Protection From Cerebral Ischemia by Brain Cooling Without Reduced Lactate Accumulation in Dogs

JoAnne E. Natale, PhD, and Louis G. D’Alecy, DMD, PhD

Hypothermia protects tissue function in ischemia. This study determined if selective brain cooling inhibits cerebral cortical lactate accumulation and thus accounts for improved neurologic outcome after complete cerebral ischemia in dogs. The brain was selectively cooled (hippocampal temperature 33°C) by nasal lavage with water at 5°C. Control dogs received nasal lavage with water at 39°C. Mean±SEM rectal temperature in both groups was 39±1°C prior to ischemia. Selective brain cooling before and during 10 minutes of cardiac arrest was associated with significantly improved neurologic function and 100% survival, whereas normothermic cardiac arrest produced marked neurologic dysfunction and 100% mortality. Cerebral cortical lactate accumulation was measured in a complementary series of dogs exposed to the same two treatments but with the addition of six cerebral cortical brain biopsies taken before, during, and immediately after cardiac arrest. Brain and rectal temperatures of dogs in the brain biopsy protocol were similar to those of dogs in the recovery protocol. There was no difference detected in cerebral lactate accumulation during ischemia between brain-cooled and control dogs. Thus, reduction in cortical brain lactate during ischemia cannot account for the postischemic functional protection afforded by preischemic selective brain cooling. (Stroke 1989;20:770–777)

During normoglycemic cardiopulmonary arrest, lactate rapidly accumulates in neuronal tissues, reaching levels 10-fold greater than preischemic concentrations but lower than those produced when blood glucose levels are elevated (J.E. Natale, unpublished observations).1 Augmented metabolism of glucose to lactate has been proposed as a mechanism of hyperglycemia-exacerbated ischemic injury.2–6 While hyperglycemia appears to be detrimental in ischemia,7–12 hypothermia is protective of tissue function in ischemia.13–19 Therefore, we asked whether selective brain cooling inhibits ischemic cerebral glucose metabolism to lactate and whether such decreased cerebral cortical lactate accumulation might therefore account for improved neurologic function following complete, global cerebral ischemia produced by 10 minutes of cardiac arrest. Selective brain cooling, rather than whole-body hypothermia, was induced to minimize broadly occurring and potentially confounding systemic changes that might otherwise contribute to the protection.

Materials and Methods

Our study consists of two complementary protocols involving two separate groups of dogs. The recovery protocol was used to determine whether improved neurologic function and decreased mortality were provided by selectively cooling the brain before complete cerebral ischemia. The biopsy protocol determined whether similar selective brain cooling inhibited ischemic cerebral cortical glucose metabolism to lactate during a 10-minute cardiac arrest and for the following 25 minutes. Surgical preparation, cardiac arrest, and resuscitation procedures were identical for each protocol, and their description has been published.20–24 Brief summaries of these procedures are provided below.

Fasted adult male mongrel dogs were premedicated with morphine sulfate and anesthetized with
halothane for implantation of arterial and venous catheters, electroencephalographic electrodes, and subcutaneous electrocardiographic electrodes. Rectal temperature was monitored and maintained at 39±1°C (mean±SEM) using a heating pad with a proportional controller and a temperature-controlled, water-circulated brass or Tygon tube serving as an esophageal heat exchanger. Plasma glucose and creatinine concentrations were assessed spectrophotometrically with a Seralyzer-Reflectance Photometer (Miles Laboratories, Inc., Elkhart, Indiana). The heart was exposed for fibrillation and direct cardiac compressions during resuscitation by a left thoracotomy and pericardiectomy. A 19-gauge stainless steel probe containing two thermocouples (at the tip and 1 cm from the tip) was inserted into the right brain at the level of the pituitary, 1 cm lateral to the midline, through a 1-cm-long 17-gauge sleeve that was secured to the skull with dental acrylic. This allowed continuous monitoring of both hippocampal (0.5 cm from the floor of the skull) and cortical temperatures with minimal tissue trauma. Selective brain cooling (n=5 for recovery protocol, n=6 for biopsy protocol) was accomplished through nasal lavage with water at 5°C. A recirculating water system pumped a constant flow of iced water (Masterflex roller pump, Cole-Parmer Instrument Co., Chicago, Illinois) from a 20-L ice-slurry reservoir through two silicone rubber tubes inserted 1.5 cm and secured in the nostrils to restrict backwash of water. The water passed through the nasoal cavity, drained from the mouth into a funnel, and returned to the reservoir. For control dogs (n=5 for recovery protocol, n=5 for biopsy protocol), the ice bucket was replaced with an 8-L temperature-controlled reservoir maintained at approximately 39°C (Haake Bucher Instruments, Saddle Brook, New Jersey). Esophageal, rectal, hippocampal, cerebral cortical, reservoir, nasal lavage inlet, and ambient temperatures were continuously recorded (multipoint recorder, Honeywell Inc., Fort Washington, Pennsylvania). Nasal lavage began after the surgical preparation was complete (approximately 10–20 minutes before arrest) and continued for 30 minutes after arrest. The dogs were randomly assigned to the cooling or control treatment groups.

When the surgical preparation was complete, the dog was switched from halothane to room air ventilation (model 607, Harvard Apparatus, Millis, Massachusetts). Upon return of corneal reflexes (stage 3, plane 1 of surgical anesthesia), ventilation was halted and the heart was fibrillated directly as previously described. After 10 minutes of ventricular fibrillation, ventilation was restored and a mean arterial blood pressure (MABP) of >75 mm Hg was maintained using direct cardiac compression. Central intravenous injections of 40 μg/kg epinephrine, 1 mg/kg lidocaine, 4 meq/kg sodium bicarbonate, and 25 mg/kg calcium chloride were administered. Dopamine (10 μg/kg/min) was infused to maintain MABP between 75 and 100 mm Hg for no longer than 6 hours after arrest. Cardioversion was attempted after the resuscitation drugs were administered (recovery protocol) or after 5 minutes of direct cardiac compression (biopsy protocol). When the nasal lavage was terminated 30 minutes after arrest, the nasal tubes, esophageal heat exchanger, and rectal temperature and brain thermocouple probes were removed and the head wound was sutured.

Spectinomycin (10 mg/kg i.m.) was administered to dogs in the recovery protocol and morphine sulfate provided for analgesia if attention to wound sites or aggressive behavior suggested the presence of pain. (No dog exhibited behaviors that required postoperative analgesia.) Dogs in the recovery protocol surviving 24 hours after arrest and dogs in the biopsy protocol surviving 35 minutes after arrest were killed with 120 mg/kg sodium pentobarbital i.v. following final blood sampling. Postmortem examinations of the heart, lungs, and wound sites were conducted to identify iatrogeny. The brain thermocouple probe was reinserted through the sleeve in the skull (coronal section) to confirm the approximate anatomic placement. This experimental procedure conformed to the guidelines established by the American Physiological Society and the Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85-23, 1985) and was approved by The University of Michigan Unit for Laboratory Animal Medicine’s Vertebrate Animal Use Committee (approval #D001068D).

A well-standardized 100-point neurologic deficit score (NDS) was assigned to dogs in the recovery protocol 1, 2, 6, 12, and 24 hours after arrest by two investigators who were aware of each dog's treatment. Interobserver variability was resolved through consultation of the detailed description of each functional level. Of the 100 points, 18 are assigned to consciousness level, 18 to respiratory function, 16 to cranial nerve function, 20 to spinal nerve function, and 28 to motor function. At each assessment, total NDS ranged from 0 (normal functioning) to 100 (maximal deficit).

The treatment groups and surgical procedures were essentially the same in the recovery and biopsy protocols. In the biopsy protocol, surgical preparation included exposure of the left parietal, occipital, and temporal brain lobes by craniotomy and excision of the dura mater for tissue sampling. Six pairs of simultaneous arterial blood and cerebral cortical samples were obtained just before arrest, after 5 and 10 minutes of ischemia, after 5 minutes of direct cardiac compression (15 minutes after arrest), and 25 and 35 minutes after arrest (when spontaneous circulation had been restored). Using these samples, lactate content in brain cortical tissue, pH in whole arterial blood, and glucose concentration in plasma were analyzed.

Cerebral cortical samples were obtained for L-lactate analysis with a pneumatic biopsy drill (Alko Diagnostic Corporation, Hollison, Massachusetts)
FIGURE 1. Survival curve comparing 24-hour survival for selectively brain-cooled (○, n=5) and control (■, n=5) dogs. At 24 hours, all cooled dogs were alive, while all control dogs were dead (p=0.004, Fisher's exact test).

since this instrument enables tissue samples to be obtained and frozen within 0.5 second. A rotating (10,000 rpm) sharpened hollow-bore (3 mm) needle was manually advanced 4–6 mm vertically into the tissue, and the cut plug of tissue (approximately 100 mg) was aspirated by high vacuum onto a liquid nitrogen-cooled strainer where it was dispersed and covered with Freon-22 and stored in liquid nitrogen before grinding into a fine powder at -20°C. Each sample was mixed in a preweighed test tube containing 1.0 ml cold 3 M perchloric acid and reweighed to calculate actual tissue weight. Distilled, deionized water (2 ml) was added to the perchloric acid–brain mixture and centrifuged at 3,200# (3,750 rpm) for 20 minutes at 4° C (GRP centrifuge, Beckman Instruments, Inc., Palo Alto, California). The supernatant was neutralized with 5 M K2CO3 and stored at -70° C until fluorometric lactate analysis by the Biochemistry Core Facility of the Michigan Diabetes Research and Training Center.

Multiple linear regression analysis was used to determine if physiologic variables before cardiac arrest were associated with neurologic outcome and survival. All prearrest, resuscitation, temperature, and outcome parameters were compared using Student's t test. Brain and rectal temperatures before nasal lavage were compared with levels achieved during lavage using the paired t test. NDSs were compared using both Student’s t test (with Bonferroni’s correction) and the Mann-Whitney U test. Fisher's exact analysis and Breslow survival curve analysis were used to evaluate significance levels for survival curves. Differences in cortical lactate accumulation were determined using Student’s t comparison of the response curves (area analysis). All data are expressed as mean±SEM.

Results

In the recovery protocol, all selectively brain-cooled dogs were alive at 24 hours (Figure 1), whereas all control dogs were dead by 22 hours after arrest (p=0.004, Fisher’s exact test). Likewise, Breslow survival curve analysis indicated that selectively brain-cooled dogs had significantly less mortality during the first 24 hours after arrest than control dogs (p=0.004). The effect of selective brain cooling on NDS is similarly striking (Figure 2). Since all control dogs were dead by 24 hours, no NDSs at 24 hours are reported for that group. At all times during the first 12 hours after arrest, cooled dogs had significantly less neurologic deficit than control dogs (p<0.01 Student’s t test with Bonferroni’s correction; p<0.05, Mann-Whitney U comparison). If dead dogs are assigned an NDS of 100 and included in the statistical comparison, the differences between groups are accentuated at 12 and 24 hours.

In the biopsy protocol, cerebral cortical lactate levels during ischemia and reperfusion were similar in both groups (Figure 3). Cerebral cortical lactate levels from a previous study in this laboratory (J.E. Natale, unpublished observation) of nonnasal lavaged control dogs are also plotted for comparison. Selective brain cooling does not significantly alter cerebral cortical lactate accumulation, indicated by p>0.09 when the area under these response curves are compared using Student’s t test.

Physiologic variables for dogs in both protocols before and after cardiac arrest are provided in Table 1. In both protocols, the brain-cooled group had a lower nasal lavage inlet temperature. The only other significant differences were a lower mean heart rate in the biopsy protocol’s control group and a shorter ventilation time in the recovery protocol’s cooled group. All 21 dogs were successfully resuscitated. Resuscitation time (defined as time to return of spontaneous circulation capable of maintaining a MABP of >75 mm Hg) was prolonged in the biopsy protocol because direct cardiac compressions were continued for 3–5 minutes to allow time for cerebral cortical tissue sampling.

In the recovery protocol, there was no difference in arterial pH between the cooled and control
groups at any time before or after arrest (Table 2). When spontaneous circulation was restored, mean plasma glucose concentration in the control group was significantly higher than in the cooled group; however, there was no difference detected at any other time. Hematocrit rose in both groups during the first 12 hours of recovery and was significantly higher in the cooled group at 0.25 and 1 hour. Plasma creatinine concentration did not differ between groups nor did it rise with time, indicating adequate renal function. In the biopsy study (Table 3), the groups did not differ with regard to arterial pH, plasma glucose concentration, or hematocrit at any time before or after arrest.

Nasal lavage with cold water significantly lowered cerebral cortical and hippocampal temperatures at the time of arrest in both protocols (Table 4). Nasal lavage significantly decreased rectal temperature in the recovery protocol; however, temperature did not differ between groups at the time of cardiac arrest. Brain and rectal temperatures at cardiac arrest were not altered by nasal lavage with water at body temperature in either protocol. Although rectal temperatures in the biopsy protocol differed significantly between groups at the time of arrest, the means for both groups were within the normal range for dogs (39±0.5°C).28

The degree of brain cooling was compared between protocols. At the time of cardiac arrest, cerebral cortical temperature in the biopsy protocol's cooled group was lower than that in the recovery protocol's cooled group (p=0.052, Table 4). Ten minutes later, cerebral cortical temperature was again lower in the biopsy group (p = 0.052). The greater cortical cooling in the biopsy protocol may be due to removal of the calvaria and dura mater on the contralateral side, exposing the left cortex to ambient temperature. Neither hippocampal nor rectal temperatures in the cooled groups differed between protocols at any time. Similar comparisons of the control groups between protocols revealed no differences except in cerebral cortical temperature before nasal lavage (p=0.021, Table 4).

Discussion

Our results provide evidence that the cerebral protection afforded by selective brain cooling is independent of cerebral cortical lactate accumulation during ischemia. In spite of these findings, it is possible that regional lactate accumulation in brain tissues other than those of the cortex may more closely correlate with neurologic outcome. Such regional correlations have not, however, been reported. Our data also do not exclude the possibility that cerebral lactate accumulation at times after the immediate reperfusion period contribute to neurologic dysfunction. It is indeed possible that the postischemic development of inadequate cerebral perfusion can augment tissue lactate accumulation and contribute to neurologic dysfunction. Nonetheless, our results are inconsistent with the hypothesis that an increase in cerebral cortical tissue lactate concentration during ischemia is the direct cause of the adverse neurologic outcome in the setting of cardiac arrest. The improvement in neurologic outcome we observed with no detectable differences in cerebral cortical lactate concentrations indicates that the elevation during ischemia of cerebral cortical lactate content alone cannot account for the neurologic injury. Our results cannot address the potential indirect effects of cooling on cerebral metabolism that could account for the preservation in function.

Proposed mechanisms for the beneficial effects of brain cooling on central nervous system injury include 1) maintenance of ionic homeostasis39; 2) prevention of cerebral edema30; 3) inhibition in biosynthesis, release, and uptake of some neurotransmitters31; 4) inhibition of adenine nucleotide depletion32;33; and 5) reduced cerebral oxygen consumption and reduction of cerebral metabolic rate for glucose.32,34,35 It is the last of these proposed mechanisms that we investigated and will discuss further.

Glucose utilization by the canine brain is reduced by approximately 40% when body temperature drops to 32°C32; thus, we proposed that cooling the brain before ischemia inhibits cerebral lactate accumulation and protects it from injury. Our data, however, confirm those of Busto et al,36 who also reported no change in ischemic brain lactate content with brain cooling to 32°C. However, they did not evaluate behavioral function. Functional protection by hypothermia has been reported in both clinical3,18 and laboratory studies15,16,19,37,38 but has not been combined with brain lactate concentration data. In a
TABLE 1. Physiologic Variables for Dogs Before and After Cardiac Arrest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Recovery</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cooled</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>(n=5)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Prearrest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body wt (kg)</td>
<td>18.2±0.6</td>
<td>18.6±0.6</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>52±9</td>
<td>56±6</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>130±16</td>
<td>129±13</td>
</tr>
<tr>
<td>Heart rate (beat/min)</td>
<td>96±8</td>
<td>82±4</td>
</tr>
<tr>
<td>End-expiratory CO₂ (%)</td>
<td>3.1±0.5</td>
<td>3.1±0.3</td>
</tr>
<tr>
<td>Nasal lavage time (min)</td>
<td>10±1</td>
<td>18±4</td>
</tr>
<tr>
<td>Nasal inlet temperature (° C)</td>
<td>4.9±1.7*</td>
<td>38.6±0.7</td>
</tr>
<tr>
<td>Pump rate (ml/min)</td>
<td>832±42</td>
<td>866±26</td>
</tr>
</tbody>
</table>
| Data are mean±SEM. MABP, mean arterial blood pressure; nasal lavage time prior to ventricular fibrillation; nasal inlet temperature, temperature of water entering nostrils; urine output during 6 hours after cardiac arrest.

Resuscitation

|                                | Cooled   | Control|
|                                | (n=3)    | (n=3)  |
| Countershocks (no.)            | 1.0±0.0  | 1.4±0.4|
| Resuscitation time (min)       | 1.8±0.1  | 1.9±0.3|
| Ventilation time (min)         | 20±2*    | 27±3   |
| Exubation time (min)           | 278±40   | 290±34 |
| Epinephrine (µg/kg)            | 41±4     | 40±0   |
| Lidocaine (mg/kg)              | 2.8±0.7  | 3.0±0.5|
| NaHCO₃ (meq/kg)                | 4.8±0.4  | 4.6±0.8|
| CaCl₂ (mg/kg)                  | 30±5     | 25±0   |
| Dopamine infusion (min)        | 17±6     | 28±12  |
| Urine output (ml/hr)           | 110±22   | 73±17  |

Data are mean±SEM. n=5 for each group unless noted.

*p<0.05 different from control by Student’s t test.

Preischemic brain glucose, glycogen, and lactate and blood lactate contents determine maximal ischemic brain lactate formation.³⁹ Although not measured in this study, it can be assumed that the levels of these lactate precursors did not differ between


<table>
<thead>
<tr>
<th>Time</th>
<th>Arterial pH</th>
<th>Plasma glucose (mg/dl)</th>
<th>Hematocrit (%)</th>
<th>Plasma creatinine (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cooled</td>
<td>Control</td>
<td>Cooled</td>
<td>Control</td>
</tr>
<tr>
<td>Before treatment</td>
<td>7.47±0.01</td>
<td>7.37±0.04</td>
<td>98±154</td>
<td>135±12</td>
</tr>
<tr>
<td>Before arrest</td>
<td>7.39±0.03</td>
<td>7.40±0.04</td>
<td>108±14</td>
<td>131±8</td>
</tr>
<tr>
<td>After arrest</td>
<td>0.25 hr</td>
<td>7.44±0.04</td>
<td>183±31*</td>
<td>44±1*</td>
</tr>
<tr>
<td></td>
<td>7.35±0.03</td>
<td>7.28±0.02</td>
<td>162±15</td>
<td>50±1*</td>
</tr>
<tr>
<td></td>
<td>7.36±0.03</td>
<td>7.39±0.01</td>
<td>149±29</td>
<td>51±14</td>
</tr>
<tr>
<td></td>
<td>7.36±0.02</td>
<td>7.38±0.02</td>
<td>159±24</td>
<td>51±2</td>
</tr>
<tr>
<td></td>
<td>7.41±0.02</td>
<td>7.40±0.02</td>
<td>121±16</td>
<td>52±2</td>
</tr>
<tr>
<td></td>
<td>7.33±0.01</td>
<td>7.40±0.05</td>
<td>106±5</td>
<td>53±1</td>
</tr>
</tbody>
</table>

Data are mean±SEM. n=5 for each group unless noted.

*p<0.05 different from control by Student’s t test.
our treatment groups since the lactate profiles were similar. So, if cooling reduces cerebral glucose metabolism by almost 50% at the temperature attained in this study and yet the quantity of total brain glucose for anaerobic glycolysis was the same in the cooled and control groups, what accounts for the similarity in ischemic lactate accumulation? Immediately upon cessation of blood flow, lactate accumulates rapidly by glycolysis. In <2 minutes of total cerebral ischemia, glucose, glycogen, and adenosine 5'-triphosphate for phosphorylation of glycolytic intermediates are depleted, and lactate and hydrogen ions accumulate. Since we obtained our first ischemic brain sample after 5 minutes, the initial rate of lactate accumulation during the first 1–2 minutes is unknown. Even if cooling reduced cerebral glycolytic flux by as much as 50%, by 5 minutes of ischemia lactate accumulation would still have reached near-maximal concentrations. Therefore, while brain cooling may have slowed the rate of lactate accumulation during the first 1–2 minutes of ischemia, by 5 minutes of cardiac arrest glucose stores would have been exhausted in both treatment groups and lactate accumulation would not differ. The pattern of decrease in cerebral cortical lactate concentration during recirculation is similar between groups, and these levels are consistent with those reported by Michenfelder and Milde.

We introduce a simple, efficient, effective, and apparently safe method for selectively cooling the canine brain without markedly lowering rectal temperature. The brain can be cooled without vascular access or opening the cranium. Dogs, sheep, rabbits, and, perhaps, humans possess the vascular architecture that has been proposed as the anatomic basis for cooling the brain by nasal lavage. The selectivity of this method depends on maintaining deep body temperature within normal ranges with heating pads and an esophageal heat exchanger while rapidly cooling the venous blood circulating through the nasal mucosa. The cooled venous blood flows adjacent to and around arteries going to the brain and exchanges heat with them, thus cooling the entire brain. This method allows for the interpretation of brain-specific versus systemic effects of cooling on neurologic recovery by eliminating hypothermia-induced systemic pathophysiologic complications. Other investigators have selectively lowered brain temperature using an extracorporeal system that circulates cold blood or other electrolyte solutions through the cerebral vasculature. This cold fluid not only cools the brain, but maintains cerebral circulation with a nonnutra-

Data are mean±SEM. n=5 for each group.

Table 3. Arterial pH, Plasma Glucose Concentration, and Hematocrit for Dogs in Biopsy Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Arterial pH</th>
<th>Plasma glucose (mg/dl)</th>
<th>Hematocrit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>Control</td>
<td>Cooled</td>
</tr>
<tr>
<td>Rectal</td>
<td>7.36±0.04</td>
<td>7.40±0.02</td>
<td>124±4</td>
</tr>
<tr>
<td>Biopsy</td>
<td>7.40±0.04</td>
<td>7.42±0.03</td>
<td>128±2</td>
</tr>
</tbody>
</table>

Table 4. Rectal and Brain Temperatures for Dogs Before, During, and After Cardiac Arrest

<table>
<thead>
<tr>
<th>Temperature</th>
<th>Before lavage</th>
<th>During arrest</th>
<th>During resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>40.1±0.4</td>
<td>39.6±0.4</td>
<td>38.4±0.5*</td>
</tr>
<tr>
<td>Biopsy</td>
<td>40.4±0.3†</td>
<td>39.3±0.3</td>
<td>38.5±0.2*†</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>38.8±0.4</td>
<td>38.6±0.3†</td>
<td>34.2±0.3*</td>
</tr>
<tr>
<td>Biopsy</td>
<td>38.7±0.3†</td>
<td>37.4±0.2</td>
<td>33.0±0.4*</td>
</tr>
<tr>
<td>Hippocampus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recovery</td>
<td>39.1±0.4</td>
<td>38.8±0.2</td>
<td>32.7±0.4*</td>
</tr>
<tr>
<td>Biopsy</td>
<td>39.5±0.5</td>
<td>38.7±0.3</td>
<td>32.8±0.6*</td>
</tr>
</tbody>
</table>

Data are mean±SEM.

* p<0.05, 0.01, respectively, different from corresponding group before lavage by paired t test.
† p<0.05, 0.01, respectively, different from control within protocol by Student’s t test.
‡ p<0.05 different from corresponding group in biopsy protocol by Student’s t test.
tive and presumably inert fluid. The potential protective effects of this extracorporeal circulation have not been evaluated independently and therefore complicate any comparison with our results.

In our study, both 24-hour survival and neurologic deficit tended to be more severely compromised in the control dogs receiving nasal lavage than in control dogs from a previous study that did not receive nasal lavage. There are two likely explanations: better maintenance of brain temperature during cardiac arrest in the body-temperature-nasal-lavage group, and marked transient, postsischemic hyperglycemia. Regardless of the mechanism for the lactate analyses.

The authors are grateful to Susan M. Rinaldi, Patricia M. O’Halloran, Thomas G. Squicciarini, and Douglas Zwemer for their excellent technical assistance and to Linda Annesley and Dennis Martin, PhD, of the Biochemistry Core Facility of the Michigan Diabetes Research and Training Center for the lactate analyses.

Acknowledgments

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