Increase in rat spinal cord blood flow with the calcium channel blocker, nimodipine

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Nimodipine, a calcium channel blocker, is known to increase cerebral blood flow. In the present study, the authors investigated the effect of nimodipine on spinal cord blood flow in normal rats. Cardiovascular parameters, including mean systemic arterial blood pressure, cardiac output, and heart rate, were recorded during infusion of nimodipine in a dose-response fashion. The experiment was a randomized blind study in which four groups of five rats received different doses of nimodipine (0.001, 0.01, 0.05, and 0.10 mg/kg) intravenously over 30 minutes, and a control group of five rats received only the diluent. The hydrogen clearance and thermodilution techniques were used to measure spinal cord blood flow and cardiac output, respectively.

The 0.05-mg/kg dose of nimodipine caused the largest increase in spinal cord blood flow, with a 40% increase over the preinfusion level, although there was a 25% reduction in mean arterial pressure. The 0.10-mg/kg dose did not increase spinal cord blood flow more than the 0.05-mg/kg dose, most likely due to the concomitant 37% reduction in mean arterial pressure. Cardiac output was significantly increased by the 0.05- and 0.10-mg/kg doses secondary to the drop in total peripheral resistance. The increase in spinal cord blood flow produced by nimodipine lasted approximately 20 minutes after the termination of the infusion. Thus, nimodipine at a dose of 0.05 mg/kg markedly increased blood flow in the normal spinal cord even though there were major changes in mean systemic arterial pressure and cardiac output. Further research is required to determine whether this drug might be beneficial in treating ischemic states of the spinal cord, such as posttraumatic ischemia.

Key Words: calcium channel blocker, nimodipine, cardiac output, spinal cord blood flow, rat
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on spinal cord blood flow in normal rats, with the long-range goal of using this agent to counteract posttraumatic ischemia in the spinal cord. At the present time, there is no useful agent for treating this condition. With drugs such as nimodipine, which has both general and local vascular effects, detailed dose-response studies are required that include measurement of several cardiovascular parameters, especially mean systemic arterial pressure and cardiac output. Such studies in normal animals allow selection of the optimum dose for further studies on traumatic or other pathological states of the spinal cord.

Materials and Methods

Operative Procedure

Male Wistar rats, weighing 400 to 500 gm each, were used in these studies. The animals were anesthetized with sodium pentobarbital (30 mg/kg intraperitoneally), and the left femoral artery, both femoral veins, and the right internal jugular vein were cannulated using PE-50 polyethylene tubing. Blood pressure, arterial blood gases, and hematocrit were measured from the femoral artery cannula. One femoral vein was used for nimodipine infusion and the other for administration of drugs such as pancuronium bromide. Body temperature was monitored by a rectal thermprobe, and was maintained at 37° to 38°C throughout the experiment with a thermal blanket. Needle electrodes were used to monitor the electrocardiogram (EKG). The above parameters were recorded by a multi-channel recorder and also in digitized form on-line by an S-100 microcomputer system. The hematocrit was measured with a microcapillary analyzer.*

Muscle relaxation was accomplished by administration of 0.7 mg pancuronium bromide intravenously every 30 minutes, and ventilation was performed by a small-animal ventilator† via a tracheostomy tube. The animals were maintained with a 1:1 mixture of N2O/O2, and PaO2 was kept in the range of 100 to 140 mm Hg. Arterial blood gases were measured with a blood gas analyzer,‡ with changes made as required.

Determination of Cardiac Output

Cardiac output was measured by the thermodilution technique. A thermistor,§ 0.10 mm in diameter, was advanced 3 cm through the right common carotid artery. It had previously been determined by postmortem examination that this distance positioned the thermistor in the ascending aorta. A PE-50 polyethylene catheter was advanced 3.5 cm into the right internal jugular vein and was connected by an adaptor to a 100-μl Hamilton syringe. At this distance, the catheter was found at autopsy to be positioned in the right atrium. Thermodilution curves were generated by injection of 100 μl of normal saline at room temperature, with thermistor sampling at 10 Hz for 7.5 seconds. From the thermodilution curve, the initial value to 70% of peak value was used for generating a mathematical gamma function closely resembling the thermodilution curve described by Starmer and Clark. The thermodilution curve and the gamma function were displayed overlapping each other on the computer video display screen. If the fit was satisfactory, the area under the gamma function was calculated by the computer and taken as an estimate of the area under the thermodilution curve. If required, the fit was improved by selecting a different set of points of the thermodilution curve from which the gamma function was derived. The modified Stewart-Hamilton formula was used to calculate the cardiac output in ml/min/kg as follows:

\[
CO = \frac{60 \cdot ds \cdot Ss \cdot Vs \cdot (T_B - T_S)}{dBsB \cdot area \ under \ thermodilution \ curve},
\]

where \(ds\) = specific gravity of saline; \(Ss\) = specific heat of saline; \(Vs\) = volume of injected saline; \(T_B\) = body temperature; \(T_S\) = saline temperature; \(dB\) = specific gravity of blood; and \(SB\) = specific heat of blood. Using the known values for specific heat and specific gravity of plasma and red blood cell mass, it was possible, by computer, to calculate specific heat (SB) and specific gravity (dB) of blood in Equation 1 on the basis of the hematocrit.

Determination of Spinal Cord Blood Flow

Spinal cord blood flow was measured by the hydrogen clearance method. Platinum-iridium rods (90%/10%)* were etched with a potassium cyanide-potassium hydroxide solution (1.5%/1.0%), and then insulated with an epoxy resin to leave a 100-μm diameter base tapering to a 10-μm diameter tip with a total exposed length of 500 μm. Electrode dimensions of these specifications were found to be the most stable, with minimal drift, while still providing sufficient output current. An Ag-AgCl reference electrode was inserted into a subcutaneous pouch in the posterior thoracic region. The hydrogen electrode was polarized to +450 mV relative to the Ag-AgCl reference electrode. The output of the electrodes was amplified sufficiently to be recorded by a strip chart recorder and in digitized form, at 1 Hz, by the S-100 microcomputer system.

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* Microcapillary reader manufactured by Damon/IEC Division, Needham Heights, Massachusetts.
† Harvard-680 rodent respirator manufactured by Harvard Apparatus Co., Inc., The Ealing Corp., 22 Pleasant Street, South Natick, Massachusetts.
‡ Radiometer BMS-MK2 blood micro system manufactured by Radiometer A/S, Emdruprej, 72 DK 2400, Copenhagen, Denmark.
§ Thermoprobe YS1 #520 manufactured by Yellow Springs Instrument Co., Yellow Springs, Ohio.

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* Hamilton syringe manufactured by Hamilton Co., 4970 Energy Way, Reno, Nevada.
* Platinum-iridium rods manufactured by Engelhard Metals, Aurora, Ontario, Canada.
With an operating microscope a five-level laminectomy was performed from C-5 to T-2 inclusive, and the dura was opened widely. With microscopy and a micro-manipulator,† three hydrogen electrodes were inserted individually into the cord to a depth of 500 μm. One electrode was inserted at each of three vertebral levels, C-5, C-7, and T-1, as close to the midline as possible but avoiding the midline dorsal veins. The wound was covered with liquid paraffin to a depth of 2 cm.

The saturation phase of each flow study began with the administration of 5% hydrogen gas and lasted 10 minutes. The amount of hydrogen delivered was determined by calculating the difference between the percentage of oxygen delivered before and after hydrogen administration, as measured by an oximeter.‡ Using the oximeter at the tracheostomy level, it was found that the animal was actually breathing the desired hydrogen concentration within 15 to 20 seconds of commencement or termination of hydrogen delivery. At the end of the saturation phase, cardiac output, mean systemic arterial pressure, arterial blood gases, hematocrit, body temperature, heart rate, and EKG were recorded. Cessation of hydrogen administration marked the beginning of the 15-minute desaturation phase, by which time the electrode recordings had returned to their respective baselines.

Spinal cord blood flow was determined from the desaturation phase of the hydrogen clearance curve. Baseline drifts were assumed to be linear. The baseline was generated by the computer by drawing a line through the initial presaturation points and the last 1-minute segment of the desaturation phase. If the slope of the baseline was greater than 5 mV/min, it was deemed to have too great a drift of the baseline and the data from that electrode were discarded. The value for the drift of the baseline was then used to correct the raw data. Next, the natural log plot of the adjusted raw data was displayed and the initial 1-minute segment was discarded to avoid possible effects of hydrogen recirculation. The initial-slope index method was then used to measure spinal cord blood flow by calculating the slope of the linear regression line in the 1- to 4-minute window of the natural log plot. All of the above data manipulations were performed with the S-100 microcomputer system.

Histological Studies

In five animals, the position of the electrodes was marked by coagulating the adjacent tissue with a 150-μAmp direct current, and is located in the dorsal column. H & E. embedded in paraffin, sectioned at 25 μm, and stained with hematoxylin and eosin. The electrode tracks were consistently located in the dorsal white columns extending to a depth of approximately 500 μm, with the electrode tip close to the dorsal gray-white matter interface. Out of 15 electrode tracks examined, 12 were found to penetrate slightly into the dorsal gray matter. There was very little associated hemorrhage or tissue damage, other than the coagulation artifact used for marking the track (Fig. 1).

Experimental Protocol

Nimodipine was supplied as a 0.02% stock solution in a polyethylene glycol, ethanol, and water diluent. The stock solution was diluted with saline to obtain the appropriate concentrations. A sodium vapor lamp was used during dilution and delivery of the drug due to the photosensitivity of nimodipine to normal light. Four doses of nimodipine (0.001, 0.01, 0.05, and 0.10 mg/kg) and a control solution containing only the same diluent as the stock solution were given in different experimental groups of five animals each. The infusion volume was kept constant at 1 ml administered over 30 minutes. The investigators were blinded to the dose administered until completion of the analysis.

After electrode insertion, a 30-minute period was allowed for stabilization. Two measurements of spinal cord blood flow were then obtained approximately 30 minutes apart. Following this, a third blood flow study, termed the "preinfusion flow," was performed. Drug or control infusion was then begun with a Harvard infusion pump.§ Mean systemic arterial pressure, EKG, and heart rate were recorded every 5 minutes for the initial 20 minutes of infusion. The desaturation phase

†Narishige MT5 micromanipulator manufactured by Medical Systems Corp., 239 Great Neck Road, Great Neck, New York.
‡Ventronics 5570 polarographic oxygen monitor manufactured by Hudson, Ltd., Temescula, California.
§Harvard 2620 infusion pump manufactured by Harvard Apparatus Co., Inc., 150 Dover Road, Millis, Massachusetts.
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### TABLE 1

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Parameter</th>
<th>Time of Determination</th>
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<td></td>
<td>PaCO₂</td>
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<td>pH</td>
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<td>nimodipine</td>
<td>Hematocrit</td>
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<tr>
<td></td>
<td>Hematocrit</td>
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* Values are means ± standard deviations for five animals in each group receiving control solution or nimodipine. There was no significant difference between doses or between infusion times as calculated by paired t-tests (p < 0.05).

**Fig. 2.** Preinfusion, infusion, and postinfusion spinal cord blood flow (SCBF) values for various doses of nimodipine and for the control solution containing only the diluent. Infusion of 0.05 mg/kg of nimodipine caused the largest increase in SCBF, with a value of 65.9 ± 18.5 ml/100 gm/min performed to evaluate the mean differences for PaCO₂, pH, and hematocrit pertaining to each dose.

### Results

**Effects on PaCO₂, pH, and Hematocrit**

The mean values for PaCO₂, pH, and hematocrit are shown for the various doses in Table 1. Paired t-tests showed no significant differences between these parameters at the time that the preinfusion, infusion, and postinfusion flows were measured (p > 0.05). Similarly, there were no significant differences in these parameters for any of the doses (p > 0.05). The animal's body temperature was maintained between 37° and 38°C, and PaO₂ varied from 100 to 140 mm Hg for all animals.

**Effect on Spinal Cord Blood Flow**

The mean flows determined preinfusion, during infusion, and postinfusion for the control group and for the groups given the various doses of nimodipine are shown in Fig. 2. The preinfusion blood flow ranged between 43.9 ± 7.2 and 51.7 ± 14.4 ml/100 gm/min for all doses. The 0.05-mg/kg dose of nimodipine caused the largest increase in flow, with a value of 65.9 ± 18.5 ml/100 gm/min, whereas the higher 0.10-mg/kg dose increased flow to 57.4 ± 11.7 ml/100 gm/min. This peak increase of blood flow with the 0.05-mg/kg
TABLE 2
Changes in SCBF, MSAP, and CO based on univariate analysis of variance

<table>
<thead>
<tr>
<th>Analysis of Variance</th>
<th>Effect of Nimodipine Infusion†</th>
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<tbody>
<tr>
<td></td>
<td>SCBF</td>
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<tr>
<td>F</td>
<td>21.48</td>
</tr>
<tr>
<td>r²</td>
<td>0.81</td>
</tr>
<tr>
<td>p value</td>
<td>0.0006</td>
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</tbody>
</table>

* Analysis of variance: F = 4 and 20 degrees of freedom; r² = correlation coefficient, significance: p < 0.05. Abbreviations: SCBF = spinal cord blood flow; MSAP = mean systemic arterial pressure; CO = cardiac output.
† Effect calculated as the mean percentage difference during infusion (Δ% during infusion = (infusion - preinfusion)/(preinfusion x 100)).

FIG. 3. Percent change (Δ%) in spinal cord blood flow (SCBF) and mean systemic arterial pressure (MSAP), with standard deviations, during infusion (infusion - preinfusion)/(preinfusion x 100)), for various doses of nimodipine and for the control solution. There was a peak increase of approximately 40% with the 0.05-mg/kg dose. Increasing doses of nimodipine caused an approximately linear decline in MSAP. The 0.10-mg/kg dose caused a 37% drop in MSAP and failed to increase the SCBF as much as the 0.05-mg/kg dose.

dose is also seen in Fig. 3, which shows a 41.0% ± 7.5% increase in spinal cord blood flow with that dose, compared to a 14.4% ± 4.4% increase for the 0.10-mg/kg dose.

There was a significant relationship between spinal cord blood flow and nimodipine dose, as shown by univariate analysis (Table 2). This relationship, as depicted in Fig. 3, consists of an increase in flow, with a peak at the 0.05-mg/kg dose level, followed by a decline. Except for the control infusion containing the diluent and the lowest dose of nimodipine (0.001 mg/kg), all other doses significantly increased spinal cord blood flow (Table 3). Multiple comparison tests (Table 4) showed that 0.05 mg/kg was the optimal dose, as it produced a significantly higher flow than all the other doses.

The postinfusion flows were recorded 20 minutes after stopping nimodipine infusion, by which time flow in most animals had returned to preinfusion values. The values were 47.9 ± 6.0 and 50.4 ± 7.0 ml/100 gm/min for the 0.05- and 0.10-mg/kg doses, respectively (Fig. 2), which was only a 4.8% and 2.6% increase over the preinfusion values (Fig. 4). In addition, these post-infusion blood flow values were not different from each other or from zero (Table 4).

Effect on Mean Systemic Arterial Pressure

The mean systemic arterial pressure for the preinfusion, infusion, and postinfusion flows, as well as the values for the 5-, 10-, and 15-minute intervals after the start of infusion, are plotted in Fig. 5. The preinfusion blood pressure ranged between 133 ± 9.2 and 142 ± 10.8 mm Hg for all doses.

The control solution caused no change in mean arterial pressure while nimodipine caused a dose-dependent decrease. This decrease was minimal with the lower two doses (0.001 and 0.01 mg/kg), whereas there was a dramatic drop with the 0.05- and 0.10-mg/kg doses. The decrease commenced within 5 minutes of the start of infusion, and at 20 minutes was profound, with values of 107 ± 13.4 and 86.0 ± 11.4 mm Hg for the 0.05- and 0.10-mg/kg doses, respectively. In Fig. 3, the approximately linear decrease in mean arterial pres-
Effect of nimodipine on spinal cord blood flow

<table>
<thead>
<tr>
<th>Infusion &amp; Dose (mg/kg)</th>
<th>Effect of Nimodipine Infusion†</th>
<th>Effect of Cessation of Nimodipine‡</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SCBF</td>
<td>MSAP</td>
</tr>
<tr>
<td>control solution</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>nimodipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.001</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>0.01</td>
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<td>B</td>
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<td>0.05</td>
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<td>C</td>
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<tr>
<td>0.10</td>
<td>B</td>
<td>D</td>
</tr>
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</table>

* Doses with the same letters are not significantly different at p < 0.05 with 20 degrees of freedom. Abbreviations: SCBF = spinal cord blood flow; MSAP = mean systemic arterial pressure; CO = cardiac output.

† Effect calculated as mean percentage difference during infusion ($\Delta%$ during infusion = (infusion - preinfusion)/(preinfusion) x 100).
‡ Effect calculated as mean percentage difference after infusion ($\Delta%$ after infusion = (postinfusion - preinfusion)/(preinfusion) x 100).

sure with increasing doses of nimodipine is also shown, with a drop of 24.6% ± 9.4% and 36.6% ± 6.1% for the 0.05- and 0.10-mg/kg doses, respectively.

There was a significant relationship between the dose of nimodipine and the mean systemic arterial pressure (Table 2), with the higher three doses (0.01, 0.05, and 0.10 mg/kg) causing a significant pressure reduction (Table 3). Multiple comparison tests showed that the decrease in blood pressure was significantly different between the 0.05- and 0.10-mg/kg doses (Table 4).

During the postinfusion period, the mean systemic arterial pressure generally increased, although the values tended to remain below the preinfusion level (Fig. 5). However, hypotension persisted 20 minutes after cessation of infusion, especially for the 0.10-mg/kg dose, which caused pressure to remain 28% below preinfusion levels (Fig. 4). This was further reflected in the multiple comparison tests (Table 4), which revealed a decrease in blood pressure for the 0.10-mg/kg dose that was statistically different from the other doses.

**Effect on Cardiac Output**

The 0.05- and 0.10-mg/kg doses caused significant increases in cardiac output of 21.5% ± 11% and 30.5% ± 4.5%, respectively (Fig. 6 and Table 3), but the results for the two doses did not differ significantly from each other or from the other doses as shown by univariate analysis and multiple comparison tests (Tables 2 and 4). Thus, nimodipine at the higher doses appeared to cause an increase in cardiac output.

Cardiac output remained elevated for the 0.05- and 0.10-mg/kg doses 20 minutes after cessation of infusion, with values of 27.8 ± 8.1 and 25.5 ± 9.9 ml/min/kg, respectively (Fig. 6). These values were significantly different from zero but they did not differ from each other (Table 4).

**Multivariate Analysis of Dose Effects**

Multiple analysis of variance confirmed that the dosage of nimodipine significantly affected the spinal cord blood flow, mean systemic arterial pressure, and cardiac output together (Wilks' criterion, $F = 8.32; df = 12$ and $47, p < 0.0001$). This implies that there were significant dose effects on at least one of these parameters or their interactions. Univariate analysis (Table 2) showed significant dose effects for blood flow and pressure. Interactions between these two parameters are probably present, since the 0.10-mg/kg dose did not increase the flow to the same extent as did the 0.05-mg/kg dose, due to the major decrease in blood pressure.

**Discussion**

In experimental studies of blood flow, the numerous systemic parameters that can affect local organ flow must be controlled. In the present study, $\text{PaCO}_2$, pH, $\text{PaO}_2$, and body temperature were controlled and no significant differences were found between doses or at the three flow times (preinfusion, infusion, and postinfusion) (Table 1). Blood rheology has been recognized as an important determinant of local organ flow; hence the hematocrit was also measured and was found not to differ significantly during the experiment (Table 1). Thus, it can be concluded that the changes in spinal cord blood flow, mean systemic arterial pressure, and cardiac output were due to nimodipine rather than to any differences in $\text{PaCO}_2$, pH, hematocrit, or body temperature.

There are numerous methods available for measuring...
spinal cord blood flow, each with inherent advantages and disadvantages. The hydrogen clearance technique allows repetitive measurements, and thus it was suitable for the current dose-response study.\(^{26,33,38,51}\) The electrodes were positioned in the dorsal columns with their tips located at the dorsal gray-white matter interface (Fig. 1). There is some controversy concerning the volume of tissue sensed by a hydrogen electrode. Meyer, et al.,\(^{29}\) in their studies of cerebral blood flow, proposed a volume as small as 0.5 cu mm, while Young\(^{51}\) placed this figure at 5 cu mm depending on electrode size. If the smaller value of 0.5 cu mm is accepted, this implies that the electrode sensed a cube of tissue with sides measuring 0.8 mm. With respect to the rat spinal cord, which is approximately 2.5 mm in diameter, it is likely that the hydrogen electrodes placed in the dorsal columns, as described above, were sensing the blood flow in both the gray and white matter. According to the bicompartimental analysis of clearance curves, the initial-slope index used in this experiment as a measure of spinal cord blood flow is dependent on both the fast and slow blood flow compartments.\(^{24,51}\) Because the volume of tissue being sensed by the electrodes included both gray and white matter in the rat spinal cord, the initial-slope index can be expected to be influenced more by the faster gray matter flow. Thus, the blood flow values of 43.9 to 51.7 ml/100 gm/min obtained in the preinfusion period are comparable to the blood flows of 53.8 and 21.0 ml/100 gm/min recorded by Hayashi, et al.,\(^{20}\) in the dorsal gray and white matter, respectively, in the rat spinal cord. Similarly, with carbon-14 (\(^{14}\)C)-iodoantipyrine autoradiography, flow values of 61.4 and 17.7 ml/100 gm/min were obtained by Rivlin and Tator\(^{36}\) for the gray and white matter, respectively, in the lower cervical cord in the rat. These latter values are also in agreement with those obtained in the present study.

The exact mechanism underlying the selective cerebrovascular action of nimodipine is not fully known, although the intrinsic properties of intracranial vessels, such as their predominant dependency on extracellular Ca\(^{++}\) for contraction, may play a role.\(^{3,46}\) The pharmacological properties of nimodipine, including permeation of the blood-CNS barrier or receptor specificity in the CNS, may also be contributory factors.\(^{34}\) Unfortunately, this selectivity is not totally specific, as shown by the profound hemodynamic changes that we found with the higher doses. McCalden, et al.,\(^{28}\) in their studies of normal baboon with the xenon-133 clearance technique, found that a nimodipine dose of 1 \(\mu g/kg/min\) administered intravenously was most effective in increasing cerebral blood flow. Using similar techniques

![Graph](image-url)
Effect of nimodipine on spinal cord blood flow

The thermodilution technique for measuring cardiac output was introduced in 1954 by Fegler and gave results similar to the indicator dye-dilution and direct Fick measurement techniques. The method we used for determining cardiac output, in which saline is injected into the right atrium with a thermistor located in the aortic arch for the detection of the thermodilution curve, has been shown to be a valid modification of the thermodilution technique. This modification is acceptable because, in the normal pulmonary bed, heat loss is negligible due to the thermal insulating effect of the air-filled alveoli. In small animals such as the rat, Hayes, et al., demonstrated that heat loss does occur directly from the right atrium to the thoracic aorta, and hence they advocated using relative differences in cardiac output as was done in this study, rather than absolute values. In addition, Evonuk, et al., advocated the use of saline at room temperature to reduce the heat loss, and we also followed this procedure in the present study.

We found that cardiac output did not differ significantly with different doses of nimodipine, although there was a significant increase following doses of 0.05 and 0.10 mg/kg as compared with the preinfusion level (Table 3). It is likely that these two higher doses caused a significant reduction in total peripheral resistance and that there was a concomitant increase in cardiac output in an attempt to maintain systemic arterial pressure. Since cardiac output depends upon stroke volume and heart rate, and heart rate did not differ significantly between the preinfusion, infusion, and postinfusion flows for any dose of nimodipine, an increase in stroke volume likely accounted for the rise in cardiac output in the 0.05- and 0.10-mg/kg doses. Further studies involving measurement of atrial pressures and direct measurement of stroke volume are required to elucidate this matter.

Administration of nimodipine by the intravenous, oral, sublingual, intracarotid, intraventricular, or topical routes has been shown to increase cerebral blood flow. Mohamed, et al., found an increase in cerebral blood flow within 60 minutes of the start of intravenous infusion. A similar time of onset was noted by Harper, et al., for the intravenous route, whereas the increase in flow was quicker after intracarotid infusion. In the present study, spinal cord blood flow increased within 20 minutes of the beginning of infusion and returned to preinfusion values within 20 minutes of completion of the infusion. The action on systemic vasculature is probably quicker because most of the decrease in systemic arterial pressure occurred within 5 minutes of the start of the infusion (Fig. 3). This was also observed by Mohamed, et al., in their studies of cerebral blood flow.

The exact pathophysiology following spinal cord trauma is not fully known. It has been postulated that posttraumatic ischemia enhances tissue destruction after the initial mechanical injury. Our results showing improvement of spinal cord blood flow with...
nimodipine in normal rat spinal cord are encouraging. Whether nimodipine will improve posttraumatic ischemia and enhance neurological recovery is a question to be answered.

Conclusions

From this investigation we were able to reach the following conclusions.

1. Intravenous nimodipine increased spinal cord blood flow in the normal rat. The optimum dose was 0.05 mg/kg (1.7 μg/kg/min) given over 30 minutes, which increased the flow by 40%. This correlates well with the results of previous cerebral blood flow experiments with nimodipine in terms of dose and maximum effect on blood flow.

2. A linear dose-dependent decrease in mean systemic arterial pressure was noted with nimodipine. At the optimum dose (0.05 mg/kg) there was a 25% decrease, while the higher dose (0.10 mg/kg, or 3.3 μg/kg/min) caused a 37% decrease in arterial pressure. It was concluded that doses higher than 0.05 mg/kg did not increase spinal cord blood flow to the same extent due to the concomitant hypotension.

3. Cardiac output did not differ significantly between doses, although a significant increase was found with the 0.05- and 0.10-mg/kg doses. This was probably due to a decrease in total peripheral resistance with a compensatory increase in stroke volume.

4. The beneficial effect of nimodipine on spinal cord blood flow ended within 20 minutes of termination of the infusion, although significant hypotension remained with the higher dose.

5. Further studies are warranted to determine whether nimodipine can prevent or counteract posttraumatic ischemia and promote neuronal protection after spinal cord trauma. This is of great interest in the ongoing search for an agent to improve neurological recovery after spinal cord trauma.

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