Effect of Graded Hypothermia (27°C to 34°C) on Behavioral Function, Histopathology, and Spinal Blood Flow After Spinal Ischemia in Rat

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Abstract

The effect of hypothermia on recovery from transient ischemia has been studied in several models of global cerebral ischemia. Even modest levels of cerebral hypothermia (34°C to 35°C) can diminish histopathologic signs of injury and improve behavioral sequelae following reversible cerebral ischemia in a variety of species including gerbil, rat, and rabbit.1-3

Although the exact mechanism of hypothermia-mediated protection is not completely understood, several biochemical variables appear relevant. Under normothermic conditions of complete cerebral ischemia the early pathobiologic changes are characterized by initial high-energy phosphate exhaustion, membrane depolarization, and increased lactate production. In parallel with these changes, excessive excitatory amino acid release and intracellular Ca2+ accumulation occurs. Higher concentrations of cytosolic Ca2+ lead to activation of a variety of enzymes including proteases, nitric oxide synthase, nucleases, and phospholipases, which subsequently affect the integrity of cellular and subcellular membranes.4-5 This simplified biochemical cascade appears to represent the main changes affecting neurons during ischemia and early reperfusion.

Conclusions These results show that a slight decrease in spinal cord temperature in the peri-ischemic period provides significant protection as measured by histopathology and neurological function. (Stroke. 1994;25:2038-2046.)

Key Words • hypothermia • neurons, argyrophilic • paraplegia • spinal cord

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Early studies employing hypothermia as a therapeutic procedure related its protective effect to a reduction of neuronal metabolism, energy consumption, and lactate production during the ischemic-hypothermic period. However, recent studies on a four-vessel occlusion model in rat show that mild intraschismic hypothermia significantly enhances neurological recovery and diminishes the extent of neuronal damage, although there is little effect on the exhaustion of high-energy phosphates or lactate production.6 Alternately, it has been shown that hypothermia may diminish the release of excitatory amino acids, notably glutamate, otherwise evoked during the interval of normothermic ischemia in gerbil, rat, and rabbit hippocampus.1-3,6 Given the apparent protective effects of N-methyl-D-aspartate receptor antagonists, this reduced release could serve as an alternative mechanism of protection.

Though less well characterized, similar protective effects of hypothermia in spinal cord ischemia have been reported. Decreasing rectal temperature to 30° to 32°C provides significant spinal cord protection against 21 to 30 minutes of abdominal aortic ligation in the rabbit.7-9 Lowering spinal cord temperature (SCT) to 28°C or 17°C by epidural cooling led to almost complete recovery of motor function after 40 minutes of double thoracic aorta cross-clamping in dogs and after 60 minutes of abdominal aorta ligation in rabbits, respectively.10,11

Recently, we initiated systematic studies characterizing the effects of reversible spinal ischemia using a simple, minimally invasive rat model employing balloon...
occlusion of the descending thoracic aorta. In this model, 20 minutes of spinal ischemia with reperfusion leads to the appearance of argyrophilic neurons in laminae III through VII that are seen as early as 120 minutes after reperfusion. Coincident with these pronounced changes in the appearance of spinal neurons, the majority of animals displayed spastic paraplegia and allodynia (pain evoked by light tactile stimulation) that developed 40 to 120 minutes postischemia and persisted for 8 hours of reperfusion. After 8 hours, spinal cord histology in these animals showed, in addition to the presence of argyrophilic neurons, the appearance of necrotic foci preferentially affecting central and dorsal gray matter in the lumbarosacral segments.

In the present study, by using this rat spinal cord ischemia model, we characterized the effect of preischemically induced hypothermia of different magnitudes on behavioral and histopathologic changes observed after a 20-minute interval of aortic occlusion. In addition, spinal cord blood flow (SCBF) and CO$_2$ responsiveness were measured by using laser Doppler technique, providing data on peri-ischemic SCBF blood flow in normothermic and hypothermic spinal cords.

**Materials and Methods**

**General Preparation**

Male Sprague-Dawley rats (300 to 325 g) were used. The animals were anesthetized in a Plexiglas box with 3% halothane in an oxygen–room air mixture (1:1). Following induction, rats were maintained with 1% to 1.5% halothane delivered by an inhalation mask. For core temperature measurements, a rectal probe was inserted 3 cm into the rectum. To monitor spinal temperature, a needle temperature probe (Omega 33-gauge hypodermic needle) was placed in the paravertebral muscles at the level of L3 to L4. Paravertebral muscle temperature corresponded closely with spinal parenchymal temperature (see below). The tail artery was cannulated with a PE-50 catheter for monitoring of distal blood pressure, which equals mean arterial blood pressure (MABP) measured below the occlusion level, and heart rate (Grass, model 7E polygraph). End-tidal CO$_2$, O$_2$, and halothane were monitored throughout the experiment in all animals.

To induce spinal cord ischemia, the left femoral artery was exposed and cannulated with a 2F Fogarty catheter (American V. Mueller model CV 1035) was passed to the thoracic aorta so that the tip of the catheter reached the level of the left subclavian artery (distance from the site of catheter insertion, 10 to 11 cm). At the appropriate time the catheter was inflated with 0.25 saline for 20 minutes. At the end of the occlusion period the catheter was deflated and removed. Immediate reappearance and stabilization of the distal blood pressure was observed. In control animals the balloon catheter was placed in the aorta but was not inflated.

**Definition of the Cooling Protocol/Temperature Groups**

In the first study, during the period of preparation the animals were kept on a circulating-water pad that maintained their core temperature at 35.4±0.3°C. The back of each animal was shaved from the neck to the base of the tail. The animal was laid supine for close contact with the thermal pad surface. The parenchymal SCT was measured by placing a needle temperature probe (Omega 33-gauge hypodermic needle) through a small hole drilled in the L2 vertebra into the central gray matter of the spinal cord. To detect the relation between the changes in SCT and paravertebral muscle temperature an additional thermocouple was also placed in the paravertebral muscle overlaying the L2 segment. The empirically defined protocols for cooling were performed as follows. In the normothermic group (n=6; SCT=37.5°C), the underbody pad was maintained at 37.5°C. In the mildly hypothermic group (n=6; SCT=34°C to 35.5°C), the underbody pad was maintained at 21°C during the period of occlusion. In the moderately hypothermic group (n=6; SCT=31°C to 33°C), the underbody pad was maintained at 7°C to 8°C from 2 minutes before aortic occlusion until the time of occlusion. At the moment of aortic occlusion, the water circulation to the thermal pad was turned off, and no additional manipulations were performed during the occlusion period. In the deeply hypothermic group (SCT=27°C to 30°C), the underbody pad was maintained at 7°C to 8°C from 12 minutes before aortic occlusion until the time of occlusion. At the moment of aortic occlusion, the water circulation to the thermal pad was turned off, and no additional manipulations were performed during the occlusion period.

At the time of reflow, in all hypothermic animals the rewarming procedure was started by using heating lamps and returning the circulating water temperature to 37.5°C. Because of the relatively invasive character of direct SCT measurement, these animals were maintained with 1.5% halothane for up to 60 minutes of reperfusion and then killed. An identical cooling protocol was used in all the studies described below except that only rectal and paravertebral muscle temperatures were measured.

**SCBF Measurement and CO$_2$ Responsivity**

To assess the changes in SCBF, a separate group of animals (n=23) was used. In 10 animals, 20 minutes of normothermic ischemia was followed by 60 minutes of reperfusion as described. Another 7 animals had their spinal cords cooled to 31°C 2 minutes before aortic occlusion (moderate hypothermia) followed by 60 minutes of normothermic reperfusion. In control animals (n=6) a balloon catheter was placed in the descending thoracic aorta for 20 minutes but was not inflated.

To measure the SCBF, the tip of a laser probe 0.8 mm in diameter (Laserflo Model BPM 403 A Blood Perfusion Monitor, TSI Inc) was placed in the epidural space through the L2 vertebra. SCBF was then continuously monitored before, during, and for 60 minutes after 20 minutes of spinal cord ischemia by using a 5-second averaging cycle. To detect SCBF-CO$_2$ responsivity, the arterial CO$_2$ tension was decreased by hyperventilating (70 to 140 respirations per minute) the animals for 2 minutes. Before and at the end of the hyperventilation period, arterial blood samples were taken for blood gas analysis. After the hyperventilation period the SCBF-CO$_2$ responsivity test was completed, this was followed by a 10-minute stabilization period prior to the initiation of cooling or induction of ischemia. The same CO$_2$ responsivity test was then repeated 60 minutes after reperfusion in both the normothermic and moderately hypothermic groups as well as at the appropriate time in control animals.

**Neurological and Histopathologic Study**

In this study SCT was decreased as described to 34°C (n=8), 31°C (n=6), 27°C (n=6), or maintained at 37.5°C (n=9) before induction of aortic occlusion. To verify the changes in SCT, paravertebral muscle temperature was monitored. Spinal cord ischemia was then induced for 20 minutes. After the initial 30 minutes of reperfusion-rewarming, the arterial line was reinserted, the wound was closed, and the animal allowed to recover. In control animals (n=6; 37.5°C), the balloon catheter was placed in the descending thoracic aorta but was not inflated. At 1, 2, 4, and 8 hours of reperfusion, motor function was graded by using the following criteria. Walking with lower extremities was graded as either 0, normal; 1, toes flat under body when walking, but with ataxia; 2, knuckle walking; 3, movement in lower extremities but unable to move; 4, no movement, drags lower extremities. The placing/stepping reflex was graded as either 0, normal; 1, weak; or 2, no stepping.
A motor deficit index was calculated for each rat at each time interval. The final index was the sum of the scores (walking with lower extremities plus placing and stepping reflex). The maximum deficit was indicated by a score of 6.

The presence of spasticity or flaccidity was determined by the presence of an exaggerated flexion response to a pinch of the hind paw. Flaccidity was defined as no tone in response to limb extension.

Allodynesia was defined as the evocation of vigorous squeaking and agitation in response to light stroking of the flank. Nonresponsiveness was defined as the failure to evoke any motor or vocal response to pinching of the flank.

At the end of the 8-hour reperfusion period, animals in all experimental groups (8-hour survival period) were anesthetized with 4% halothane and transcardially perfused with 100 mL saline followed by 150 mL 10% buffered formalin. After 24 hours the spinal cords were removed and postfixed in the same fixative for at least 14 days. Five lumbar segments from each spinal cord were dissected and immersed overnight in 30% sucrose, and frozen sections were cut. Every tenth section (30 μm thick) was saved, and the bulk of subserial sections from individual segments (10 to 25 sections) was processed separately. Silver impregnation technique was employed to detect histopathologic changes. Each section was scored on a four-part scale: grade 0, no damage; grade 1, <5% neurons affected; grade 2, 5% to 50% neurons affected; and grade 3, >50% neurons affected. Average values from each segment were added so that the final score for one spinal cord ranged between 0 (no detectable damage) and 15 (more than 50% of neurons damaged in each segment).

Scores were tabulated, and an analysis was prepared by the observer without knowledge of either the behavioral outcome or the temperature group.

### Statistical Analysis

Statistical analysis of neurological/neuropathological scoring, temperature, blood pressure, and continuous SCBF data were carried out with ANOVA by using multiple means analysis followed by the Tukey-Kramer test. \( P < .05 \) was considered significant. Data were expressed as mean±SD. Laser Doppler values were expressed as a percent of baseline value.

### Results

#### Changes in Blood Pressure

The baseline MABP was 84±9 mm Hg in all animals with no significant differences between groups. During the initial 60 seconds of cooling, transient increases in MABP to 95±13 mm Hg were detected followed by gradual normalization after 2 to 3 minutes. After the balloon inflation, distal blood pressure dropped to 18.5±5.7% of the preischemic value and returned to control values during 10 to 15 minutes of reperfusion without significant differences between groups.

#### Changes in Temperature

The data presented in Fig 1 summarize the changes in SCT and rectal temperature as well as the correlation between the paravertebral muscle temperature and SCT. There were no significant differences in baseline SCT (37.3±0.2°C) or rectal temperature (35.4±0.3°C). Similarly, no significant differences 30 minutes after reperfusion-rewarming were seen.

In normothermic animals, SCT decreased to 37.1±0.1°C at the end of ischemia.

In the mildly hypothermic group (34°C), SCT decreased to 34.2±0.6°C at the end of ischemia and returned to 36.7±0.2°C 30 minutes after reperfusion.

In the moderately hypothermic group (31°C), SCT dropped to 34.6±0.4°C after 2 minutes of preischemic cooling and to 30.9±0.8°C after 4 minutes of occlusion. At the end of the 20-minute ischemic period, SCT was 31±0.7°C.

In the deeply hypothermic group (27°C), SCT decreased to 30.4±0.8°C during the 12 minutes of preischemic cooling and to 27.1±0.3°C after 4 minutes of occlusion. After 20 minutes of occlusion SCT was...
28.1±0.6°C. In this group one animal died during the initial 5 minutes of reperfusion.

A highly significant correlation (P<.01) was noted between SCT and paravertebral muscle temperature during the preischemic, cooling, ischemic, and rewarming-recirculation periods. No significant correlations between the rectal temperature and SCT or between the rectal and paravertebral muscle temperatures were clearly seen during the initial 6 to 8 minutes of preischemic cooling, when a sharp decrease of SCT occurred with minimal or no effect on the rectal temperature. Similar discrepancies during the early reperfusion-rewarming period were detected when SCT and paravertebral muscle temperature normalized more rapidly than rectal temperature.

SCBF and CO2 Responsivity

In normothermic animals SCBF dropped to 6±3% of baseline immediately after the balloon inflation without significant differences during the entire 20-minute occlusion period. After 15 minutes of reperfusion, SCBF was 124±39% and decreased to 80±14% after 60 minutes of reperfusion (Fig 2).

In the 31°C group, the 2-minute period of preischemic cooling had no effect on baseline SCBF. After occlusion, SCBF decreased from control preischemic values to 10±4% and was 11±6% at the end of 20 minutes of ischemia. No significant differences during the period of occlusion were seen. At the end of 20 minutes of ischemia SCBF was significantly higher in the 31°C group compared with the normothermic group (P<.05). After 15 minutes of reperfusion, SCBF was 96±14% (calculated from the preischemic value) and was 98±19% at 60 minutes of reperfusion. In this group (31°C) no significant differences in SCBF during the early (10- to 15-minute) or late (50- to 60-minute) reperfusion periods were seen.

During the 2-minute period of hyperventilation arterial PCO2 decreased from 39±2 mm Hg to 26±2 mm Hg with no significant differences between groups. MABP increased to 111±12% of baseline in the normothermic group and to 107±13% in the moderately hypothermic group during the preischemic hyperventilation period and to 119±8% and 116±14%, respectively, after ischemia. No significant differences in arterial PCO2 or in MABP changes were found between groups.

Under preischemic conditions, 2 minutes of hyperventilation induced a decrease in SCBF to 73±9% of baseline in normothermic and to 72±10% of baseline in the moderately hypothermic group. In contrast, in the normothermic group, postischemic hyperventilation increased SCBF to 117±37% (calculated from postischemic baseline) at 60 minutes of reperfusion, which was significantly different (P<.05) from the preischemic response (Figs 2 and 3). This increase corresponded with increases in MABP. However, in moderately hypothermic animals SCBF decreased to 76±14% during postischemic hyperventilation without significant differences in comparison with the preischemic response (Figs 2 and 3).
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Histopathologic Evaluation

The degree of histopathologic changes covaried closely with the magnitude of spinal cord hypothermia and loss of neurological function (Fig 5).

In animals with fully developed spastic paraplegia (37.5°C group) the histopathologic damage was characterized by the occurrence of heavy argyrophilic neurons preferentially affecting the dorsolateral part of the dorsal horn. In some animals irregularly distributed necrotic cavities were seen, usually affecting central areas of lumbar enlargement (Fig 6, left). However, the neurons localized in the peripheral areas of gray matter, ie, laminae I and II, X, and VIII through IX, showed near normal structure. Two animals in the 34°C group displayed a moderate degree of histopathologic changes (final scores, 0.8 and 0.2, respectively) with selective neuronal argyrophilia in laminae II and III; however, no detectable changes in the intermediate zone (lamina VII) or in the ventral horn were seen (Fig 6, right). In one animal that suffered from spastic paraplegia, histopathologic changes comparable to normothermic paraplegic animals were detected. In the 31°C and 27°C groups, the animals showed no evidence of any destructive neuronal changes at any level of the neuraxis examined, and all neuronal pools showed normal structure comparable to those seen in control nonischemic animals.

Discussion

Spinal cord ischemia as a result of transient aortic occlusion represents a major complication during operations on the thoracoabdominal aorta. Depending on the duration and completeness of the ischemia, the neurological deficit may be initially expressed as a transient loss of motor and sensory function, or, after a longer ischemic interval, as a completely developed spastic or flaccid paraplegia. Consistent with the degree of neurological deficit, histopathologic analysis shows initially selective degeneration of small interneurons during 30 to 120 minutes of reperfusion, followed by a progressive loss of A-motoneurons that is typically seen after longer ischemic intervals. In the present study we demonstrated that these ischemia-induced deficits are strongly modulated by the decreased spinal temperature.

Induction of Spinal Cord Hypothermia

Several approaches have been used to lower SCT, including whole body hypothermia, selective cooling of the epidural or intrathecal space, or the vascular perfusion of the cord. Whole body hypothermia may induce undesirable changes in clotting, pulmonary, or cardiovascular function. Selective spinal cooling by superfusion of the neuraxis with a cooling solution or by cooling of the vasculature (as in bypass) can be successfully accomplished in larger animals, but also involves significant preparation. In the present study with the rat, anatomic conditions (a relatively thin tissue layer between the skin of the back and the spinal cord) allowed the use of an underbody cooling system to achieve significant, rapid, and reliable cooling of the spinal axis with a smaller decrease in core temperature. This method allows a minimally invasive model with minimal consequences to other organ systems. The dissociation between core and spinal temperature also emphasizes that rectal temperature is a poor predictor.
of cooling in this model. In contrast, paravertebral muscle temperature was found to closely follow spinal parenchymal temperature. These observations indicate that the paraspinal muscle temperature provides a minimally invasive method of verifying the dependent variable (SCT) in each experimental animal.

Following induction of hypothermia, the initial elevation in blood pressure normalized. The mechanism of this increase is not known, but it may reflect the loss of descending inhibition onto intermediolateral cell column neurons or to a noxious event associated with activation of cold thermosensors and/or peripheral vasoconstriction. Measurement of lumbar SCBF with laser Doppler (see below) revealed that at temperatures down to 34°C there was little effect on resting flow.

Behavioral and Histopathologic Effects of Spinal Ischemia and Hypothermia

In the present rat model, with normothermic SCTs, 20 minutes of ischemia reliably results in a failure of coordinated motor function. In some animals rigidity, typically seen during the initial 1 to 3 hours postischemia, progressed to flaccidity over time and remained unchanged for 8 hours. Similarly, in the majority of animals, the initial 45 to 60 minutes of nonresponsivity was followed by the development of prominent allodynia. These effects last for a period in excess of 8 hours and are associated with a marked increase in the number of argyrophilic neurons and/or gray matter necrosis.

The silver impregnation techniques used in the present study provide a sensitive histopathologic tool to detect the early state of neuronal degeneration evoked by a variety of experimental conditions such as trauma, electrical stimulation, or ischemia.23-25 In spinal cord after transient ischemia, heavy neuronal argyrophilia is seen as soon as 30 to 120 minutes after reperfusion in rabbit, rat, and dog. After an identical ischemic interval but with the reperfusion period extended for 8 to 24 hours, clearly developed gray matter necrosis is found in areas that show the highest density of argyrophilic neurons during the early period of reperfusion.10,13,17,27 These data suggest that the neuronal argyrophilia detected during the initial hours after ischemia reflects an early state of neuronal deterioration that later leads to neuronal loss. Consistent with these findings, we have found that neuronal argyrophilia corresponds with electron-dense types of neuronal degeneration, extensive degranulation of endoplasmic reticulum, and increased density of free ribosomes. In addition, an advanced state of chromatin clumping and partial disruption of mitochondrial cristae has been detected.13 Similar, ischemically induced neuronal argyrophilia in selective vulnerable areas in the brain (hippocampal CA1 sector) has been described.25 In the present study, after 20 minutes of normothermic ischemia, such neuronal argyrophilia was largely found within the lateral and central portions of laminae III through VII, with particular injury associated with smaller interneuronal populations that may mediate an inhibitory influence on spinal function (accounting for the rigidity and allodynia).16-19

Spinal cord cooling during the period of ischemia resulted in a temperature-dependent preservation of
normal motor and sensory function. Thus, mild hypothermia (34°C) provided significant protection against the motor and sensory dysfunction otherwise evoked by the normothermic ischemia of the same duration. Moderate (31°C) and deep (27°C) hypothermia provided complete protection at this interval of ischemia. The preservation of function correlated closely with the failure of 20 minutes of ischemia to evoke the appearance of the spinal argyrophilic neurons or gray matter necrosis seen in normothermic animals. These results, showing significant protection at relatively modest levels of hypothermia, are consistent with studies in the brain of rat, gerbil, and rabbit and in the spinal cord of hypothermia, are consistent with studies in the brain of rat, gerbil, and rabbit and in the spinal cord of rat, gerbil, and rabbit. Although not systematically examined, it appears likely that the maximum ischemic interval that can be tolerated without neurological dysfunction after rewarming will increase with deeper hypothermia. Using epidural perfusion cooling in the rabbit (SCT lowered to 14° to 16°C just before aortic occlusion), we have found complete recovery of motor and sensory function after 60 minutes of abdominal aorta ligation. Spinal cooling to a temperature of 28°C or below in the dog resulted in significant recovery of neurological functions after 40 to 45 minutes of spinal ischemia.

**Peri-Ischemia SCBF and CO2 Responsivity**

In the present study, a laser Doppler probe was used to measure regional SCBF. Although this technique provides only relative SCBF data, covering approximately 1 mm³ of superficial spinal cord tissue, experiments have shown a significant correlation between the SCBF measured by microspheres and by the laser Doppler technique. The main advantage of the laser Doppler is its ability to provide continuous data on the SCBF for an extended period.

Using laser Doppler flow, it was observed that in the absence of interventions flow was stable over time, and the SCBF showed a predictable CO2 reactivity when the rat was rendered hypocarbic by hyperventilation. In all animals after aortic occlusion there was a sharp decrease in SCBF to a nonzero level followed by an initial postischemic hyperemia that persisted for 15 to 30 minutes, after which there was a subsequent slight decline over the next hour. Examination of the postreflow CO2 responsivity revealed that this CO2 reactivity was completely abolished only in the normothermic group. In normothermic animals similar failure of CO2 reactivity has been reported in the brain after significant levels of ischemia. While the mechanism of this failure is not known, its loss has been considered to be evidence of an important index of postischemic injury. In the present model a decrease in SCBF below 9% to 10% during the period of occlusion was associated with the loss of postreflow CO2 responsivity measured 60 minutes after reflow. The small residual flow assessed by the laser Doppler flow after the occlusion likely reflects the modest contribution to lumbar perfusion by the suprasegmental arteries supplying the spinal anterior artery and posterior arteries. The reliable loss of distal perfusion pressure immediately after inflation of the balloon emphasizes that direct local perfusion is abolished.

**Mechanism of Hypothermia-Mediated Protection**

There are several mechanisms by which cooling may alter the progression of the severity of ischemia from partial to complete flow occlusion. First, cerebrospinal fluid pressure is known to rise after the initiation of spinal ischemia. Flow is improved with cerebrospinal fluid drainage, and because hypothermia decreases cerebrospinal fluid pressure, improved residual flow may provide sufficient nutritive flow for a relatively prolonged occlusion period before neuronal energy failure. Second, hypothermia is known to diminish clotting which would retard the development, if any, of the evolution of microemboli. Third, ischemia might evoke the release of active factors, such as thromboxane B2, which alter vascular tone. This prostanoid is a potent vasoconstrictor and platelet aggregator in cerebral and spinal vasculature and is released from brain and spinal cord during and after ischemia. Blocking thromboxane B2 synthesis increases regional cerebral blood flow in the ischemic penumbra and improves postischemic cerebral blood flow. Preliminary studies in this spinal model and in brain have indicated that hypothermia can reduce postischemic thromboxane B2 release (M. Marsala and T.L. Yaksh, unpublished data, 1993).

Reductions in cerebral metabolic rate, neurotransmitter release, and enzymatic activity may also contribute to the protective effects of hypothermia. The Q0 for the cerebral metabolic rate of oxygen (CMRO2; Q0 is the ratio of two CMRO2 values over a 10°C range) is around 2.2 in dogs when the cerebral temperature ranges between 27° and 37°C and 4.5 when cerebral temperature is between 14° and 27°C. Using deep hypothermia (14° to 17°C; complete electroencephalographic activity suppression), CMRO2 is reduced to around 10% of normothermic levels. Such reduction, reflecting decreased metabolic activity and a preservation of a favorable energy state, could explain the protective effect of hypothermia. However, hypothermia may be protective without affecting lactate accumulation during global cerebral ischemia in the dog, suggesting that additional mechanisms other than a suppression of metabolic substrate utilization may play a role in the effects of hypothermia.

Decreasing brain temperature by 2° to 3°C during global cerebral ischemia suppresses glutamate release from brain in rats, gerbils, and rabbits. Given the ability of hypothermia to delay anoxic depolarization in vitro, it is probable that attenuation of neuronal depolarization is in part responsible for the decreased glutamate release. This effect can be particularly potentiated under the condition of incomplete ischemia, such as during aortic occlusion. Comparable effects have been reported in vitro, where mild hypothermia provides a powerful protective effect. This profound temperature sensitivity suggests that moderate reductions in temperature may induce significant reductions in release. We have found that mild spinal cord hypothermia (34°C) before aortic occlusion completely prevented glutamate release in the dorsal horn but only partially blocked the release of taurine observed during reperfusion.

Protein synthesis (as measured by the incorporation of amino acids into cerebral proteins) is decreased about 7.8% for each 1°C decrease in body temperature between 32.5° and 37.5°C. However, hypothermia, with brain temperature 30°C, does not affect free fatty acid accumulation during 30 minutes of global cerebral ischemia in the rat, and the concentrations are compa-
rable with those seen in normothermic ischemia. This indicates that during mild hypothermia (30°C), phospholipases retain significant activity, and the liberation of arachidonic acid is reduced only modestly.

These observations emphasize that lowered temperature can preserve spinal and brain function following certain degrees of ischemia. While the mechanisms of this are not completely clear, a variety of the systems that are likely to contribute to spinal ischemia injury, including probable reductions in metabolic activity and depression of transmitter release and enzymatic activity as well as an apparent preservation of residual flow, have a steep inverse relation with temperatures above the range of 27° to 37°C. The steepness of these temperature-effect relationships likely account for the pronounced preservation at relatively high spinal temperatures (34° to 35°C) of spinal morphology and function, the latter defined by behavioral (sensory and motor) and physiological (SCBF-CO₂) indices.

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References


Editorial Comment

Studies designed to test the therapeutic potential of hypothermia on spinal cord ischemia grew out of a need to protect the spinal cord during surgical procedures requiring aortic cross-clamping. In the accompanying article, Marsala and colleagues report that mild (34°C), moderate (31°C), and profound (27°C) levels of intraischemic hypothermia are protective in a rat model of reversible spinal cord ischemia. With moderate and deep hypothermia, preservation of CO₂ responsivity and complete recovery of neuronal function with no detectable histopathologic changes were documented.

Morphological assessment of the spinal cords was conducted 8 hours after the ischemic insult with a silver impregnation technique. It would be extremely important to know whether the beneficial effects of hypothermia seen at this 8-hour survival period were also present with more prolonged recirculation periods. In this regard, it should be mentioned that hypothermia may have delayed but not prevented neuronal cell death. Without providing more long-term pathological or neurobehavioral data, this important question cannot be critically assessed.

Silver impregnation techniques have been shown to be sensitive indicators of early neuronal changes after ischemia. However, it would also be useful to determine the effects of the hypothermic manipulations with more conventional histopathologic methods. Such an end point could provide useful information regarding the frequency of ischemic cell injury and patterns of selective vulnerability.

Finally, although numerous studies have demonstrated that postischemic brain hypothermia may be neuroprotective, there is a lack of information regarding the effects of hypothermia induced after a period of spinal cord ischemia. Because regional ischemia may be a consequence of spinal cord trauma, it would be important in future studies to determine the therapeutic window for postischemic spinal cord cooling.

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