>143 ± 5.4</td>
<td>3.4 ± 0.2</td>
<td>2.1 ± 0.3</td>
<td>286 ± 9.0</td>
<td>6.5 ± 2.4</td>
</tr>
<tr>
<td>Treated v untreated animals (p value)</td>
<td>NS</td>
<td>†</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Treated animals (n = 5)</td>
<td>Preinfusion</td>
<td>146 ± 2.0</td>
<td>3.1 ± 0.2</td>
<td>1.8 ± 0.5</td>
<td>291 ± 9.0</td>
<td>8.2 ± 2.9</td>
</tr>
<tr>
<td>45 min post-infusion (n = 1)</td>
<td>147</td>
<td>3.3</td>
<td>1.5 ± 0.5†</td>
<td>300</td>
<td>10.4</td>
<td>39 ± 3.6*</td>
</tr>
<tr>
<td>(n = 2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Terminal</td>
<td>149 ± 4.0</td>
<td>4.2 ± 0.6</td>
<td>1.5 ± 0.4†</td>
<td>311 ± 13*</td>
<td>13 ± 4.3†</td>
<td>39 ± 5.6</td>
</tr>
</tbody>
</table>

* $p < 0.05$; † $p < 0.025$; ‡ $p < 0.005$.

The preinfusion values have been compared to those for the untreated series (as shown in table 4). The significances have been calculated as described in the legend to table 4.

---

[13] Poole-Wilson

[14] Henry

[22] Church and Zsoter

[26] Poole-Wilson

[29] Church and Zsoter

[35] Poole-Wilson
This was almost certainly due to the greater severity of exsanguination necessary to achieve the desired range of blood flows, since immediate post-clip flows were higher in the treated group.

Group 2 — Cerebrovascular Effects

Nimodipine did not significantly affect basal blood flow in this closed skull preparation, which suggests that the craniectomy in some way affects the response to nimodipine. This lack of effect on basal flow is in keeping with the results of Ott and Lechner16 and Craigen et al.,28 possibly because of differences in blood flow measurement methodology between the studies.

It has been shown in 3 animals that lingual arterial cannulation did not affect the autoregulatory index, indicating that any influence of cannulation and infusion on the carotid body was insignificant. The hypertensive phase of the experiments was always preceded by at least 2 hypertensive episodes but, in two untreated animals, this sequence was without influence on autoregulatory capacity.

The lack of effect of nimodipine upon autoregulation to increased blood pressure indicates that the ability of the vessels to constrict was unaffected. This was unexpected in the light of the severe impairment of CO2 reactivity. The effect of nimodipine upon CO2 reactivity suggests that a pH mechanism of autoregulation was not involved, but that any other chemical, myogenic and/or neurogenic mechanisms were still intact.

Under the influence of nimodipine there was a major loss of autoregulation to reduced blood pressure, a finding consistent with a vascular bed being unable to dilate. However, vasodilation should be normal under the influence of a calcium antagonist according to the mechanism proposed by Fleckenstein.1 This mechanism does not rule out a reduction in intracellular free calcium and hence vasodilation. An intracellular action25 of nimodipine may manifest itself in this way.

There was a small but statistically significant difference between the serum potassium of untreated (open skull preparation), and treated animals. The rest of the changes were similar to those found in the treated open skull preparation animals of group 1.

In regard to the possible therapeutic use of nimodipine, as discussed by Ott and Lechner11 and Craigen et al.,28 our results indicate that there may be both good and bad effects of this drug. Specifically, the intracarotid infusion of nimodipine did not increase blood flow in a closed skull preparation, and severely reduced the cerebrovascular responses to alterations in arterial pCO2 and to haemorrhagic hypotension. Autoregulation to amine-induced hypertension was not affected. Also the critical level of blood flow at which oedema formation begins and ion homeostasis is disturbed was increased, and nimodipine did not inhibit the fall in extracellular calcium during ischaemia. Cerebrovascular physiological responses were severely impaired and areas where blood flow is critically reduced would, therefore, be more susceptible to ischaemic damage. On the positive side the immediate post-occlusion flow was doubled, an interesting effect which would tend to maintain blood flow above the thresholds of loss of electrical activity, ion homeostasis and of formation of ischaemic oedema.

References

PERIOPERATIVE STROKE IS UNCOMMON, occurring in 0.38% of male general surgical patients over age 50 in one large survey. Even in elderly patients, who have a higher incidence of all types of perioperative complications, perioperative cerebral infarction occurs in only 1.0–2.5% of major general surgical procedures, the latter figure applying to octogenarians. Patients who undergo aortoiliac surgery, considered to be at special risk for perioperative stroke due to the relatively high prevalence of coexistent carotid atherosclerosis and intraoperative hypotension, have a perioperative stroke rate of only 1%.  

Despite the infrequency of perioperative stroke, prophylactic carotid endarterectomy has been recommended for preoperative patients with asymptomatic stenosis based on the assumption that perioperative stroke is related to untreated carotid occlusive disease. Presumably, intraoperative hypotension or hypoxemia, inconsequential in the absence of carotid stenosis, when combined with occlusive carotid atheroma, results in cerebral hypoperfusion and stroke. Such a recommendation requires a critical examination of the mechanism(s) of perioperative cerebral infarction.

It has been our impression that many perioperative cerebral infarctions occur in the postoperative period, not intraoperatively, and that the mechanism is often uncertain. Review of the literature of the temporal occurrence of perioperative stroke in 10 patients undergoing aortoiliac reconstruction showed that all 10 events had onset in the postoperative period.  

The mechanism(s) of perioperative stroke are thus not limited to intraoperative hypotension potentiated by carotid stenosis. It is likely that mechanisms of perioperative cerebral
The effects of a calcium antagonist, nimodipine, upon physiological responses of the cerebral vasculature and its possible influence upon focal cerebral ischaemia.

R J Harris, N M Branston, L Symon, M Bayhan and A Watson

*Stroke*. 1982;13:759-766
doi: 10.1161/01.STR.13.6.759

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 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/13/6/759

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/