Use of Neuroanesthesia Adjuncts (Hyperventilation and Mannitol Administration) Improves Neurological Outcome After Thoracic Aortic Cross-Clamping in Dogs

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Background and Purpose: Using a canine model of thoracic aortic cross-clamping, we compared the incidence and severity of paraplegia with and without standard neuroanesthesia adjuncts (mannitol administration and deliberate hyperventilation). Better outcome was predicted for animals treated with mannitol and hyperventilation.

Methods: Nineteen dogs (mean ± SD weight, 21 ± 3 kg) were anesthetized with methohexital to an isoelectric electroencephalogram. Animals were randomized to group C (control; n = 9) or group M (mannitol administration and deliberate hyperventilation; n = 10). In group C, animals were maintained normocapnic (PaCO₂, 38 to 42 mm Hg). In group M, animals were hyperventilated to a PaCO₂ of 28 to 32 mm Hg and received mannitol 2 g·kg⁻¹ during surgical preparation, then 1 g·kg⁻¹·h⁻¹ by continuous infusion. The thoracic aorta was cross-clamped for 30 minutes. Systemic hemodynamics, cerebrospinal fluid pressure, and arterial blood gases were measured at (1) baseline, (2) 2 minutes after cross-clamp, (3) 20 minutes after cross-clamp, (4) 5 minutes after cross-clamp release, and (5) 30 minutes after resuscitation. No attempt was made to control the hemodynamic consequences of cross-clamping in either group. With release of the cross-clamp, PaCO₂ was not controlled in group C; in group M the minute ventilation was further increased to maintain PaCO₂ constant. At precisely 24 hours after cross-clamp the animals were assessed for incidence and severity of paraplegia, using the Tarlov score, by an observer unaware of the experimental protocol. The animals were killed, and the entire spinal cord was removed for histological assessment. Multiple sections of the lumbar spinal cord were processed and stained with hematoxylin and eosin.

Results: With application of the cross-clamp, cerebrospinal fluid pressure and central venous pressure increased significantly in both groups. However, in group M the maximal mean cerebrospinal fluid pressure never exceeded baseline values in group C. With cross-clamp release, spinal cord perfusion pressure (distal mean aortic pressure minus mean cerebrospinal fluid pressure) was significantly greater in group M (86±23 to 65±17 mm Hg; P = .0017 between groups). Acid-base balance was better maintained in group M. The incidence and severity of paraplegia were significantly lower in group M (P = .043; Mann-Whitney rank-sums test, two-tailed). In this group 10 of 10 animals could walk and 4 of 10 had complete recovery. In group C 4 of 9 animals were paraplegic. There was a strong negative correlation between the Tarlov score and the ratio of dead to total anterior spinal cord neurons in the lumbar region as assessed by light microscopy (P = .0004; Spearman’s rank test).

Conclusions: We conclude that a protocol using standard neuroanesthesia adjuncts (mannitol administration and deliberate hyperventilation) is associated with improved neurological outcome after thoracic aortic cross-clamping of 30 minutes’ duration in dogs anesthetized with methohexital. 

Key Words • hyperventilation • mannitol • paraplegia • spinal cord • dogs

Cross-clamping of the thoracic aorta entails a risk of paraplegia.1-3 Paraplegia may occur because the spinal cord situated anatomically below the cross-clamp site is hyperperfused. Spinal cord perfusion pressure (SCPP), defined as the difference between distal mean aortic pressure (MAPₐ) and mean cerebrospinal fluid pressure (CSFP), decreases for two reasons after cross-clamping: the MAPₐ decreases and the CSFP increases. Interventions to maximize SCPP, such as drainage of CSF, are associated with improved neurological outcome in canine models of thoracic aortic cross-clamping.4-6 We hypothesized that the increase in CSFP seen with cross-clamping of the thoracic aorta could be controlled by deliberate hyperventilation and administration of mannitol. Such interventions are stan-
standard neuroanesthesia practice to lower raised CSFP or prevent increases in CSFP. Use of these neuroanesthesia adjuncts was expected to improve SCPP during cross-clamping and possibly modify the severity of spinal cord ischemia through the neuronal protective effects of mannitol. In this study, we compared the incidence and severity of paraplegia at 24 hours after cross-clamping of the proximal descending aorta in a control group of dogs anesthetized with a barbiturate, methohexital, with a group of animals receiving the same anesthetic but also administered mannitol and deliberately hyperventilated. In addition, in both groups of animals, after fixation and staining, the lumbar spinal cord was examined histopathologically by light microscopy. The degree of anterior horn cell death in the lumbar spinal cord was correlated to neurological outcome.

Materials and Methods

This study was approved by the Committee for Animal Experimentation at the University of Manitoba. Nineteen mongrel dogs (mean±SD weight, 21±3 kg) were randomly assigned to one of two groups: (1) a control group with methohexital anesthesia alone, group C (n=9); and (2) a group with methohexital anesthesia plus mannitol and hyperventilation, group M (n=10).

Preparation

After induction of anesthesia with methohexital 19±5 mg·kg⁻¹ IV, the trachea was intubated and mechanical ventilation instituted. In both groups, animals received 500 mL lactated Ringer’s after induction of anesthesia. Anesthesia was maintained with isoflurane in oxygen, 1.4% end-tidal (1 minimal alveolar concentration), and the Paco₂ was adjusted to approximately 40 mm Hg for the duration of the surgical preparation. End-tidal CO₂ was continuously monitored. The dogs were placed in a modified sphinx position with the head fixed in a stereotoxic frame. A nasopharyngeal temperature probe was inserted, and body temperature was maintained at 37±1°C by a servo-controlled heating lamp and pad. A Foley catheter was inserted to measure urine output. Bipolar electroencephalographic (EEG) electrodes were placed over the parietal hemispheres bilaterally. The EEG was continuously recorded by an Interspec Medical Neurotrac EEG monitor. Through the right femoral vein, a flow-directed catheter was advanced to the right ventricle and withdrawn slightly into the right atrium. A right femoral arterial catheter was advanced into the distal aorta. A 7.5F double-lumen catheter was inserted in the left internal mammary artery and advanced to the proximal aorta. Using a micromanipulator, a 22-gauge spinal needle was inserted in the cisterna magna to measure CSFP. All pressures were referenced to the level of the right atrium. The proximal descending aorta was exposed through a left thoracotomy. In group C during surgical preparation, animals received 500 mL lactated Ringer’s solution intravenously. In group M, animals received 20% mannitol intravenously at 2 g·kg⁻¹ followed by a continuous infusion of mannitol at 1 g·kg⁻¹·h⁻¹. A pilot series indicated that such a dose of mannitol would ensure a vigorous diuresis before thoracic aortic cross-clamping.

Experimental Protocol

At least 30 minutes elapsed between completion of preparatory invasive procedures and the start of the experiment. With completion of surgery, isoflurane was discontinued and the EEG made isoelectric by a methohexital bolus followed by a continuous infusion at 20 mg·kg⁻¹·h⁻¹ to maintain EEG isoelectricity. In group C, normocapnia (38 to 42 mm Hg) was maintained during the period of cross-clamping. In group M, minute ventilation was increased to decrease Paco₂ to approximately 28 to 32 mm Hg. Hypocapnia was maintained during the period of cross-clamping. When the Paco₂ was stable, measurements of hemodynamics and CSFP were made (Baseline). The aorta was cross-clamped 2.5 cm distal to the left subclavian artery and 2 minutes later, all measurements were repeated (Clamp On 2 minutes). At 20 minutes all measurements were again repeated (Clamp Off 20 minutes). The aortic cross-clamp was left in place for 30 minutes. Immediately after cross-clamp release, the methohexital infusion was stopped. Five minutes after unclamping, all measurements were repeated (Clamp Off). No attempt was made to control proximal MAP (MAPp) or Paco₂ immediately after unclamping in group C. In group M, minute ventilation was further increased to counteract the increase in Paco₂ seen with cross-clamp release. In both groups the animals were then resuscitated by blood volume expansion with crystalloid to restore baseline blood pressure. Ventilation was adjusted, as required, to restore Paco₂ to baseline for both groups (a Paco₂ of 30 and 40 mm Hg in groups M and C, respectively). Sodium bicarbonate was administered if the base deficit exceeded 10 mmol·L⁻¹. A final set of measurements was made 30 minutes after complete resuscitation (stable MAP, central venous pressure (CVP), and acid-base status) (Resuscitation). Timed urine collections were made up to the time of aortic cross-clamping, during the period of aortic cross-clamping, and after cross-clamp removal during the 30-minute period of resuscitation.

At the completion of the experiment, all wounds were sutured and infiltrated with 0.5% bupivacaine. The trachea was extubated after transport of the animal to the animal holding area. Oxygen was administered by face cone at 5 L·min⁻¹, and lactated Ringer’s was infused at 100 mL·h⁻¹ until the next day. Buprenorphine (0.015 mg·kg⁻¹) was administered intramuscularly for analgesia. If necessary, morphine 0.5 mg·kg⁻¹ was administered the next morning. Exactly 24 hours after application of the aortic cross-clamp, neurological assessment was performed by a veterinarian who was unaware of the treatment group to which each animal belonged. She assessed the severity of paraplegia in each dog using the Tarlov score: grade 0, no voluntary movement; spastic or flaccid paraplegia; grade 1, perceptible movement of joints; grade 2, good movement of the joints but unable to stand; grade 3, ability to stand and walk; grade 4, complete recovery. The animals were then killed by Euthanyl injection.

Data Acquisition

At each of the five measurement periods (Control, Clamp On 2 minutes, Clamp On 20 minutes, Clamp Off, and Resuscitation), we recorded temperature, MAPp, MAPa, CVP, and CSFP. Arterial blood gases and
hemoglobin were measured before each measurement period by an ABL3 Acid-Base Laboratory (Radiometer) and OSM3 Hemoximeter programmed for canine blood (Radiometer). Pressures were measured by calibrated Gould P23 transducers positioned at the level of the right atrium. Data were recorded on paper continuously by a polygraph (Gould Recorder 2600S) and intermittently on hard disk by a Gateway 2000 386 computer-based digital acquisition system (Dataq Instruments). Data presented are from the digital acquisition system.

**Light Microscopy**

After injection of Euthanyl, the spinal cord was immediately removed and placed in 10% buffered formalin. After fixation, six representative cross-sectional tissue samples were obtained from the lumbar spinal cord and embedded in paraffin. Glass slides having 7-µm-thick sections were stained with hematoxylin and eosin. An observer, unaware of the dog's neurological outcome and anesthetic protocol, examined each slide by light microscopy to count the total number of neurons in the anterior spinal cord (anterior to a line drawn through the central canal perpendicular to the vertical axis). These cells were considered dead if the cytoplasm was diffusely eosinophilic and total if the cells demonstrated basophilic stippling (that is, contained Nissl substance). The ratio of dead to total anterior spinal cord neurons was calculated.

**Data Analysis**

Data were evaluated by analysis of variance (ANOVA) for repeated measures. The time effect on the possible differences between the two groups was tested by group×time interaction. When ANOVA revealed either a significant group×time interaction or time effect, appropriate multiple comparisons were made by the least-squares means test. Bonferroni's correction was applied (P<.05/n, where n=number of comparisons) when multiple comparisons were made. Tarlov scores were analyzed by the Mann-Whitney rank-sums test using a significance level of P<.05. The ratio of dead to total lumbar anterior spinal cord neurons was correlated to the severity of lower limb dysfunction as assessed by Tarlov's score using Spearman’s rank test and compared between groups by unpaired t test (P<.05 considered significant). SCPP was calculated as MAP minus mean CSFP or mean CVP (whichever outflow pressure was greater). Data are presented as mean±SD.

**Results**

The temperature and blood gas data from the experiments are shown in Table 1. The nasopharyngeal temperature was the same between the two groups (P=.3816; group×time interaction). With resuscitation both groups had a significant but small decrease in core temperature compared with the control period. As designed, a difference in PaCO₂ was present at all time periods between groups (P=.0001; group×time interaction). In group C a significant increase in PaCO₂ occurred with release of the cross-clamp. This did not occur in group M, where the minute ventilation was deliberately increased before cross-clamp release. The pH was also different between groups at all time periods (P=.0001; group×time interaction). A significant decrease in pH occurred at time periods 3 and 4 in the control group. The hemoglobin was greater in group M at all time periods (P=.0018; group×time interaction), which resulted in a greater arterial oxygen content in this group at all times as well (P=.0017). No animal required administration of sodium bicarbonate.

The hemodynamic data from the experiments are shown in Table 2. There were no significant group×time interactions for MAPp and MAPd (P=.8391 and P=.6609, respectively). As expected, MAPp increased sharply with application of the cross-clamp and MAPd decreased sharply. At all time periods the CVP was less in group M (P=.0010). In both groups CVP increased significantly with application of the cross-clamp compared with baseline values. In both groups CSFP increased with application of the cross-clamp, but at all

**Table 1. Temperature and Blood Gas Data in a Canine Model of Thoracic Aortic Cross-Clamping**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measurement period</th>
<th>Baseline</th>
<th>Clamp On 2 minutes</th>
<th>Clamp On 20 minutes</th>
<th>Clamp Off</th>
<th>Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature (°C)</td>
<td></td>
<td>Mannitol</td>
<td>36.5±0.6</td>
<td>36.6±0.7</td>
<td>36.6±0.7</td>
<td>36.0±0.9*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>36.9±0.7</td>
<td>36.7±0.8</td>
<td>36.7±0.7</td>
<td>36.5±0.6*</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td></td>
<td>Mannitol</td>
<td>29.2±0.82†</td>
<td>28.0±2.4†</td>
<td>29.4±2.1†</td>
<td>28.0±2.2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>40.3±1.44</td>
<td>39.8±1.5</td>
<td>41.7±3.1</td>
<td>46.4±4.1*</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td>Mannitol</td>
<td>7.40±0.04†</td>
<td>7.41±0.06†</td>
<td>7.38±0.05†</td>
<td>7.38±0.06†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>7.33±0.02</td>
<td>7.33±0.02</td>
<td>7.29±0.02*</td>
<td>7.25±0.04*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td></td>
<td>Mannitol</td>
<td>13.7±1.2†</td>
<td>13.2±1.2†</td>
<td>13.8±1.9†</td>
<td>13.9±2.2†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>10.9±0.9</td>
<td>10.8±1.0</td>
<td>11.5±1.2</td>
<td>11.6±1.2</td>
</tr>
</tbody>
</table>

Values are mean±SD. Mannitol group, n=10; control group, n=9. See “Materials and Methods” for explanation of measurement periods.

†P<.05 vs baseline groups.

*P<.05 vs. groups.
times the CSFP was significantly less in group M ($P=.0002$). The maximal mean CSFP in group M was less than baseline mean values in group C. There was no significant group$\times$interaction for SCPP ($P=.0873$). However, SCPP was significantly greater after cross-clamp release in group M ($P=.0017$ between group comparisons).

The urine output for the two groups is seen in Table 3. Urine output was greater in group M for collection periods 1 and 3.

The severity of motor function deficit at 24 hours as assessed by Tarlov's score is shown in Table 4. A significantly increased incidence and severity of paraplegia were seen in group C ($P=.043$; Mann-Whitney rank-sums test, two-tailed). All 10 animals in group M could walk, and 4 of 10 showed complete recovery. In group C, 4 of 9 animals were paraplegic.

In 18 experiments, six representative slides of the lumbar spinal cord were examined by light microscopy. A significant inverse correlation between Tarlov's score and the ratio of dead to total anterior spinal cord neurons was evident (Spearman’s correlation coefficient $= -.7451$; $P=.0004$) (Figure). In addition, the mean value of the ratio of dead to total neurons in group M was 0.02$\pm$0.03 and in group C was 0.11$\pm$0.13; this was significantly different between the two groups ($P=.0429$; unpaired $t$ test).

### Discussion

In this study, in dogs administered methohexital to an isoelectric EEG, we have shown that the changes in CSFP that occur with cross-clamping of the thoracic aorta could be controlled by administration of mannitol and deliberate hyperventilation. Control was afforded not by preventing the increase in CSFP seen with cross-clamping, but by cushioning these pressure effects by significantly decreasing CSFP at baseline and thereby controlling the absolute magnitude of the increase. Animals in group M always had mean CSFP values less than the baseline mean value of CSFP in animals in the control group. At baseline, CSFP was only 70% of that in group C. This difference was more dramatic with cross-clamp release when CSFP in group M was only 57% of that in group C. Most importantly, animals treated with mannitol and deliberately hyperventilated had improved neurological outcome (significantly lower incidence and severity of paraplegia) compared with the control group of animals. All animals in group M could walk after mannitol and hyperventilation. In group C only 55% of animals could walk. More than 30 years ago, Blaisdell and Cooley$^{12}$ showed that control of

#### Table 2. Hemodynamic Data in a Canine Model of Thoracic Aortic Cross-Clamping

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>Clamp On 2 minutes</th>
<th>Clamp On 20 minutes</th>
<th>Clamp Off</th>
<th>Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{MAP}_p$ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>94$\pm$17</td>
<td>133$\pm$14$^*$</td>
<td>156$\pm$21$^*$</td>
<td>100$\pm$23</td>
<td>114$\pm$19$^*$</td>
</tr>
<tr>
<td>Control</td>
<td>100$\pm$23</td>
<td>134$\pm$13 (n=8)$^*$</td>
<td>157$\pm$18$^*$</td>
<td>88$\pm$15</td>
<td>110$\pm$20</td>
</tr>
<tr>
<td>$\text{MAP}_d$ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>94$\pm$18</td>
<td>26$\pm$4$^*$</td>
<td>29$\pm$5$^*$</td>
<td>98$\pm$24</td>
<td>113$\pm$17$^*$</td>
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<tr>
<td>Control</td>
<td>100$\pm$21</td>
<td>25$\pm$4$^*$</td>
<td>30$\pm$7$^*$</td>
<td>88$\pm$16</td>
<td>109$\pm$20</td>
</tr>
<tr>
<td>$\text{CVP}$ (mm Hg)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>3.6$\pm$1.0</td>
<td>5.8$\pm$1.5$^*$</td>
<td>6.4$\pm$1.4$^*$</td>
<td>4.2$\pm$1.5</td>
<td>4.1$\pm$1.3</td>
</tr>
<tr>
<td>Control</td>
<td>6.4$\pm$1.6</td>
<td>9.1$\pm$1.5$^*\dagger$</td>
<td>8.7$\pm$2.1$^*\dagger$</td>
<td>6.1$\pm$1.5$\dagger$</td>
<td>6.1$\pm$1.6$\dagger$</td>
</tr>
<tr>
<td>$\text{CSFP}$ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>12.5$\pm$1.9</td>
<td>15.4$\pm$2.3$^*$</td>
<td>16.0$\pm$2.6$^*$</td>
<td>12.0$\pm$1.9</td>
<td>12.6$\pm$3.0</td>
</tr>
<tr>
<td>Control</td>
<td>18.0$\pm$4.0</td>
<td>21.0$\pm$4.4$^*\dagger$</td>
<td>22.6$\pm$5.4$^*\dagger$</td>
<td>22.0$\pm$4.9</td>
<td>18.8$\pm$4.0$\dagger$</td>
</tr>
<tr>
<td>$\text{SCPP}$ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mannitol</td>
<td>82$\pm$18</td>
<td>10$\pm$6$^*$</td>
<td>13$\pm$5$^*$</td>
<td>86$\pm$23</td>
<td>100$\pm$18$^*$</td>
</tr>
<tr>
<td>Control</td>
<td>82$\pm$23</td>
<td>4$\pm$7$^*$</td>
<td>7$\pm$10$^*$</td>
<td>65$\pm$17$\dagger$</td>
<td>90$\pm$22</td>
</tr>
</tbody>
</table>

Values are mean$\pm$SD. Mannitol group, n=10; control group, n=9. See "Materials and Methods" for explanation of measurement periods. $\text{MAP}_p$, proximal mean aortic pressure; $\text{MAP}_d$, distal mean aortic pressure; $\text{CVP}$, central venous pressure; $\text{CSFP}$, cerebrospinal fluid pressure; $\text{SCPP}$, spinal cord perfusion pressure.

* $P<.05$ vs baseline within groups.

† $P<.05$ between groups.

#### Table 3. Urine Output in a Canine Model of Aortic Thoracic Cross-Clamping

<table>
<thead>
<tr>
<th>Group</th>
<th>Before clamp</th>
<th>During clamp</th>
<th>After resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol (n=10)</td>
<td>484$\pm$79</td>
<td>49$\pm$41$^*$</td>
<td>247$\pm$93$^*$</td>
</tr>
<tr>
<td>Control (n=8)</td>
<td>49$\pm$22†</td>
<td>16$\pm$13</td>
<td>48$\pm$29†</td>
</tr>
</tbody>
</table>

Values are mean$\pm$SD in milliliters per hour.

* $P<.05$ within groups.

† $P<.05$ between groups.

#### Table 4. Severity of Motor Function Deficit at 24 Hours in a Canine Model of Aortic Thoracic Cross-Clamping

<table>
<thead>
<tr>
<th>Group</th>
<th>Tarlov score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mannitol</td>
<td>0 0 0 6 4</td>
</tr>
<tr>
<td>Control</td>
<td>3 1 0 4 1</td>
</tr>
</tbody>
</table>

$P=.043$ mannitol vs control group by Mann-Whitney rank-sums test, two-tailed.
raised CSFP by administering urea decreased the incidence of paraplegia after cross-clamping of the thoracic aorta in dogs. However, theirs was a very small series, and the improvement in neurological outcome did not reach statistical significance, nor were their animals hyperventilated.

The present study also clearly indicates that the "clinical" assessment of neurological dysfunction accurately reflected the histology of the neurons in the anterior spinal cord in the lumbar region. There was a very strong inverse correlation by Spearman's rank test of Tarlov's score vs the ratio of dead to total lumbar anterior spinal cord neurons. In addition, the mean value of this ratio differed between groups by unpaired t test. The ratio was significantly lower in group M, indicating greater viability of lumbar spinal cord neurons.

Previous work from this laboratory has demonstrated that the increase in CSFP seen with thoracic aortic cross-clamping is directly correlated with the increase in CVP. This finding is confirmed in this study. Both groups had a significant increase in CSFP with cross-clamping of the thoracic aorta (from 12.5 to 15.4 mm Hg in group M and from 18.0 to 21.0 mm Hg in group C). The corresponding mean increase in CVP in the two groups was 3.2 mm Hg and 2.7 mm Hg, respectively. The CVP was consistently lower in group M at all time periods, most likely a consequence of the osmotic diuresis with mannitol. Before application of the cross-clamp, the mean urine output in group M was 10 times greater than that in group C (Table 3). The CSFP in both groups was greater than previously recorded measurements from this laboratory because in this experiment, CSFP was referenced to the level of the right atrium, not to the level of the interauricular line with the dog in the modified sphinct position. This resulted in significantly greater CSFP because of the hydrostatic gradient seen with lowering the transducer a mean value of 16.7±1.6 cm from the level of the interauricular line. For this experiment it was believed that CSFP measured at this site was more indicative of the lumbar CSFP in these animals. The CSFP was thus consistently greater than CVP, simplifying calculation of SCFP. We have previously demonstrated that the lumbar spinal cord is at greatest risk of ischemia in this model.

We suggest that the relation between improved neurological outcome and the administration of mannitol and deliberate hyperventilation may be due to a number of mechanisms. We can identify at least five possible mechanisms for improved outcome in group M. First, CSFP was significantly lower with cross-clamp release in group M. This was the time of greatest difference in SCFP between groups. In group C, with cross-clamp release CSFP remained elevated despite the return of CVP to baseline values. We have previously demonstrated that the increase in CSFP that occurs after cross-clamp release correlates with an increase in total cerebral blood flow, which, in turn, is dependent on the elevation in Paco2. In group M, an additional increase in minute ventilation to maintain Paco2 constant after cross-clamp release has prevented an increase in CSFP above baseline values. In contrast, in group C the CSFP remained elevated at values seen with cross-clamping. These differences contribute to a significantly greater SCFP with cross-clamp release in group M vs group C (86±23 mm Hg and 65±17 mm Hg, respectively; P=.0017). Crawford's group has shown, in humans, that the incidence of paraplegia after surgical reconstruction of the thoracic or thoracoabdominal aorta is strongly correlated to perioperative hypotension. Single ischaemic insults are better tolerated than multiple insults of similar total duration. Such multiple insults result in markedly worsened neurological outcome in animal models.

Recent work, described in a review article on head injury, provides corroborating evidence. Neurological outcome from head injury was most adversely affected by arterial hypotension as the secondary insult. Thus, we believe that the improvement in hemodynamics in group M at the time of cross-clamp release may have contributed to improved outcome.

Second, the lower CSFP in group M contributed to SCFP values greater than 7.5 mm Hg during cross-clamping (10±6 and 13±5 mm Hg at 2 and 20 minutes after cross-clamping, respectively). In group C the corresponding SCFP values are 4±7 and 7±10 mm Hg. Oka and Miyamoto, using a canine model similar to ours, have shown that if SCFP during thoracic aortic cross-clamping exceeds 7.5 mm Hg, neurological outcome improves. Additionally, Aasdal et al have recently demonstrated that spinal cord blood flow as assessed by the laser Doppler technique is critically CSFP dependent. In their porcine model, spinal cord pulsatile flow increased 51% with removal of 1 mL of CSF. In the present study animals in group M maintained SCFP greater than 7.5 mm Hg during cross-clamping, which may have contributed to an improved outcome.

Third, mannitol may provide neuronal protection in its own right. Mannitol has been identified as a free radical scavenger and may have salutary effects on blood rheology. Mannitol has not been shown to be uniformly beneficial during neuronal ischemia, but several recent studies have indicated benefits. Shirane and Weinstein have shown that pretreatment by mannitol improved cerebral blood flow after 30 minutes of tem-
porary global ischemia in rats. They also demonstrated that in animals treated with mannitol there was decreased postischemic obstruction of the cerebral microvasculature. Sutherland et al\(^1\) demonstrated that pretreatment with mannitol significantly decreased hippocampal neuron death in rats subjected to 10 minutes of forebrain ischemia. In dogs subjected to reproducible spinal cord trauma, those administered mannitol by infusion had significantly better restoration of spinal cord evoked potentials compared with those managed with a bolus of mannitol or saline.\(^2\) These studies suggest neuronal sparing after administration of mannitol. Similar advantages may have contributed to the improved neurological outcome seen in this study.

Fourth, the hypocapnia associated with deliberate hyperventilation has prevented a respiratory acidosis from becoming manifest after cross-clamp release. Carbon dioxide represents a diffusible acid that potentially can decrease interstitial pH in the spinal cord. Increased interstitial H\(^+\) concentration is associated with neurotoxicity.\(^3\) Interstitial acidosis may have been better controlled at the ischemic site with deliberate hyperventilation, thereby contributing to improved outcome.

Finally, with mannitol administration and subsequent diuresis the hemoglobin and arterial oxygen content were consistently greater in group M. Improved oxygen transport to the ischemic spinal cord tissue is possible under these circumstances. However, the association between arterial oxygen content, possible altered blood rheology due to mannitol, and the increase in hemoglobin concentration and neuronal protection in the presence of marked ischemia is not clear in this circumstance. If this effect is important, similar outcome results, in theory, could be obtained after furosemide administration. Salutary effects of mannitol administered before cross-clamping on renal and limb ischemia are also possible.\(^4\) In this experiment, we have demonstrated significantly greater urine output after cross-clamp release in animals administered mannitol.

Results from this experiment suggest that administration of mannitol and hyperventilation may be as effective as draining CSF to control fluctuations in CSFP with thoracic aortic cross-clamping, as used in other canine models.\(^4\)\(^,\)\(^6\) In canine experiments in which CSF has been drained (usually to a negative CSFP), others have usually assumed outflow pressure to be equal to CSFP, disregarding the true outflow pressure represented by CVP in this situation.\(^2\)\(^,\)\(^6\)\(^,\)\(^7\) Thus, CSFP is usually reported as being spuriously high in these previous studies. The error introduced is not usually of an important magnitude in such canine experiments, but it can become significant in the clinical situation if cardiac filling pressures become pathologically high from the combination of increased preload and afterload with thoracic aortic cross-clamping in those patients with myocardial dysfunction. In such situations if the CVP is elevated to pathological levels, CSFP may not be the appropriate downstream pressure to control. However, draining CSF to control the increase in CSFP seen with cross-clamping has been shown to consistently decrease the incidence and severity of paraplegia in canine models of thoracic aortic cross-clamping.\(^4\)\(^,\)\(^6\) Lumbar CSF drainage is now performed in some centers during surgical reconstruction of the thoracoabdominal aorta in an attempt to decrease the incidence of paraplegia. However, epidural or subarachnoid hemorrhage can occur when the drainage catheter is placed. Bleeding is especially worrisome when partial bypass is considered and systemic heparinization required. Crawford et al\(^1\) have demonstrated no difference in neurological outcome if CSF was drained in patients having descending thoracic and thoracoabdominal aortic surgery. However, in that study, the CSFP was not reduced to very low levels (not less than 15 mm Hg). Thus, the use of lumbar CSF drainage during surgical reconstruction of the thoracic aorta remains controversial.

In conclusion, we have demonstrated that the incidence and severity of paraplegia seen with thoracic aortic cross-clamping in this canine model were significantly less if standard neuroanesthesia adjuncts were used (mannitol administration and deliberate hyperventilation). If managed with this protocol, 100% of the animals could walk. The CSFP increase that occurs with cross-clamping of the thoracic aorta can be effectively controlled by cushioning this effect through a decrease in baseline CSFP. These results also suggest an alternate means to control the CSFP increase that occurs with thoracic aortic cross-clamping in the clinical situation. The risks associated with CSF drainage (specifically epidural or subarachnoid hemorrhage with catheter placement) can be avoided if CSF increases are controlled by mannitol administration and deliberate hyperventilation. These results suggest that a comparison between this protocol and CSF drainage to control raised CSFP after thoracic aortic cross-clamping is warranted.

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**References**

Paraplegia is the most serious complication of operations to repair aneurysms of the descending thoracic or thoracoabdominal aorta. The mechanism of its occurrence is probably multifactorial, but interruption of the circulation to the spinal cord is generally regarded to be the most important, and it is well known that the incidence of paraplegia increases with increases in aortic cross-clamp time. But other factors are almost certainly involved, especially in the type of paraplegia that is delayed in onset. Mechanisms proposed for this situation, in addition to cross-clamp–induced ischemia, include spinal cord edema, free-radical–mediated neuronal injury, and vasoconstriction (vasospasm) of vessels supplying the cord.

Methods used to reduce the risk of paraplegia have involved efforts to (1) limit the severity of spinal cord ischemia; (2) reduce the metabolic demands of the ischemic spinal cord; and (3) limit the reperfusion injury.

The greatest amount of clinical effort has been directed toward limiting the ischemic insult, by reattachment of intercostal arteries, minimizing the duration of aortic cross-clamping, augmenting distal aortic perfusion during cross-clamping (shunts, cardiopulmonary bypass), and augmentation of spinal cord perfusion pressure (SCPP). This last method has undergone intensive experimental and clinical evaluation in recent years and has led to widespread clinical use of cerebrospinal fluid (CSF) drainage during thoracic aortic surgery. Unfortunately, augmentation of SCPP by CSF drainage is not sufficient to reliably prevent postoperative paraplegia. In the only randomized prospective human trial, no difference in paraplegia rate was found among patients who had or did not have drainage of CSF.

Other methods have also been tested experimentally and used clinically. Efforts to reduce cellular injury have included hypothermia, specific neuroprotective agents, corticosteroids, and free-radical scavengers. Intraaortic administration of papaverine or other vasodilators has also been used to reduce or prevent vasospasm. All of these methods and agents have some theoretical and experimental basis for their continued evaluation.

In the preceding article, Mutch and associates provide additional insights into this problem. They seem to accept the hemodynamic hypothesis of spinal cord dysfunction after thoracic aortic clamping, but they propose a slightly different method of preserving spinal cord perfusion. In their canine experiments, a combination of deliberate hyperventilation (hypocapnia) and diuresis was used to maintain normal or near normal SCPP. The hypocapnia prevented the respiratory acidosis that occurred in their control animals after removal of the thoracic-aortic clamp, which may have better preserved the intraneuronal and extraneuronal pH. The vigorous diuresis that they induced with mannitol, while contributing to the maintenance of SCPP, may also have had a beneficial effect at the cellular level by virtue of its free-radical scavenger properties. The authors discuss several other possible neuroprotective mechanisms that might have contributed to the marked improvement in neurological function in the treated animals. The contribution of the barbiturate-induced isoelectric electroencephalogram cannot be assessed because both groups of animals received the methohexital, but this does not preclude a beneficial effect of this agent. Indeed, bar-
Use of neuroanesthesia adjuncts (hyperventilation and mannitol administration) improves neurological outcome after thoracic aortic cross-clamping in dogs.

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