Effect of regional spinal cord blood flow and central control in recovery from spinal cord injury

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Forty-two cats were subjected to decerebration, thoracic and lumbar laminectomies, and isolation of the sciatic nerves. Spinal evoked potentials in response to bilateral sciatic nerve stimulation were recorded at L-3, and the spinal cord blood flow (SCBF) was measured by the hydrogen clearance technique. Thoracic cordotomy did not alter the lumbar SCBF or the central conduction time as determined by spinal evoked potentials. Thoracic cordotomy significantly lowered the lumbar spinal cord injury threshold. Continuous sciatic nerve stimulation increased the lumbar SCBF in normal and traumatized animals; however, it did not affect the spinal cord injury threshold as measured by recovery of the spinal evoked potentials. It appears that rostral spinal cord integrity is far more significant in recovery from spinal cord injury than the maintenance of regional SCBF.

KEY WORDS  •  spinal cord injury  •  sciatic nerve stimulation  •  spinal cord blood flow  •  cat

A number of studies have reported a direct correlation between spinal cord blood flow (SCBF) in the area of injury immediately posttrauma and the functional outcome after spinal cord injury (SCI). Investigations conducted by Osterholm, et al.,16-21 and Albin, et al.,1,2 about 20 years ago presented the hypothesis that SCI induces focal abnormal metabolic processes and release of substances which cause focal posttraumatic ischemia, resulting in secondary injury to the spinal cord. Although later studies22-25 did not support the finding of focal accumulation of vasoactive substances, this hypothesis instigated a revival of interest in experimental spinal cord concussion and application of new techniques to study SCBF in intact and injured animals, with often conflicting results.22-25,29,30

A number of investigators10,12,19,22,30,34 have reported correlation between the white matter ischemia in the acute phase and the severity of trauma, with the suggestion that the degree of functional recovery is dependent on the return of blood flow. Preservation of regional SCBF by various therapeutic modalities has been implicated in the improved recovery of spinal cord conduction.5,11,15,19,35-37 Nevertheless, a causal relationship has not been established between the reported posttraumatic spinal cord ischemia and outcome; furthermore, the site of action of the various reportedly effective treatment modalities remains in question.

It has long been known that peripheral nerve stimulation results in a regional increase in SCBF.18,23,32 Scremin and Decima32 demonstrated that dorsal root stimulation can produce a sustained increase in segmental SCBF in the gray matter of intact and decerebrated animals. This study was designed to evaluate the effect of maintenance of regional SCBF by sciatic nerve stimulation as well as the effect of severing the descending central nervous system input to the site of trauma with regards to the outcome of SCI.

Materials and Methods

Protocol

Forty-two cats, each weighing 2 to 4 kg, were anesthetized under 2% halothane in a mixture of 60% N2O and 40% O2. Cannulation of a common carotid artery and external jugular vein, and tracheotomy were performed. The end-tidal CO2 was monitored continuously with a Beckman LB-2 gas analyzer.* Blood pressure

* Gas analyzer, Model LB-2, manufactured by Beckman Instruments, Inc., Fullerton, California.
was monitored continuously with a Statham transducer and reported as its mean value.† A craniectomy was fashioned and the animals were decerebrated at the intercollicular level under the operating microscope. Laminectomies were performed at T11–13 and L3–5 and the sciatic nerves were isolated bilaterally. After completion of the surgical procedures and removal of halothane anesthesia, the animals were paralyzed by a continuous infusion of pancuronium (Pavulon) at a rate of 0.02 mg/kg/hr and ventilated on room air with an end-tidal CO₂ of 3% to 4%. The animals were fixed rigidly in a spinal frame and the exposed dura was covered with a pool of mineral oil maintained at 37°C. Body temperature was monitored with an esophageal thermometer and maintained at about 37°C. Spinal evoked potentials (SEP’s) were measured initially by stimulation of each sciatic nerve and thereafter by bilateral simultaneous sciatic nerve stimulation. The evoked potentials were recorded at the L-3 vertebral level from the surface of the dura over the dorsal columns with a silver-ball spring electrode. The SEP’s were conventionally amplified and presented on a storage oscilloscope because averaging of the transients was not needed for signal identification at this level. Stimulation parameters were: pulse duration, 1 msec; pulse amplitude, 5 × threshold; and pulse frequency, 0.5 Hz.

Baseline SCBF was estimated using the H₂ clearance technique.6,24,33 Two glass insulated platinum wire electrodes, 50 to 75 μm in diameter, were used as the H₂ sensor electrodes and were inserted in the dorsal columns to 1 mm below the surface at the L-4 level and at a distance of 1 cm apart in the rostral caudal direction. Two subcutaneous calomel electrodes were used as reference electrodes. A steady-state level of tissue H₂ was achieved by the administration of 5% H₂ in the inspired gas. The slope of the desaturation curve after the first 50 seconds was used for estimation of the SCBF. After measurement of the baseline blood flow, the H₂ sensing electrodes were removed and, with the aid of a micromanipulator, the trauma device was lowered onto the dura at the site of the caudal electrode. To injure the cord a 20-gm weight was dropped onto a platform 7 mm in diameter that was resting on the dura spanning the width of the lumbar enlargement at the L-4 level.3,4 A vented tube directed the weight from a precalibrated height. The injury dose was presented in units of gm/cm (gm · cm) as the product of the weight of the impounder (20 gm) times the distance it had to fall onto the platform measured in centimeters. There was a transient rise in the mean systemic blood pressure after the impact lesion was induced. After injury, the trauma device was removed and, by means of the micromanipulators, the H₂ electrodes were repositioned in their original location on the spinal cord. The local-† Transducer manufactured by Statham Instrument Co., Oxnard, California.

tions of the electrode tips within the spinal cord were verified later on histological examination of the formalin-fixed and serially sectioned cord segments. The animals were separated into four groups.

**Experimental Groups**

Group 1 received no thoracic cordotomy and no stimulation. The 15 animals in this group were subjected to a trauma dose (in gm · cm) of: 0 (two cats), 120 (one cat), 240 (two cats), 360 (four cats), 400 (five cats), or 500 (one cat). The lumbar SEP’s in response to bilateral sciatic nerve stimulation of a few seconds at a time and the lumbar SCBF were measured hourly for the next 5 hours.

The 12 cats in Group 2 received a thoracic cordotomy but no stimulation. After the dura was incised at the level of the thoracic laminectomy, a small amount of lidocaine was injected into the spinal cord and complete spinal cord transection was performed under an operating microscope, taking care not to traumatize the anterior spinal artery. Lumbar SCBF and SEP’s were measured before and after the T-11 cordotomy. After 4 hours of observation, lumbar spinal cord injuries were delivered at trauma doses (in gm · cm) of: 0 (one cat), 60 (three cats), 120 (two cats), 240 (three cats), or 360 (three cats). The lumbar regional SCBF and SEP’s were monitored for 3 and 5 hours, respectively. For SEP monitoring, the stimulator was turned on for brief periods of a few seconds at a time.

Group 3 (10 cats) received stimulation but no thoracic cordotomy. After measurement of the baseline SCBF and evoked potentials, 10 animals were subjected to impact injury (in gm · cm) of: 0 (three cats), 240 (one cat), 400 (five cats), and 500 (one cat). Continuous stimulation of both sciatic nerves was started after repositioning of the H₂ electrodes (within 10 minutes of the time of trauma) and carried on for 5 hours by an isolated pulse and waveform generator producing a 1-msec square-wave stimulation of 20 Hz and 50 V. The SCBF and the SEP’s were monitored hourly for 5 hours.

Group 4 included five cats, which received both thoracic cordotomy and stimulation. Five animals were subjected to cordotomy at T-11 and, after 4 hours of observation, lumbar spinal cord injuries were delivered at trauma doses of 0 gm · cm in three cats and 360 gm · cm in two. Continuous stimulation was started within 10 minutes after the trauma and was continued for 3 hours. Lumbar SCBF and SEP’s were measured for 3 and 5 hours, respectively.

**Statistical Analysis**

Significance of differences between means of SCBF and arterial pressure for the various experimental groups were assessed by the Bonferroni procedure. The chi-square test was used to evaluate the significance of SEP recovery rates.
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Results

The SEP's were polyphasic evoked potentials in response to sciatic nerve stimulation. The evoked potentials recorded at the L-3 level did not need averaging for identification, remained stable over a period of several hours, and were undisturbed by anesthesia, decerebration, and thoracic cordotomy. Subsequent to the lumbar SCI, only a monophasic (killed-end) potential could be recorded. When the SEP's could not be detected by this form of analysis, further averaging of the transients failed to bring out an evoked potential. In instances when there was recovery of SEP's following a complete loss, the waveforms were disrupted and the peak latencies were elongated with gradual return of the waveform toward the baseline in time.

Arterial pressure and SCBF remained stable over a period of several hours, provided that the temperature and the end-tidal CO2 remained constant. Two simultaneous recordings of SCBF, 1 cm apart, were made at all times. The lower electrode was placed at the site of injury. Reproducibility of the SCBF measurement was assured by comparing the values from the two simultaneous recordings. The baseline SCBF measurements ranged from 5 to 25 ml/100 gm/min in 22 pairs of recordings with a mean (± standard deviation) of 10.73 ± 4.67 ml/100 gm/min. Baseline arterial pressure ranged from 69 to 106 mm Hg with a mean of 85.3 ± 13.7 mm Hg.

Lumbar SCBF was undisturbed by decerebration or thoracic cordotomy. Bilateral sciatic nerve stimulation in decerebrate animals without SCI (Fig. 1) resulted in persistent and significant elevation of lumbar regional SCBF during the 5 hours of continuous stimulation (p < 0.05, using the Bonferroni procedure). Similar elevation of the SCBF in response to stimulation was noted in animals with thoracic cordotomy, however, with a more marked initial increase in the flow followed by a progressive decline toward the baseline in time (Fig. 2).

A transient increase in arterial pressure was observed in noncordotomized animals when the continuous electrical stimulation of sciatic nerves was started. At the time of SCBF determination, however, arterial pressure was not different between noncordotomized animals that did receive stimulation (mean ± standard error of the mean: 86.9 ± 3.50 mm Hg) and those that did not (92.5 ± 2.14 mm Hg). Also, no difference was observed in arterial pressure between stimulated and nonstimulated cordotomized animals (stimulated cordotomized group: 78.5 ± 6.11 mm Hg, nonstimulated cordotomized group 84.9 ± 7.13 mm Hg). Arterial pressure before and after trauma did not show significant variations in any of the experimental groups.

After a 400-gm · cm injury there was an immediate and permanent loss of SEP's in all animals. Noncordotomized animals that did not receive sciatic nerve stimulation showed a transient rise in white matter blood flow in the 1st hour, with subsequent progressive and significant loss of blood flow in the next 4 hours as compared to the baseline control level (Fig. 1). Bilateral sciatic nerve stimulation after trauma resulted in nonsignificant elevation of the SCBF in the 1st hour as compared to the control baseline level. This elevation of blood flow progressively decreased toward baseline within the next 4 hours. The SCBF values in traumatized stimulated animals were not statistically different from baseline values and were at variance with SCBF values in traumatized nonstimulated animals, which were reduced. After thoracic cordotomy, the alterations in SCBF in response to a 300-gm · cm injury (Fig. 2) mimicked those in the animals without cordotomy in the fact that trauma was followed with an early nonsignificant elevation of the SCBF in the 1st hour followed by a rapid and significant (p < 0.05) drop below baseline during the next 2 hours. Continuous sciatic nerve stim-
FIG. 2. Lumbar spinal cord blood flow in cats with thoracic cordotomy at the T-12 level. Stimulation significantly increased the blood flow, which rapidly fell toward baseline in animals with and without focal trauma. Stimulation was continuous stimulation of both sciatic nerves. The 360-gm \( \times \) 9 cm trauma was induced by dropping a 20-gm weight 18 cm onto a platform resting on exposed dura at the L-4 level. The number of animals in each group is presented in parentheses. Asterisks denote a statistically significant difference when compared with the control group without stimulation or trauma (p < 0.05, by the Bonferroni procedure).

Fig. 3. Return (+) or failure to return (–) of spinal evoked potentials (SEP's) shown for each animal after lumbar spinal cord injury (SCI) doses of 60, 120, 240, 360, 400, or 500 gm \( \times \) 9 cm in response to spinal stimulation in animals with intact thoracic cord (A), and spinal stimulation in animals with thoracic cordotomy (B). The effect of prior thoracic cordotomy on return of SEP's after lumbar SCI irrespective of spinal stimulation is shown in C. The asterisk indicates a statistically significant (p < 0.05) break in recovery of SEP's between 120- and 240-gm \( \times \) 9 cm injuries for the groups with cordotomy, and between 360- and 400-gm \( \times \) 9 cm injuries for the group without.

ulation after cordotomy resulted in an early significant (p < 0.05) elevation of the lumbar SCBF in the 1st hour, followed by a progressive decline toward baseline in the next 2 hours in a fashion very similar to that seen in the animals with thoracic cordotomy and no lumbar SCI.

Evaluation of the effect of bilateral sciatic nerve stimulation on the return of SEP's after lumbar SCI in animals with intact thoracic spinal cord showed no difference between the animals undergoing stimulation as compared to those without. All of the five animals receiving a 400-gm \( \times \) 9 cm injury permanently lost SEP's in each group, while a 240-gm \( \times \) 9 cm injury resulted in no loss of SEP's in either group (Fig. 3A). In animals with thoracic cordotomy and lumbar SCI, again no improvement of the SEP's was documented in response to sciatic nerve stimulation. Both animals with a 360-gm \( \times \) 9 cm injury permanently lost SEP's despite stimulation, as did all three animals that did not receive stimulation (Fig. 3B). Despite significant improvement in the regional SCBF, no improvement in recovery of SEP's after SCI was realized in response to bilateral continuous sciatic nerve stimulation in animals with intact thoracic spinal cord or in animals with thoracic cordotomy.

The effect of thoracic cordotomy on the threshold of SCI as measured by recovery of SEP's was studied by combining the results of all 33 experimental animals into two groups, one with thoracic cordotomy and one without (Fig. 3C). In animals with thoracic cordotomy all of the eight animals receiving a 240-gm \( \times \) 9 cm injury or more had permanent loss of SEP's. One of the two animals receiving a 120-gm \( \times \) 9 cm injury had permanent loss of SEP's and one had return of SEP's within 1 hour. A 60-gm \( \times \) 9 cm injury resulted in one of three animals not losing SEP's at all and the other two recovering SEP's within 30 minutes. In the group of
animals subjected to thoracic cordotomy there was a statistically significant \((p < 0.05)\) break in recovery of SEP's between 120- and 240-gm-cm injuries. Evaluation of comparable data from animals without thoracic cordotomy revealed that all of the 12 animals receiving 400-gm-cm injury or more had permanent loss of SEP's. An injury level of 240 gm-cm or less was not associated with loss of SEP's. Two of the four animals with 360-gm-cm injury had permanent loss of SEP's, and two had return of evoked potential within 30 minutes. In the group of animals with intact thoracic spinal cord there was a statistically significant \((p < 0.05)\) break in recovery of SEP's between 360- and 400-gm-cm injuries. Furthermore, of the 15 animals receiving 240- or 360-gm-cm injuries those with thoracic cordotomy had a significant loss of SEP's (eight of eight animals) as compared to those without thoracic cordotomy (two of seven) \((p < 0.005\), as measured by chi-square test). Thus, animals with thoracic cordotomy appeared to have a significantly lowered tolerance threshold to SCI. Furthermore, although thoracic cordotomy did not affect baseline lumbar SEP's, SCBF, or arterial pressure, it altered the pattern of blood flow changes in the lumbar spinal cord in response to sciatic nerve stimulation.

**Discussion**

The discovery and description of progressive central hemorrhagic necrosis of the spinal cord following injury dates back to Schmaus and Ferraro. A decrease in intramedullary blood flow and oxygen tension in the traumatized segment in the first few hours after SCI was reported by Ducker and Perot. Albin, et al., had already reported that if local hypothermic therapy was instituted within 4 hours after spinal contusion the animals regained most sensory and motor function. Osterholm, et al., reported an increase in norepinephrine in contused spinal cord of the monkey which could be blocked by administration of alpha-methyltyrosine with associated improvement in the posttraumatic hemorrhagic changes in the spinal cord. The above studies implied that there remains a grace period after spinal cord injury during which therapeutic intervention may improve the outcome. Subsequent work by Ducker and Assenmacher, Wagner, et al., Fairholm and Turnbull, and Lohse, et al., described transitory posttraumatic changes in the traumatized spinal cord perfusion, and the association of a significant decrease in blood flow with injuries that would result in permanent paraplegia, while injuries that would result in only a transient paraplegia were not associated with a decrease in segmental SCBF during the first several hours postinjury. In the past two decades, alterations of the SCBF in response to trauma have been investigated and the concept of secondary injury due to a reactive spinal cord ischemia after the initial injury has become well established. A large number of therapeutic modalities aimed at improvement of posttraumatic spinal cord ischemia have been undertaken. Treatments that have resulted in improved functional outcome have often been associated with improved postinjury SCBF. Despite effective amelioration of the postinjury ischemia, however, unequivocally successful therapeutic measures have not been identified.

Nevertheless, contradictory reports are not uncommon, and lack of knowledge about the site of action of the beneficial therapeutic agents has confounded identification of the role of postinjury hypoperfusion of the spinal cord in causing a secondary injury.

In 1951, Field, et al., and later Marcus, et al., demonstrated that peripheral nerve stimulation resulted in elevation of SCBF. Scremin and Decima demonstrated that dorsal root stimulation resulted in persistent elevation of the SCBF above the stimulated segment. It is interesting to note that the increase in SCBF with sciatic nerve stimulation persisted for a period of 5 hours in animals without thoracic cordotomy (Fig. 1) while it declined rapidly in cordotomized animals (Fig. 2). Capon reported that vasodilation of spinal cord to hypercapnia was abolished below a cordotomy; however, this could not be confirmed by Scremin and Decima. Furthermore, Senter and Venes found preservation of regulation of the regional SCBF after SCI. Our observation of a decay in the SCBF in response to continuous stimulation in animals with thoracic cordotomy suggests that integrity of the central connections, although not necessary for modulation of blood flow, is essential for a sustained vasodilation in the spinal cord. Whether this is related to severance of the central portion of axons affecting the regulation of blood flow through release of vasoactive substances or to suppression of descending pathways cannot be ascertained with the available data.

In this study, despite a significant increase in the regional SCBF by segmental stimulation, there was no improvement in the threshold of spinal cord recovery from SCI as measured by SEP's. The integrity of the more rostral spinal cord, however, was associated with a significant increase in the threshold of spinal cord to injury. These results suggest that the mechanisms of secondary injury after spinal cord trauma, if in fact not fully the direct result of the initial impact injury, may have a mediator other than the observed reduction in focal SCBF during the 5 hours following injury. The decreased SCBF following a severe SCI may be a passive result of injury to the blood vessels or may in part reflect the disruption of the metabolism in the injured tissue rather than the cause of focal spinal cord ischemia and progressive SCI.

It appears that heretofore unidentified descending neural or chemical regulatory mechanisms may have a far more significant effect in recovery of spinal cord from injury than the focal drop in SCBF. The basis for this phenomenon remains obscure and we can only speculate. Integrity of axons rostral to the lesion perhaps allows axoplasmic flow to continue and provide materials required to seal or resynthesize damaged mem-

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branes. If this were the case, surgical section limited to the dorsal columns (which mediate the electrical response to test) should reproduce the effects observed, while the opposite would be true if only anterior or lateral cordotomies were performed. On the other hand, an anterolateral cordotomy that would sever descending pathways could be used to test their role in this phenomenon.

It is unlikely that the observed increase in segmental SCBF in relation to stimulation is in response to increased neuronal metabolism, because the increased blood flow persists after SCI with documented loss of neuronal electrical activity as measured by the SEP's. This study suggests that the integrity of the spinal cord at a more central level plays a far more significant role in determining the spinal threshold to injury and recovery of the electrical conduction across the injury than does the regional SCBF at the site of injury. This may reflect the significance of integrity of central pathways in modifying the response to focal injury. The demonstrated decrease in the regional blood flow may reflect the severity of the initial injury and the interplay of the central control and may be an epiphenomenon.

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