Combined use of an epidural cooling catheter and systemic moderate hypothermia enhances spinal cord protection against ischemic injury in rabbits

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Background: Epidural placement of a cooling catheter can protect against ischemic spinal cord injury. With the use of rabbits, we investigated whether this epidural cooling technique, when combined with systemic moderate hypothermia, can protect the spinal cord against ischemic metabolic stress.

Methods: New Zealand white rabbits (n = 28) were assigned to 1 of 4 different groups. Animals underwent abdominal aortic occlusion for 30 minutes using a 3F balloon catheter. Group 1 (n = 7) underwent epidural cooling by the catheter and systemic moderate hypothermia (35°C) induced with a cooling blanket. Group 2 (n = 7) underwent epidural cooling under systemic normothermia (38.5°C). Group 3 (n = 7) underwent systemic moderate hypothermia (35°C) without epidural cooling. Group 4 (n = 7) underwent neither epidural nor blanket cooling as a negative control. Neurologic status of their hind limbs was graded according to the modified Tarlov scale at 1, 2, and 7 days after surgery.

Results: During infrarenal aortic ischemia, epidural temperature was significantly lower in group 1 (18.5°C ± 0.8°C) than in group 2 (28.6°C ± 1.0°C; $P = .0001$), group 3 (34.2°C ± 0.06°C; $P = .0001$), or group 4 (38.5°C ± 0.2°C; $P = .0001$). Hind limb function recovery was greater in group 1 (mean Tarlov score, 4.9 ± 0.057) than in group 2 (2.6 ± 0.3; $P = .0028$), group 3 (2.1 ± 0.34; $P = .0088$), or group 4 (0.0 ± 0.0; $P = .0003$).

Conclusions: Epidural cooling catheter combined with systemic moderate hypothermia produced additive cooling ability and protected the spinal cord against ischemia in rabbits more effectively than either intervention alone. (J Thorac Cardiovasc Surg 2013;146:696-701)

Although cardiovascular surgeons have achieved a substantial reduction in the incidence of paraplegia associated with surgery for thoracic aortic aneurysm and thoracoabdominal aortic aneurysm (TAA), this dreaded complication has not been completely eliminated. Since the 1950s, hypothermia has been demonstrated to protect against ischemic spinal cord injury.[1-3] However, general body hypothermia involves various risks, including coagulopathy, arrhythmia, and respiratory dysfunction. Local spinal cord cooling was developed to avoid the detrimental effects of systemic hypothermia while preserving its protective effects. Although favorable clinical experience with regional cooling by infusing iced saline into the epidural space was reported, elevated intrathecal pressure resulting from the infused saline presented a major concern.[4,5]

To overcome the problem of local cooling via infusion of cold saline into the epidural space, we developed a novel epidural cooling technique using a U-looped catheter containing circulating iced saline in its closed lumen. In an experimental study in pigs, the cold epidural catheter protected the spinal cord against paraplegia without elevating intrathecal pressure.[6] Since the original design, we have incorporated a counter current lumen within the epidural cooling catheter, which permits percutaneous installation. This revised system also was protective against ischemic spinal cord injury.[7] We have further refined the system by reducing the catheter diameter to facilitate clinical use.[8]

Systemic moderate hypothermia (32°C-34°C) induced by partial extracorporeal bypass is used in the clinical setting to protect the spinal cord during aortic surgery.[6] The goal of this study was to determine whether combined use of our epidural cooling technique and systemic moderate hypothermia may cool the spinal cord more effectively and whether this combination results in better protection against ischemic spinal cord injury.

MATERIAL AND METHODS

Continuous Cord Cooling System and Epidural Cooling Catheter

The basic concept of our cooling catheter has been described in a previous study.[6] The cooling system is composed of 3 units: a saline-filled

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Abbreviation and Acronym
TAA = thoracoabdominal aortic aneurysm

cooling catheter in the epidural space, an external cooling unit, and an external circulating pump. In the current study, saline was cooled by the outer cooling unit to 4°C and circulated at a rate of 40 mL/min by an external pump (AST Co, Ltd, Higashimatsuyama, Japan).

The polyurethane cooling catheter (Unitika, Tokyo, Japan), in which iced saline could circulate without leakage, was 15 cm in length and had an 18-gauge outer diameter (Figure 1). A smaller-diameter catheter (18-gauge) was designed for use in rabbits. The coolant entered the inlet limb of the cooling catheter, passed through the lumen to the tip of it, and returned back to the outlet limb. The fluid is not able to leak out of the inner lumen to the epidural space.

Animal Model, Surgical Procedure, and Cooling Protocol

A total of 28 New Zealand white rabbits (weighing 3.0-3.5 kg) were used. Animals were randomly assigned to 1 of 4 different groups: a regional cooling by epidural catheter combined with systemic moderate hypothermia (35°C) by cooling blanket (group 1), a regional cooling by epidural catheter under systemic normothermia (38.5°C) (group 2), systemic moderate hypothermia (35°C) by cooling blanket without epidural cooling (group 3), and a negative control group without regional cooling under systemic normothermia (group 4).

Rabbits were initially anesthetized with 1.5% isoflurane added to a mixture of 30% oxygen and 68.5% air. Animals underwent endotracheal intubation and breathed spontaneously without mechanical ventilation. Electrocardiogram, arterial pressure, and rectal temperature were monitored continuously.

First, rabbits were placed in the prone position. A dorsal midline skin incision, 5 cm in length, was made at the levels of Th12 and L1. The spinous process and intervertebral ligament were excised to expose the ligamentum flavum, which was incised between Th12 and L1 to create a small defect for entry into the epidural space. An epidural cooling catheter was then introduced at that site and advanced into the epidural space. It was directed caudally along the midline of the space to the L7 level, followed by connection to the external unit. A thermistor probe was placed on the dorsal dural surface at the level of L1 to record the epidural temperature (Figure 2, *A* and *B*).

Next, with the rabbit in the supine position, the right femoral artery was dissected. In all groups, animals underwent 30 minutes of infrarenal aortic ischemia via balloon occlusion. Heparin sulfate (50 U/kg) was administered as an intravenous bolus. A Fogarty balloon catheter (3F) was introduced from the right femoral artery into the abdominal aorta. Under fluoroscopic guidance, the balloon of the catheter was placed immediately below the renal arteries. In rabbits, arteries that feed the spinal cord arise from the abdominal aorta. Therefore, the inflation of the balloon at this position results in abdominal aortic occlusion and spinal cord ischemia.

A cooling/warming blanket was used to control systemic temperature. In groups 1 and 3, the animals were cooled to 35°C (rectal temperature) by a cooling blanket. In groups 2 and 4, a cooling/warming blanket was used to maintain normal body temperature (38.5°C). In groups 1 and 2, animals underwent local cooling with the epidural catheter 30 minutes before balloon occlusion. During the 30 minutes of balloon occlusion, epidural cooling was continued via the catheter. After deflation of the balloon, epidural cooling was continued for 30 minutes to slow the increase of spinal temperature accompanying reperfusion. In groups 3 and 4, the epidural catheter was placed in the same fashion as in groups 1 and 2, but the rabbits did not undergo epidural cooling at any point during the procedure.

After surgery, the epidural catheter, the Fogarty balloon catheter, and all measuring probes were removed, and the wounds in the back and groin were closed. The animals were extubated and returned to cages with free access to water and food. They received humane care and treatment in accordance with the ''Guide for the Care and Use of Laboratory Animals'' (www.nap.edu/catalog/5140.html). Further, the experimental and animal care protocols were approved by the Animal Care Committee of the Saitama Cardiovascular and Respiratory Center, Saitama, Japan.

Neurologic Evaluation

Neurologic status with respect to hind limb function was assessed at 1, 2, and 7 days after the operation according to a modified Tarlov scale: 0 = no movement, 1 = slight movement, 2 = sits with assistance, 3 = sits alone, 4 = weak hop, 5 = normal hop.

Histologic Examination

On the seventh day after surgery, animals were reanesthetized and killed with an intravenous overdose of pentobarbital. After perfusion fixation with 4% phosphate-buffered paraformaldehyde, the spinal cords were removed rapidly. This was followed by immersion fixation in the same solution for 2 weeks. Cross-sections of the spinal cord were stained with hematoxylin–eosin. Histologic assessment was performed using light microscopy.

For quantitative histopathologic analysis, the spinal cord was divided into the 4 lumbar segments. Twenty-eight specimens in each group were reviewed by a pathologist who was blinded to the experimental group. Motor neurons with normal appearance were counted in each segment.

Statistical Analysis

The Mann–Whitney *U* test was used to compare the postoperative neurologic status between any 2 groups of animals, and the Student *t* test was used to compare the number of motor neurons. Analysis of variance for repeated measures was carried out on variables assessed at multiple times.

RESULTS

Temperature

Epidural temperatures of the 4 groups are shown in Figure 3.

In group 1, epidural temperature at 30 minutes before aortic occlusion was 38.7°C ± 0.6°C and decreased to 20.0°C ± 2.5°C by the time of aortic occlusion ($P < .0001$). At the termination of aortic occlusion, epidural temperature had decreased further to 17.9°C ± 2.2°C. Baseline rectal temperature (38.9°C ± 0.2°C) had decreased significantly to 35.2°C ± 0.2°C by the time of aortic occlusion ($P < .0001$). A significant difference was evident between epidural (17.6°C ± 2.2°C) and rectal (35.0°C ± 0.2°C) temperatures at the termination of aortic occlusion in group 1 ($P < .0001$).

During the aortic interruption, epidural temperature was significantly lower in group 1 (18.5°C ± 0.8°C) than in group 2 (28.6°C ± 1.0°C; $P < .0001$), group 3 (34.2°C ± 0.06°C; $P < .0001$), or group 4 (38.5°C ± 0.2°C; $P < .0001$). Epidural temperature during aortic occlusion was significantly lower in group 2 than in group 4 ($P < .0001$), significantly lower in group 3 than in group 4 ($P < .0001$), and significantly lower in group 2 than in group 3 ($P < .0001$).

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