# Epidural regional hypothermia for prevention of paraplegia after aortic occlusion: Experimental evaluation in a rabbit model

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***Purpose:*** **The efficacy of epidural regional hypothermia in the prevention of acute and delayed-onset paraplegia, as well as possible complications and limitations of this technique to a clinically acceptable form, were evaluated in 49 New Zealand white rabbits.**
***Methods:*** **A modified rabbit spinal cord ischemia model of infrarenal aortic occlusion for 30 minutes was employed. The study was performed in two phases. In phase I (n = 20), regional hypothermia induced by epidural perfusion of iced normal saline solution (4° C) was tested versus control in 10 rabbits each (groups A and B). In phase II (n = 29) the animals were subdivided into three groups to study the kinetics of absorption and distribution of methylene blue (group C; n = 10), radiographic contrast material (group D; n = 9), and measurement of cerebrospinal pressure while an epidural iced solution was or was not infused (group E; n = 10).**
***Results:*** **At 24 and 48 hours, all of the normothermic animals showed irreversible paraplegia (Tarlov score 0). In contrast, at 24 hours none of the rabbits undergoing epidural cold infusion were paraplegic, although at 48 hours one animal had weakness of a hindlimb (Tarlov score 3). Plasma concentration-time profiles of a continuous epidural perfusion with methylene blue showed that the spinal canal is a highly compliant space. Epidurographs showed that epidural perfusion tends to spread more in a cephalic than caudal direction and the main uptake is by the vascular compartment. Despite the large volumes infused (78.75 ml/hr; range, 50 to 100 ml), we observed only a modest transient increase in cerebrospinal fluid pressure (from 2.5 ± 0.3 mm Hg to 5.4 ± 0.1 mm Hg), although some animals had intracranial hypertension.**
***Conclusions:*** **Regional hypothermia induced by epidural cold perfusion has a highly protective effect against the ischemic spinal cord damage. However, this method probably does not avoid the risk of delayed-onset paraplegia. An important limitation of this technique is the difficulty of controlling the intrathecal pressures. (J VASC SURG 1996;23:446-52.)**

The most devastating and unpredictable complication after surgery of the descending and thoracoabdominal aorta is paraplegia. This complication ranges from 0.5% to 38%,[1] depending on factors such as the type and extent of reconstruction, the presence of dissection, and the duration of aortic cross-clamping. Several adjunctive techniques and drugs have been used for protecting the spinal cord, but none of these measures has completely prevented paraplegia.[2-12]

Induced hypothermia, either systemic or local, seems to provide the most potent protection against ischemia-reperfusion neural injury.[1,13-17] Hypothermia has been shown to reduce the oxygen consumption of neural tissue by approximately 6% to 7% for each degree of core temperature reduced and results in an increase in safe ischemia time of the spinal cord by approximately 5 to 6 minutes for each degree Celsius of temperature reduction.[18] Systemic hypothermia carries a risk of cardiac disorders and coagulopathy.[19,20] Regional spinal cord hypothermia has been obtained experimentally by perfusing the

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vessels supplying the cord with cold blood or crystalloid[21-23] or by perfusing the subarachnoid[24,25] or epidural[26-30] space with hypothermic solutions. The results show that hypothermia produces a favorable outcome with regard to neurologic deficits; however, sometimes cooling is not controlled and systemic hypothermia may develop. Other times its clinical application is limited. Recently Davison et al.[31] reported their clinical experience in eight patients with a technique of selective spinal cord hypothermia by epidural cooling. They showed that the epidural cold perfusion was a satisfactory method of achieving regional spinal cord hypothermia (range, 25° to 28.8° C).

Given that the spinal cord cooling can provide protection from ischemic spinal cord injury during the critical period of aortic cross-clamping and intercostal vessel reanastomosis, the purposes of this study have been, first, to evaluate the efficacy of epidural regional hypothermia in a rabbit model of aortic occlusion, with special attention to acute and delayed-onset paraplegia and, second, to determine possible complications and limitations of this technique to a clinically acceptable form.

## MATERIAL AND METHODS

Forty-nine New Zealand white rabbits of both sexes (2.0 to 3.5 kg) were used for this study. A modified rabbit spinal cord ischemia model of infrarenal aortic occlusion for 30 minutes was employed. All experiments were conducted in compliance with the "Principles of Laboratory Animals Care" formulated by the European Council and published by the National Institutes of Health (Spain, B.O.E. No. 67: 8509-12, 1988).

### Study phases

The study was performed in two phases. In phase I (n = 20), epidural regional hypothermia was tested versus control in 10 rabbits each (groups A and B). A total of 30 minutes of infrarenal aortic occlusion was performed followed by strict neurologic examination at 24 and 48 hours. Neurologic outcome was evaluated according to Tarlov's criteria[32]: grade 0, spastic paraplegia and no movement of the lower limbs; grade 1, spastic paraplegia with slight movement of the lower limbs; grade 2, good movement of the lower limbs but unable to stand; grade 3, able to stand but not able to walk normally; and grade 4, complete recovery.

In phase II (n = 29) the rabbits were subdivided into three groups: (1) animals that underwent a 0.25% solution of methylene blue by epidural regional perfusion (group C; n = 10); (2) animals that underwent radiographic contrast study by epidural perfusion (group D; n = 9); and (3) animals with measurement of cerebrospinal fluid (CSF) pressure while an epidural iced normal saline solution was or was not infused (group E; n = 10). The kinetics of absorption and distribution of methylene blue and radiographic contrast material were determined by spectroscopic methods[33] and radiography, respectively. The relationship between CSF pressure and epidural perfusion was analyzed.

### Surgical procedure

The animals were anesthetized with intramuscular ketamine hydrochloride (40 mg/kg). Intraoperative fractional doses were used to maintain appropriate levels of anesthesia and prevent the need for endotracheal intubation and mechanical ventilation. The animals were immobilized on the operating table, and the fur in the skull, neck, lumbar spine, and abdomen was clipped with electric shears, and the skin was prepared with iodine solution. After local infiltration of mepivacaine hydrochloride (10 mg/kg), a midline incision was performed at L4-L5. The musculature and the spinal process of the fourth lumbar vertebra were removed. A small incision was made in the intervertebral ligament. A cannula (Epidural Minipack, 18 gauge; Portex Ltd.; Hythe, Kent, U.K.) was inserted into the epidural space about 5 cm cranially and then fixed and the wound was closed with reabsorbible suture.

In the supine position a laterocervical incision of the neck was made to allow identification of the cervical vessels: Two 20-gauge heparinized saline-filled catheters were inserted into the jugular vein and carotid artery. An intravenous infusion of isotonic saline solution at a rate of 1 ml/min was administered during the operation to replace surgical losses. Continuous on-line monitoring of systemic blood pressure was maintained through the carotid catheter (Statham pressure transductor; Viggo-Spectramed, Inc., Critical Care Division, Oxnard, Calif.). After local infiltration of mepivacaine hydrochloride (10 mg/kg) at the abdominal alba line, the infrarenal aorta was approached by a xiphopubic midline laparotomy. After systemic heparinization (1.5 mg/kg intravenously), the aorta was clamped for 30 minutes. For the body temperature measurement, a flexible temperature probe was placed in the rectum. The direct spinal cord temperature was not measured in the hypothermic animals. The effectiveness of epidural cooling was assumed based on other studies in the literature.[27,31]

### Epidural regional hypothermia

An infusion of iced normal saline solution (4° C) was begun into the epidural catheter with the goal to decrease the temperature of the CSF. The infusion was begun 30 minutes before clamping, maintained during aortic cross-clamping (30 minutes), and stopped at the end of the period of ischemia. Perfusion cooling started at a rate of 1.4 ml/min and was modified (increased or decreased) depending on the neurologic tolerance of the animal. When the infrarenal aorta was unclamped, the epidural catheter was removed and the wounds sutured. The animals were placed in cages for neurologic evaluation at 24 and 48 hours.

### Study of the absorption and distribution of the epidural perfusion

Plasma methylene blue concentrations were determined in 10 rabbits (group C) after epidural administration of a 0.25% solution of methylene blue (1.4 ml/min). Venous blood samples were collected 15, 30, 45, 60, and 70 minutes from the inferior vena cava (0.5 ml) by puncture with an insulin syringe and the jugular catheter (0.5 ml). Plasma was separated and kept frozen until analyzed by spectrophotometry. To minimize errors, all determinations were calculated twice in each period. The value was expressed as the mean of each sample studied.

In nine animals (group D) radiographic contrast material (Omnigraf-300, Juste, S.A.Q.F.; Schering AG, Berlin, Germany) was infused into the epidural catheter. The rabbits were separated into three subgroups of three animals according to the rate of perfusion. Three animals received a bolus of 10 ml, three received a 10 ml solution for 30 seconds, and, finally, another three had an infusion of 10 ml for 1 minute. Radiography was performed at the beginning, middle, and end of each perfusion.

### Measurement of CSF pressure

CSF pressure was measured in 10 rabbits (group E) under two different conditions: with and without the epidural cold perfusion (control, n = 5; hypothermia, n = 5). To measure CSF pressure (Statham pressure transductor; Viggo-Spectramed, Inc., Critical Care Division), the animals were turned with their shoulder upright, exposing the posterior aspect of the neck and base of the skull. After local infiltration of mepivacaine hydrochloride (10 mg/kg), a posterior midline incision was made and an 18-gauge angiocatheter was placed into the cisterna magna. The cannula was fixed with dental cement to avoid fluid leak. Correct placement was checked by observing the waveform of the CSF pressure, in particular looking for respiratory and cardiovascular variation.

### Histologic study

The animals were killed at the completion of the project with a lethal intravenous dose of phenobarbital and potassium chloride. The spinal cord (proximal and distal to the level of aortic occlusion) was removed for fixation in 10% neutral buffered formalin for at least 10 days. After embedding in paraffin wax, specimens were sectioned at 5 μm and the sections were stained with hematoxylin and eosin.

### Statistical analysis

The values obtained were entered as a data matrix in the statistical program SIGMA (Horus Hardware, Madrid, Spain). Results are shown as the mean ± SEM. Hemodynamic and temperature comparisons were analyzed by the paired or unpaired Student $t$ test. Neurologic outcome in the different groups (Tarlov's score) was compared with Fisher's exact test. Statistical significance was assumed at $p < 0.05$.

## RESULTS

Proximal carotid arterial pressure was similar in all groups at baseline (95 ± 10 mm Hg in control animals; 90 ± 15 mm Hg in animals with hypothermia). With aortic occlusion, a significant increase ($p < 0.05$) was observed in proximal pressures in all groups of rabbits compared with respective baselines (125 ± 12 mm Hg and 115 ± 11 mm Hg, respectively). No differences were observed between the normothermic and hypothermic groups. After removal of the aortic clamp, the proximal blood pressure stabilized to a point not significantly different from the baseline value.

In the normothermic animals, body temperature did not change during ischemia. The rectal temperature of hypothermic animals decreased from the control level of 37.5° ± 0.6° C to 35.1° ± 0.8° C at the end of the ischemic period ($p < 0.001$).

### Neurologic outcome

Evaluation of the neurologic outcome is shown in Table I. At 24 hours all of the normothermic animals (n = 10) showed irreversible paraplegia (Tarlov score 0). No differences were found at 48 hours. In contrast, at 24 hours none of the rabbits undergoing epidural cold infusion were paraplegic, although at 48 hours one animal had a weakness of the left hindlimb (Tarlov score 3). The difference in Tarlov score between animals undergoing normothermic spinal cord ischemia and hypothermic perfusion was significant (Fisher's exact test, $p < 0.001$). In addition, four animals showed clinical signs of intracranial hypertension (exophthalmos) during the hypothermic epidural perfusion (phase I). In these cases, the

**Table I.** Neurologic outcome at 24 and 48 hours

| | *24 Hours* | | *48 Hours* | |
|---|---|---|---|---|
| | *Group A* | *Group B** | *Group A* | *Group B** |
| No. of rabbits | 10 | 10 | 10 | 10 |
| Tarlov' score | | | | |
| 0 | 10 | 0 | 10 | 0 |
| 1 | 0 | 0 | 0 | 0 |
| 2 | 0 | 0 | 0 | 0 |
| 3 | 0 | 0 | 0 | 1 |
| 4 | 0 | 10 | 0 | 9 |

*Group A*, Normothermic animals; *Group B*, hypothermic animals.
*$p < 0.001$, Fisher's exact test.

rate of infusion was stopped or decreased to avoid the death of the animals.

### CSF pressures

Three animals with incorrect placement of the catheter into the cisterna magna and one with a bloody spinal tap were excluded from the study. The CSF pressure was similar in both groups at baseline determination (2.9 ± 0.5 mm Hg and 2.5 ± 0.3 mm Hg, respectively). Immediately after aortic clamping, the CSF pressure rose in both groups (4.77 ± 0.4 mm Hg and 4.5 ± 0.35 mm Hg). With the epidural iced infusion, the CSF pressure remained intact in three animals (5.4 ± 0.1 mm Hg), but a rabbit showed signs of intracranial hypertension (exophthalmos) and CSF pressure of 13.23 mm Hg at the end of the experiment. Statistical analysis of CSF pressure was not performed because of small sample size (control group, n = 2; hypothermic group, n = 4).

### Absorption and distribution of the epidural perfusion

The mean volume administered was 78.75 ± 5.0 ml/hr (range, 50 to 100 ml/hr). After 1 minute of epidural perfusion, methylene blue appeared in the retroperitoneal space into the lymphatic ducts. Determination of the plasma concentration-time profiles showed that absorption after epidural perfusion is biphasic: a rapid initial absorption was followed by a much slower second phase (Fig. 1). The maximal concentration (120.12 ± 7.37 μg/100 ml) was reached at 60 minutes. The concentration-time curve increased following a linear relationship ($Y = 20.975 + 1.6186X$; $r = 0.72341$; $p < 0.001$). The spinal cord necropsy at the end of the experiment showed that the methylene blue injected into the lumbar epidural space tend to spread more in a cephalic than caudal direction. Likewise, the spinal roots and cord appeared dyed, although detailed distribution within CSF was impossible to determine. Three animals showed exophthalmos and conjuntival edema with blue eyes.

On the other hand, the epidurographs after injection of a radiographic contrast agent corroborated the rostral movement from the lumbar space. Vascular uptake occurred rapidly into the epidural veins (Batson's plexus). Transport to general circulation was predominantly by the azygos collection system and inferior vena cava. The radiographs taken after 1 minute of epidural perfusion showed the heart and both kidneys with contrast material (Fig. 2). Five animals died during the experiment, with signs of intracranial hypertension: three rabbits undergoing a bolus of 10 ml and two rabbits undergoing 10 ml of epidural perfusion for 30 seconds. The other four animals showed a diverse degree of intracranial hypertension (exophthalmos) that disappeared rapidly after several minutes.

### Histopathology

The histopathologic findings clearly correlated with the neurologic status. Normothermic animals showed total destruction of anterior horn cells with pronounced vacuolization and gliosis. The spinal cord structure was well preserved in hypothermic animals that were spared neurologic deficit. No infarctions were detected in this group. The animal with delayed-onset paresis of a hindlimb had an intermediate degree of ganglion cell destruction with hyperchromatic nuclei and mild to moderate vacuolization of cytoplasm. The animals from phase II, killed immediately after the experiment, showed some congested areas and vessels with abundant red blood cells.

## DISCUSSION

The rabbit model of aortic occlusion was described by Zivin and de Girolami[34] and has been tested by other authors[15,23] as a reliable model for producing neurologic deficits from ischemic spinal cord injury, including acute and delayed paraplegia.

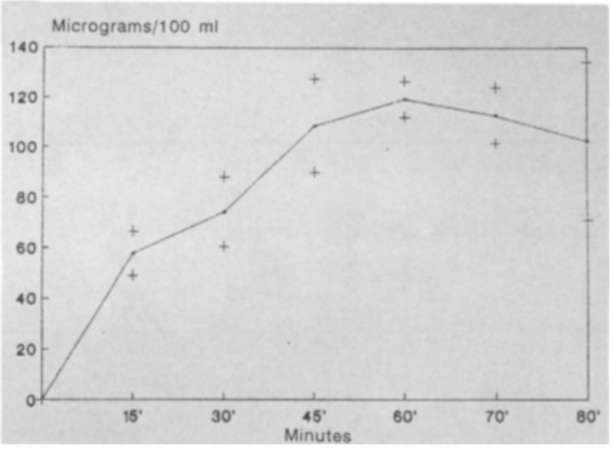


**Fig. 1.** Plasma methylene blue concentration-time profile shows that absorption after epidural perfusion is biphasic: rapid initial absorption is followed by much slower second phase. Concentration-time curve follows linear relationship ($Y = 20.975 + 1.6186X$; $r = 0.72341$; $p < 0.001$).

Moore and Hollier[35] also showed that prolonged spinal cord ischemia (more than 27 minutes) produced permanent paraplegia. With this model, we have evaluated the influence of an epidural cold perfusion on ischemic spinal cord injury. This study demonstrates that the regional hypothermia induced by epidural cold perfusion has a highly protective effect against ischemic spinal cord damage. In fact, epidural cooling was associated with postoperative preservation of neurologic function after 30 minutes of infrarenal aortic cross-clamping, although one animal had delayed-onset paresis of a hindlimb at 48 hours. These results suggest that the moderate cooling reached by this method may be enough to provide full protection during the acute ischemic injury but not during the reperfusion period. The precise cause of delayed-onset paresis remains unresolved, although the ischemia-reperfusion of the spinal cord may have a role. Some animals killed immediately after the aortic unclamping showed some congested areas and vessels with abundant red blood cells. This could be interpreted as a hyperemic phenomenon after the ischemic insult. Probably the epidural cooling should combine other strategies (e.g., free radical scavenger and neurotransmitter antagonist)[3,10,12] for avoiding paraplegia completely.

Regional hypothermia is a common method of prolonging the ischemic tolerance of many tissues by reduction of the metabolic rate (and thus oxygen demand). However, Allen et al.[23] showed that the use of moderate spinal cord hypothermia slows the consumption of energy substrate but does not prevent anaerobic metabolism. Although the optimal

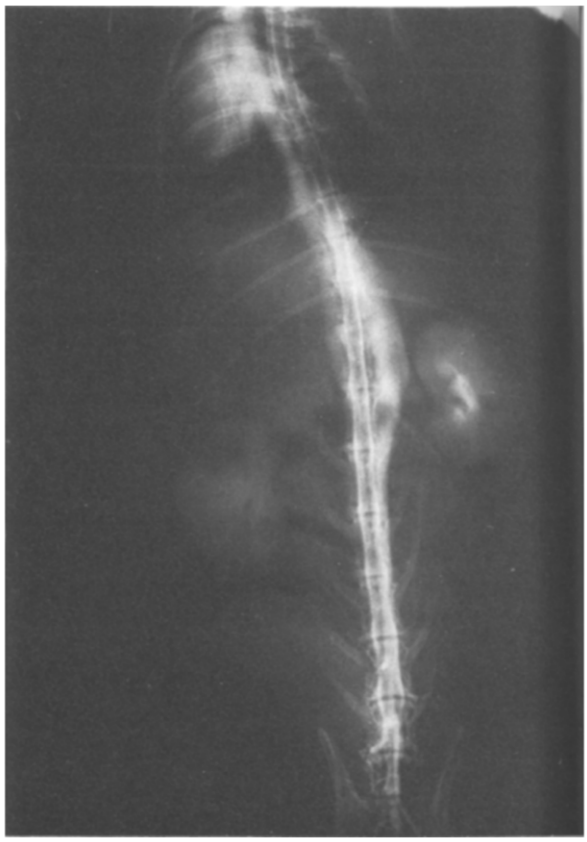

**Fig. 2.** Radiograph taken after 1 minute of epidural perfusion shows heart and both kidneys with radiographic contrast agent. Vascular uptake occurs rapidly into epidural veins (Batson's plexus).

degree of spinal cord cooling has not been determined, some authors recommend deep hypothermia to provide complete spinal cord protection. The effectiveness of deep hypothermia was shown by Berguer et al.[24] and was recently confirmed by Wisselink et al.,[25] who used a subarachnoid cold fluid-perfusion system. They demonstrated that spinal cord neurons can tolerate temperatures of 15° to 17° C with no histologically identifiable damage after rewarming to 37° C. Vanicky et al.[28] achieved, by an epidural cooling system, hypothermia below 15° C. This was confirmed by us in preliminary studies, in which the infused cooling fluid was allowed to flow extracorporally. However, these techniques remain fraught with potential complications. An important limitation that we have encountered with the technique of epidural cooling described in this investigation has been the difficulty of controlling the intrathecal pressure. Some animals had increased intracranial pressures (four in phase I, three in the methylene group, and nine in the group given

contrast material) that disappeared rapidly after several minutes when the epidural perfusion was stopped. Because of the clinical use of epidural perfusion on humans, the high incidence of intracranial hypertension recorded in this study should be brought to everyone's attention. Although Davison et al.[31] have described that CSF pressure can be controlled by epidural fluid drainage, this is not possible because epidural fat collapses the epidural catheter during suction. Because intracranial hypertension is due to an increase of CSF pressure, obviously the CSF drainage would eliminate this complication.

To understand the kinetic properties of epidural space, we evaluate the concentration-time profiles of a continuous epidural perfusion with methylene blue. This study demonstrates that the spinal canal is a highly compliant space: large changes in volume are accompanied by only small changes in pressure. The plasma concentration curve with a rapid and linear absorption implies that the main uptake is by the vascular compartment. Because the primary factor governing the absorption rate is local blood flow, this could explain the wide ranges of volume infused in the animals and that the rate of perfusion has more influence on the risk of intracranial hypertension than the volume administered. Indeed, with the same doses (10 ml radiographic contrast agent) five animals died, whereas four other animals were alive according to the speed of perfusion. In addition, the epidural absorption may be particularly sensitive to changes in osmolarity. Given that the diffusion of a solution toward the vascular compartment is bigger when the perfusion is hypotonic or isotonic than when it is hypertonic, this could also explain the fact that the incidence of intracranial hypertension was higher in the group with radiographic contrast material than in the group with methylene blue or iced normal saline solution. So, theoretically, the best epidural perfusion would be a hypotonic iced saline solution.

On the other hand, the core temperature measured in the rectum decreased only around 2° C. Thus it appears that epidural cooling is a local phenomenon lacking systemic repercussion. The radiographs and spinal cord necropsy at the end of the experiment showed that the epidural perfusion tend to spread more in a cephalic than caudal direction. In addition, after epidural perfusion, we observed that the spinal roots and cord appeared dyed of methylene blue. This fact indicates that iced solution can penetrate the dura, although the amount that enters the subarachnoid space is probably small because of competing uptake into epidural fat and rapid systemic absorption. The iced solution will cross biologic membranes relatively slowly by passive diffusion through the dura. Because CSF was generally collected from a single site in the cisterna magna, and because the distribution within CSF is inhomogeneous, detailed kinetic evaluation was impossible.

Despite the protective effect against the ischemic spinal cord damage shown in this work by epidural cooling, we must say that we have not performed epidural normothermic infusion in any group of rabbits to compare groups, so it could partially obscure experimental clarity. However, in pilot experiments designed to match the experimental conditions, the epidural catheter insertion and infusion of normothermic solution did not provide any protective effect. Similarly, it should be mentioned that the high incidence of intracranial hypertension in our study is based on clinical signs (exophthalmos), and not on quantitative objective data, because unfortunately the elevated CSF pressure could be documented in only one animal.

In view of these data, we suggest that the epidural catheter in human beings should be placed into the T12-L1 interspace and advanced only 5 cm, because of the longitudinal spread of the hypothermic solution. The placement of a subarachnoid catheter becomes imperative to avoid neurologic repercussions (intracranial hypertension). This catheter will allow CSF drainage and lower CSF pressure. The reduction of CSF pressure will permit an increase of passive diffusion of iced solution into the subarachnoid space. Consequently, the epidural perfusion system for regional cord hypothermia will be safer and more effective in lowering CSF temperature. We believe the technique described by Davison et al.[31] is simple and effective in lowering CSF temperature and will provide protection from ischemic spinal cord injury during the critical period of aortic cross-clamping and intercostal vessel reanastomosis. However, this method probably does not avoid the risk of delayed-onset paraplegia, as it has been showed in our study. In addition, the osmolarity and rate of epidural perfusion are the most important factors in the development of intracranial hypertension. Further investigations are necessary to explain these observations and the possibility of reperfusion injury.

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