Effect of a calcium channel blocker on posttraumatic spinal cord blood flow

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The normal rat spinal cord blood flow (SCBF) has been shown to increase after administration of nimodipine, a calcium channel blocker. The present study investigates the capability of nimodipine to improve SCBF, as measured by the hydrogen clearance technique, after a 53.0-gm clip compression injury to the T-1 segment of the rat spinal cord.

The profound drop in mean systemic arterial blood pressure (MSAP) after cervical cord injury precluded any improvement in posttraumatic SCBF by nimodipine alone. Hence, in a randomized controlled study with five rats per group, pressor agents (whole blood, angiotensin, or adrenaline) were infused to maintain MSAP between 100 and 120 mm Hg after injury. Control animals received only a saline infusion. Nimodipine at the optimal dose found in normal animals (1.5 μg/kg/min) was added to the pressor agents. The MSAP and other physiological parameters were measured in rats receiving the pressor agents only and in those receiving pressor agents combined with nimodipine.

In rats receiving whole blood, angiotensin, or adrenaline the posttraumatic MSAP improved to between 100 and 120 mm Hg, but there was no improvement in SCBF compared to the saline group. The addition of nimodipine decreased MSAP and SCBF in all groups except those animals also receiving adrenaline, where the MSAP was maintained at 109 ± 5 mm Hg. In these animals a significant increase in posttraumatic SCBF from 16.5 ± 2.1 to 20.2 ± 2.3 ml/100 gm/min (mean ± standard error of the mean) occurred at the site of injury with the addition of nimodipine.

The maintenance of an adequate MSAP by a pressor agent was crucial for nimodipine to improve posttraumatic SCBF by its ability to dilate the spinal vascular bed. Adrenalin was the only pressor agent that could fulfill the above criteria, although other pressor agents need to be investigated. Experiments are underway with the combination of adrenaline and nimodipine to further verify these encouraging results demonstrating an improvement in posttraumatic ischemia of the spinal cord.

Key Words: spinal cord injury • spinal cord blood flow • nimodipine • posttraumatic ischemia • calcium channel blocker • pressor agent • rat

There is evidence that spinal cord injury in the acute phase results from two separate mechanisms: the initial mechanical damage, and secondary changes due to vascular or biomechanical effects. The initial mechanical damage to the cord includes both the impact force and any persistent compression by intracanalicular space-occupying lesions such as bone fragments. The subsequent biochemical and vascular changes triggered by the initial mechanical injury may promote further destruction of the spinal cord. Measurements of spinal cord blood flow (SCBF) as well as microangiographic studies after spinal cord injury have shown ischemia at the injury site and extending considerable distances.

The understanding and treatment of posttraumatic ischemia are therefore of great interest. Calcium channel blockers, especially nimodipine with its selective vasodilatation of cerebral vessels, are being investigated for the treatment of cerebral ischemic states such as post-subarachnoid hemorrhage vasospasm. Previously, it was shown in our laboratory that nimodipine also increased the SCBF in normal rats. There was approximately a 40% increase in SCBF with a 0.05 mg/kg intravenous infusion of nimodipine given over 30 minutes; however, higher doses were not as efficacious due to the concurrent systemic hypotension. The present study was designed to determine whether a similar intravenous dose of
nimodipine (1.5 μg/kg/min) could improve posttraumatic ischemia of the injured spinal cord, the etiology of which is not known. In fact, the list of possible mechanisms causing that condition is quite lengthy and similar to that of post-subarachnoid hemorrhage vasospasm.5,7,44 We have shown that injury to the cervical and thoracic regions of the spinal cord produces a marked reduction in mean systemic arterial pressure (MSAP) and have postulated that this may lead to a further reduction of SCBF,10,34 especially in the injured cord incapable of autoregulation.12,38 In the present study of the ability of nimodipine to improve SCBF in rats after injury to the T-1 segment of the spinal cord, various pressor agents were used along with nimodipine to maintain adequate MSAP so that the effects of nimodipine on posttraumatic SCBF could be investigated.

Materials and Methods

Operative Procedure

Male Wistar rats* (each weighing 400 to 500 gm) were anesthetized with sodium pentobarbital, 30 mg/kg intraperitoneally. Samples for analysis of arterial blood gases, MSAP, and hematocrit were obtained from the left femoral artery which was cannulated with No. 50 polyethylene (PE 50) tubing. Both femoral veins were cannulated with PE 50 tubing: the left vein was used for administration of nimodipine, while the right vein was used for infusion of the various pressor agents. Rectal temperature was maintained between 36° and 38°C by a warming blanket, and needle electrodes were inserted for electrocardiographic data. Measurements were recorded using a multichannel physiograph and an on-line microcomputer system.†

The animals were paralyzed with pancuronium bromide, 0.7 mg given intravenously every 30 minutes, and ventilated through a tracheostomy tube by a small-animal ventilator.‡ The arterial blood gases were monitored and any required changes made prior to each SCBF measurement.

Injury Model

A five-level laminectomy (C5-T2) was performed under an operative microscope. The pedicle of T-1 was removed bilaterally until the superior articulating facets of T-2 and the exiting roots could be seen. The anterior epidural space of T-1 was cleared just caudal to the anterior epidural space previously cleared by the dental probe. The clip was applied under the operating microscope, and positioned so that the cord occupied approximately two-thirds of the distance from the fulcrum to the end of the blade. The clip was then rapidly released from a pre-set opening on the applicator. After 1 minute of compression, the clip was removed with the applicator and hemostasis was obtained.

Spinal Cord Blood Flow Measurements

The SCBF was measured using the hydrogen clearance technique and a S-100 microcomputer system as previously described by Guha, et al.23 Three hydrogen electrodes were inserted under microscopy into the cord just lateral to the dorsal veins to a depth of 500 μm, using a micromanipulator.¶ One electrode was inserted at C-6 (1 cm proximal to the injury site) and two at T-1 (the site of injury).

The saturation phase, beginning with administration of 5% hydrogen gas lasted 10 minutes. The duration of the desaturation phase differed depending on pre- and postinjury measurements because, with the faster preinjury SCBF, the electrodes returned to baseline within 15 minutes, while it took 30 minutes to return to baseline with the slower postinjury SCBF. The initial-slope index method26 was used to measure SCBF. The 1- to 4-minute segment from the start of desaturation was used for both the preinjury flows and for all the measurements from the C-6 electrode, while the 3- to 11-minute segment was used for the postinjury measurements at the T-1 segment. The arterial blood gases were measured and alterations made as required prior to each SCBF measurement.

Experimental Protocol

Twenty rats were allocated randomly after injury into four groups with five rats in each group. After injury, three groups received a pressor agent (either whole-blood transfusion, angiotensin, or adrenaline) to maintain MSAP at or near preinjury levels, and the fourth served as a control group and received saline only. The experimental protocol is schematically represented in Fig. 1. Thirty minutes after insertion of the electrodes (one at C-6 and two at T-1) the “preinjury” SCBF was measured. The electrodes were then removed and a 53.0-gm clip compression injury was delivered for 1 minute to the T-1 segment of the spinal cord. Then all animals were immediately given a 1.0-ml bolus of saline to counteract blood loss, followed by administration of

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* Rats obtained from Charles River (Canada), Inc., St. Constant, Quebec, Canada.
† Multi Channel recorder, No. 7758A, manufactured by Hewlett-Packard (Canada), Ltd., Mississauga, Ontario, Canada; Microcomputer System, System 3 S-100, manufactured by Jade, Rochester, New York.
‡ Rodent respirator, No. 680, manufactured by Harvard Bioscience, South Natick, Massachusetts.
¶ Device manufactured by Walsh Manufacturing, Ltd., Oakville, Ontario, Canada.
†† Narishige MT5 micromanipulator manufactured by Medical Systems Corp., Great Neck, New York.

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![Diagram](image)

**Fig. 1.** Schematic representation of the experimental protocol. Spinal cord blood flow with corresponding mean systemic arterial blood pressure, arterial blood gases, hematocrit, and rectal temperature were measured at three times: prior injury (Pre-Injury); with only the pressor agents (Pressor agent); and after the addition of nimodipine (Pressor agent + Nimodipine).

one of the four agents described above within 1 minute of injury. The electrodes were then reinserted and the postinjury "pressor agent SCBF" was measured 30 minutes after injury. Nimodipine (1.5 μg/kg/min) was then infused intravenously into all 20 animals, and 20 minutes later the "pressor agent + nimodipine SCBF" was measured.

**Pressor Agents and Nimodipine**

On the day of each experiment, autologous whole blood was obtained from donor male Wistar rats of the same litter through PE 100 cannulae inserted into the abdominal aorta. Every 5 minutes 1.0 ml of blood was removed and anticoagulated with citrate. Randomly selected samples of donor blood were found to have normal electrolyte concentrations. Angiotensin powder* was diluted in normal saline to make a 500-μg/ml solution. A 1/100,000 solution of adrenalin† was prepared by diluting the stock 1/1000 solution. The 0.02% stock solution of nimodipine‡ was diluted in normal saline according to the animals' body weight to enable a 1.5-μg/kg/min infusion to be given at a rate of 0.026 ml/min through a Harvard infusion pump.§ Due to its photosensitivity, during the preparation and administration of nimodipine, a sodium vapor lamp was used.||
The infusion rates of the pressor agents were varied using an infusion pump in an attempt to maintain MSAP between 100 and 120 mm Hg. The control group received an infusion of saline at 3.0 ml/hr which approximated the volume infused into the other three groups.

**Statistical Analysis**

The measured values of SCBF, MSAP, arterial blood gases, hematocrit, and rectal temperature were categorized into three time intervals according to the experimental protocol. The first set was labeled the "preinjury values," the second set the "pressor agent values," and the third set the "pressor agent + nimodipine values" (Fig. 1). Two SCBF values were generated for each animal: one for the electrode at the noninjured C-6 segment and the other an average of the two electrodes at the injured T-1 segment. The raw SCBF and MSAP values measured at the three time intervals are shown in Tables 2 and 3 and in Figs. 2 and 3.

The differences in SCBF and MSAP between the "pressor agent values" compared with the "preinjury values" and the "pressor agent + nimodipine values" compared with the "pressor agent values" were calculated. These differences were submitted to a univariate analysis of variance to determine whether the average differences noted above were consistently observed for all four treatment groups. The changes in SCBF and MSAP were further analyzed using Duncan's multiple comparison testing to determine which treatment groups were significantly different (p = 0.05). Paired t-tests were used to detect differences between the three time intervals for arterial blood gas values, hematocrit, and rectal temperature.

**Results**

**Blood Gases, Hematocrit, and Temperature**

The hematocrit, pH, PaCO₂, and rectal temperature at each of the three time intervals ("preinjury," "pressor agent," and "pressor agent + nimodipine") for the four groups are listed in Table 1. The PaCO₂ and pH ranged from 33.7 ± 1.6 to 40.7 ± 1.0 mm Hg and from 7.35 ± 0.01 to 7.46 ± 0.03, respectively (mean ± standard error of the mean), for all groups regardless of the time intervals. The rectal temperature averaged between 36.0° ± 0.4° and 38.2° ± 0.3°C for all the animals. The hematocrit decreased between the "preinjury" and postinjury "pressor agent" measurements by 3% to 7%. Subsequently, the hematocrit remained stable except in the animals receiving whole blood + nimodipine where a 2% increase was recorded (Table 1).

**Blood Flow and Blood Pressure**

The "preinjury SCBF" at C-6 and T-1 ranged from 52.1 ± 3.2 to 57.6 ± 4.4 and from 42.1 ± 1.7 to 46.4 ± 2.1 ml/100 gm/min, respectively, in all four groups (Fig. 2 and Table 2). These flow values were not significantly different among the four groups (p > 0.05), but the C-6 spinal segment did have a significantly higher SCBF than did T-1 (p < 0.05, using paired t-tests). The "preinjury MSAP" ranged from 123 ± 3 to 141 ± 2 mm Hg for all groups (Fig. 3 and Table 3). Immediately after injury there was a hypertensive peak which ranged between 173 ± 2 and 184 ± 4 mm Hg and lasted for about 2 minutes (Fig. 3). This was followed by a hypo-
Fig. 2. Mean spinal cord blood flow (SCBF, ml/100 gm/min) ± standard error of the means (vertical lines) for the "preinjury," "postinjury, pressor agent," and "postinjury, pressor agent + nimodipine" time intervals at the C-6 (left) and T-1 (right) spinal segments. The addition of nimodipine to the animals already receiving adrenaline postinjury caused a significant increase (p < 0.05) in SCBF at both segments.

Fig. 3. Mean values for mean systemic arterial blood pressure (MSAP) ± standard error of the means (vertical lines) for the four groups at the various time intervals. Spinal cord injury caused a brief hypertensive peak followed by marked hypotension in all animals. The postinjury hypotension was counteracted by all three pressor agents (whole blood, angiotensin, and adrenaline) and the MSAP was maintained between 100 and 120 mm Hg. The addition of nimodipine significantly decreased the MSAP in all animals except those already receiving adrenaline, in which it could be kept between 100 and 120 mm Hg.

The pressor agent phase with MSAP between 54 ± 4 and 72 ± 4 mm Hg, which continued until the pressor agents had their effect (Fig. 3). The preinjury MSAP values did not differ significantly between the groups (p > 0.05).

Analysis of variance showed that the postinjury SCBF values with the pressor agent only or with saline did not significantly differ among the four groups at either C-6 or T-1 (p > 0.05). The SCBF values at C-6 and T-1 ranged from 41.8 ± 2.8 to 47.5 ± 1.2 and from 15.8 ± 0.7 to 17.7 ± 1.5 ml/100 gm/min, respectively, 30 minutes after injury (Fig. 2 and Table 2). This corresponded to an approximate 16% to 22% decline at the C-6 level and a 55% to 62% decline at the T-1 segment compared with the "preinjury" values. After injury the MSAP differed significantly between the four groups (p < 0.05). Multiple comparison testing showed that the control animals receiving saline had a significantly lower MSAP of 68 ± 3 mm Hg (Fig. 3 and Table 3) than the other groups. The MSAP was maintained between 101 ± 4 and 118 ± 4 mm Hg in the animals receiving either whole blood, angiotensin, or adrenaline.

These was a further decline in SCBF at both C-6 and T-1 20 minutes after nimodipine infusion in all groups except the animals receiving adrenaline. The SCBF at T-1 was 14.6 ± 1.3 and 13.3 ± 0.9 ml/100 gm/min for the animals receiving nimodipine plus whole blood or angiotensin, respectively (Fig. 2 and Table 2). This was slightly but not significantly (p > 0.05) higher than the levels in the control animals in which the SCBF at T-1 was 11.8 ± 1.3 ml/100 gm/min. In contrast, the SCBF increased significantly at both C-6 and T-1 in the animals receiving adrenaline plus nimodipine (p < 0.05): the SCBF was 56.0 ± 3.2 ml/100 gm/min at C-6 and 20.2 ± 2.3 ml/100 gm/min at T-1, representing a 18% and 25% increase, respectively, over the SCBF in rats with adrenaline alone. The addition of nimodipine caused a decrease in MSAP in all groups. Indeed, MSAP could not be maintained above 100 mm Hg even with maximum infusion rates of whole blood or angiotensin, although these two groups had a higher MSAP than the control animals. However, in the animals receiving
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**TABLE 1**
Changes in hematocrit, blood gases, and rectal temperature in three time intervals*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Preinjury</th>
<th>Postinjury</th>
<th>Postinjury, Pressor Agent</th>
<th>Postinjury, Pressor Agent + Nimodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Whole Blood</td>
<td>Angiotensin</td>
<td>Adrenaline</td>
</tr>
<tr>
<td></td>
<td>Saline</td>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hematocrit (%)</td>
<td>43 ± 2</td>
<td>43 ± 1</td>
<td>45 ± 1</td>
<td>45 ± 1</td>
</tr>
<tr>
<td></td>
<td>7.35</td>
<td>7.35</td>
<td>7.37</td>
<td>7.35</td>
</tr>
<tr>
<td>pH</td>
<td>± 0.02</td>
<td>± 0.01</td>
<td>± 0.02</td>
<td>± 0.01</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>37.2</td>
<td>34.1</td>
<td>35.9</td>
<td>35.4</td>
</tr>
<tr>
<td></td>
<td>± 1.0</td>
<td>± 0.7</td>
<td>± 1.5</td>
<td>± 0.7</td>
</tr>
<tr>
<td>rectal temperature (°C)</td>
<td>37.5</td>
<td>36.4</td>
<td>37.7</td>
<td>37.9</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means. There were no significant differences in pH, PaCO2, and rectal temperature between the groups at any time interval. The hematocrit decreased between the "preinjury" and the "postinjury, pressor agent" measurements for all groups, then subsequently remained stable, except for an increase in those animals being transfused with whole blood.

**TABLE 2**
Spinal cord blood flow (SCBF) groups at three time intervals*

<table>
<thead>
<tr>
<th>Group</th>
<th>Preinjury</th>
<th>Postinjury, Pressor Agent</th>
<th>Postinjury, Pressor Agent + Nimodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-6</td>
<td>T-1</td>
<td>C-6</td>
</tr>
<tr>
<td>control (saline)</td>
<td>55.1 ± 3.9</td>
<td>43.3 ± 7.3</td>
<td>46.8 ± 7.3</td>
</tr>
<tr>
<td>whole blood</td>
<td>54.0 ± 2.7</td>
<td>46.4 ± 2.1</td>
<td>42.0 ± 4.5</td>
</tr>
<tr>
<td>angiotensin</td>
<td>52.1 ± 3.2</td>
<td>42.1 ± 1.7</td>
<td>41.8 ± 2.8</td>
</tr>
<tr>
<td>adrenaline</td>
<td>57.6 ± 4.4</td>
<td>42.8 ± 3.0</td>
<td>47.5 ± 1.2</td>
</tr>
</tbody>
</table>

* The measurements are mean values ± standard error of the means (in ml/100 gm/min) from two sites: C-6 (proximal to the injury site) and T-1 (site of injury).
† Significantly different (p < 0.05) SCBF between groups at a given time interval according to Duncan’s multiple comparison testing. The animals given a combination of adrenaline + nimodipine had a significantly higher SCBF.

**TABLE 3**
Mean systemic arterial pressure (MSAP), for the four groups at three time intervals*

<table>
<thead>
<tr>
<th>Group</th>
<th>Preinjury</th>
<th>Postinjury, Pressor Agent</th>
<th>Postinjury, Pressor Agent + Nimodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-6</td>
<td>T-1</td>
<td>C-6</td>
</tr>
<tr>
<td>control (saline)</td>
<td>123 ± 3</td>
<td>68 ± 3</td>
<td>42 ± 4</td>
</tr>
<tr>
<td>whole blood</td>
<td>131 ± 4</td>
<td>101 ± 4†</td>
<td>82 ± 6††</td>
</tr>
<tr>
<td>angiotensin</td>
<td>140 ± 5</td>
<td>105 ± 7††</td>
<td>62 ± 5††</td>
</tr>
<tr>
<td>adrenaline</td>
<td>141 ± 2</td>
<td>118 ± 4††</td>
<td>109 ± 5†††</td>
</tr>
</tbody>
</table>

* Values are means ± standard error of the means in mm Hg.
† Significantly different (p < 0.05) from other groups at a given time interval if not labeled with the same number of daggers, using Duncan’s multiple comparison test. Whole blood, angiotensin, or adrenaline could all improve the postinjury MSAP between 100 and 120 mm Hg. The addition of nimodipine decreased the MSAP in all groups, but the MSAP could be maintained between 100 and 120 mm Hg in those animals also receiving adrenaline.

Discussion
Within 30 minutes of trauma, there was a marked decline in SCBF both at T-1 (the site of injury) and at C-6. In our laboratory, posttraumatic ischemia has also been documented with the carbon-14 (14C) antipyrine autoradiographic and the radioactive microsphere techniques for SCBF measurement after moderate to severe spinal cord injury. The severity of injury used in experimental spinal cord injury is crucial, and may explain why some authors have questioned the existence of posttraumatic ischemia of the spinal cord.4,27 In animals that were rendered paraparetic or recovered completely, Ducker, et al.,3,13-15 noted normal to increased SCBF, while there was a definite decrease in SCBF in the totally paraplegic animals. Microangiographic demonstration of the injured spinal cord vasculature has also contributed a convincing body of evidence that posttraumatic ischemia is a significant pathophysiological component of spinal cord trauma.8,9,18,19,30

The present study showed a 50% to 60% decline in SCBF at the injury site with a 15% to 20% decrease at C-6 (1 cm rostrally). Sandler and Tator35,36 demonstrated that the area of ischemia spread rostrally and caudally from the point of injury and caused discrete wedge-shaped areas of spinal cord infraction up to 2 cm away. Senter and Venes,27 using the hydrogen clearance technique, also demonstrated decreased SCBF which began 1 hour after injury in segments located 1 cm distal to the site of injury. The present study also

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showed that the ischemic process may extend great distances from the injury site and that distal ischemia occurred within 30 minutes of trauma. It should be noted that in the present study both the experimental animal and the method of injury differed from the study of Senter and Venes.

Our laboratory and others have shown that the blood pressure shows a characteristic patterned response to major cervical cord trauma with an initial hypertensive peak followed by a prolonged period of hypotension (Fig. 3). Young, et al., attributed the initial hypertensive peak to a neurally and humorally mediated sympathetic discharge. It has been our clinical practice to treat the posttraumatic hypotension in order to maximize neuronal recovery, but experimental or clinical proof of the value of this practice is lacking. Similarly, the ideal level of MSAP and the duration of treatment are unknown. In clinical practice, the aim has been to restore normal MSAP to counteract the hypotension that might aggravate the posttraumatic ischemia. In accordance with this practice, we attempted to maintain MSAP between 100 and 120 mm Hg in the present study.

In the animals receiving either whole blood, angiotensin, or adrenaline, the MSAP could be maintained equally well between 100 and 120 mm Hg after injury (Fig. 3 and Table 3). In contrast, the control group treated with saline showed marked hypotension. Although MSAP was restored by the three pressor agents, there was an improvement in SCBF at either T-1 or C-6 for any of the three groups compared to the control animals (Fig. 2 and Table 2). There are several possible reasons for this lack of improvement. First, the injured spinal cord may still have been capable of autoregulation and therefore there was no improvement in SCBF with increased MSAP. True autoregulation involving active contraction of the spinal cord microvasculature may have persisted in response to increased MSAP, or “false autoregulation” involving passive contraction of the spinal vessels may have developed as a result of increasing edema secondary to the increased MSAP. These explanations are unlikely because the loss of autoregulatory capability by the injured spinal cord has been well documented.

A second possible reason is that the MSAP was not increased sufficiently to result in improved postinjury SCBF. The exact relationship between SCBF and MSAP after injury is not known and the shape, position, and slope of the posttraumatic SCBF versus MSAP relationship is uncertain. For example, if the curve or line is shifted to the right (such as when a higher MSAP is required for the same SCBF) and/or the slope is too flat, the range achieved in this experiment of posttraumatic MSAP between 100 to 120 mm Hg may have been too low. Studies are currently underway to provide a better understanding of this fundamental relationship between the postinjury SCBF and MSAP in our experimental model.

A third possibility is that the disrupted spinal microvasculature may have been incapable of allowing perfusion of the tissue even though an adequate MSAP was present. Microangiography with administration of thioflavin, barium, or colloidal carbon has shown major changes in the spinal microvascular bed after injury. Dohrmann, et al. attributed the lack of microvascular filling to immediate mechanical damage, especially to the venules, along with a delayed ischemic endothelial injury. Fried and Goodkin demonstrated narrowed and focally constricted vessels together with areas of dilation. Fairholm and Turnbull classified two zones of microvascular changes present 1 to 2 weeks postinjury. Zone 1 consisted of hemorrhagic and nonviable tissue, with the microvascular bed progressively losing the capability to be perfused in the acute stages of injury. In Zone 2 the vascular bed remained patent, and upon its perfusion depended the recovery of damaged but viable tissue. Successful therapeutic intervention in the acute stage of spinal cord injury would, according to Fairholm and Turnbull, act by limiting the extent of Zone 1, and also by maintaining perfusion resulting in recovery of the viable tissues in Zone 2. Thus, microangiographic studies have demonstrated major posttraumatic microvascular changes and lack of flow; these are not due entirely to the destruction of vessels: they also result from an inability of structurally intact vessels to be perfused. The mechanisms whereby intact vessels are not able to conduct blood flow after trauma are not fully known, but in our opinion there may be pathophysiological similarities to post-subarachnoid hemorrhage vasospasm.

The results of the addition of nimodipine in the present study support this possible explanation. Nimodipine has previously been shown to produce spinal cord and cerebral vasodilatation. In the present study nimodipine increased postinjury SCBF only when an adequate MSAP was maintained. Adrenaline was the only one of the three pressor agents to maintain MSAP above 100 mm Hg after nimodipine was added (Fig. 3 and Table 3) and this allowed approximately an 18% and 25% improvement in SCBF at the C-6 and T-1 segments, respectively. This is strong evidence that nimodipine may have counteracted or prevented a mechanism such as vasospasm, which may have rendered structurally intact vessels incapable of being perfused.

In comparison with the vasoconstriction of peripheral vessels due to adrenaline, similar vasoconstriction caused by angiotensin is more effectively counteracted by nimodipine and other related calcium antagonists. This fact, along with the B1 cardiac effects of adrenaline which increase the heart rate and contractility, allowed adrenaline to maintain the MSAP during administration of nimodipine. The ability of calcium antagonists to counteract the pressor effects of a hyperactive renin-angiotensin system has led to interest in using these drugs for treatment of hypertension due to this etiology. In the injured spinal cord with its loss of autoregulation, MSAP must be maintained while using nimodipine. For example, in the
groups in which nimodipine caused a significant decline in MSAP (saline, whole blood, and angiotensin) (Fig. 3 and Table 3), there was a further reduction of SCBF which may aggravate the injury. Therefore, adjuvant agents such as adrenaline are required to maintain MSAP during administration of nimodipine in order to improve the posttraumatic SCBF.

There have been several reports of attempts to treat posttraumatic ischemia of the spinal cord. In our laboratory, dopamine and whole-blood transfusion were found to be of some benefit, as proven by the 14C antipyrine autoradiographic SCBF measurement technique. Megadose steroids, naltrexone, gamma hydroxybutyrate have all been reported to improve posttraumatic ischemia, although there have been some conflicting reports. Furthermore, none of these agents which improved SCBF has been shown to definitely improve neurological function in the same animal. The present report of improved posttraumatic SCBF by a combination of nimodipine and adrenaline requires further study, especially to determine whether the improved SCBF and maintained MSAP will increase functional recovery. Faden, et al., recently reported that nimodipine failed to benefit histopathological or neurological recovery 24 to 48 hours after an ischemic spinal cord injury in rabbits with doses of nimodipine comparable to the present study, although measurements of SCBF or MSAP were not reported. In addition, they did not use adjuvant agents to maintain MSAP.

The present study has shown that nimodipine can counteract posttraumatic ischemia if MSAP can be maintained. It is not known whether this will improve neurological recovery. It is known that calcium channel blockers including nimodipine have a protective action against calcium-mediated cell death, and this provides an additional impetus to perform studies to assess the effects of nimodipine on neurological recovery after spinal cord trauma.

Conclusions

1. Spinal cord injury causes a marked decrease in SCBF both at the site of injury and spreading away from the injury site. The ischemia may result in infarction and further injury to the spinal cord.
2. Spinal cord injury at T-1 results in a marked decrease in MSAP which can be counteracted equally well by whole-blood transfusion, angiotensin, or adrenaline infusion; however, there was no improvement in posttraumatic SCBF with these agents alone.
3. The addition of nimodipine after administration of adrenaline caused a significant improvement in posttraumatic ischemia and MSAP could be maintained. The addition of nimodipine to the administration of either whole blood or angiotensin did not restore posttraumatic hypotension to normal levels and failed to improve posttraumatic ischemia.
4. Nimodipine can improve posttraumatic ischemia of the spinal cord if given with an adjuvant agent to maintain an adequate MSAP.
5. Further studies are required to investigate whether nimodipine can improve neurological recovery.

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