POSTISCHEMIC HYPERTHERMIA EXACERBATES NEUROLOGIC INJURY AFTER DEEP HYPOTHERMIC CIRCULATORY ARREST

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Background: Aggressive surface warming is a common practice in the pediatric intensive care unit. However, recent rodent data emphasize the protective effect of mild (2°-3°C) hypothermia after cerebral ischemia. This study evaluates different temperature regulation strategies after deep hypothermic circulatory arrest with a survival piglet model. **Methods:** Fifteen piglets were randomly assigned to 3 groups. All groups underwent 100 minutes of deep hypothermic circulatory arrest at 15°C. Brain temperature was maintained at 34°C for 24 hours after cardiopulmonary bypass in group I, 37°C in group II, and 40°C in group III. Neurobehavioral recovery was evaluated daily for 3 days after extubation by neurologic deficit score (0, normal; 500, brain death) and overall performance category (1, normal; 5, brain death). Histologic examination was assessed for hypoxic-ischemic injury (0, normal; 5, necrosis) in a blinded fashion. **Results:** All results are expressed as mean $\pm$ standard deviation. Recovery of neurologic deficit score (12.0 ± 17.8 , 47.0 ± 49.95 , 191.0 ± 179.83 ; $P = .05$ for group I vs III), overall performance category (1.0 ± 0.0 , 1.4 ± 0.6 , 2.8 ± 1.3 ; $P < .05$ for group I vs III), and histologic scores (0.0 ± 0.0 , 1.0 ± 1.2 , 2.8 ± 1.8 ; $P < .05$ for group I vs III cortex) were significantly worse in hyperthermic group III. These findings were associated with a significantly lower cytochrome aa₃ recovery determined by near-infrared spectroscopy in group III animals ($P = .0041$ for group I vs III). No animal recovered to baseline electroencephalographic value by 48 hours after deep hypothermic circulatory arrest. Recovery was significantly delayed in the hyperthermic group III animals, with a lower amplitude 14 hours after the operation, which gradually increased with time ($P < .05$ for group III vs groups I and II). **Conclusions:** Mild postischemic hyperthermia significantly exacerbates functional and structural neurologic injury after deep hypothermic circulatory arrest and should therefore be avoided. (J Thorac Cardiovasc Surg 1998;116:780-92)

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The importance of maintaining normothermia has been a fundamental premise in the neonatal and cardiac intensive care unit for many years. This has led to the application of aggressive surface rewarming for even modest degrees of hypothermia, such as occurs frequently, for example, after hypothermic cardiopulmonary bypass (CPB). However, the benefits and risks of this practice have not been thoroughly studied in patients who have sustained a hypoxic-ischemic insult, such as hypothermic circulatory arrest. Furthermore brain temperature has been reported to increase after cerebral ischemia, despite normal ambient and core body temperature.¹⁻³ Such hyperthermic episodes have been implicated in the exacerbation of neurologic injury.⁴ Recently, several rodent studies have suggested that mild hypothermia (2°-3°C) introduced early after

ischemic injury to the brain provides a neuroprotective effect.⁵⁻⁷ In addition, the beneficial effects of some neuroprotective agents have been found to be related to their induction of hypothermia.⁸

Methods

Experimental preparation. Details of the surgical instrumentation in the survival piglet model have been described elsewhere.⁹ Five-week-old Yorkshire piglets weighing 9.1 ± 1.1 kg were sedated with intraperitoneal methohexital sodium (45 mg/kg) and intubated with a 5F endotracheal tube. Each animal was supported with a pressure control ventilator (Healthdyne model 105; Healthdyne Technologies, Marietta, Ga) at a peak inspiratory pressure of 20 cm H₂O, an inspired oxygen fraction of 21%, and a rate of 12 to 13 breaths/min to achieve normal pH and arterial carbon dioxide tension. Cutaneous electroencephalographic leads were then placed and secured with collodion, and electroencephalographic recording was started. After an intravenous bolus of fentanyl (25 µg/kg) and pancuronium (0.2 mg/kg), anesthesia was maintained with a continuous infusion of fentanyl (25 µg/kg/h), midazolam (0.2 mg/kg/h), and pancuronium (0.2 mg/kg/h) throughout the entire experiment and for 24 hours after the operation except during the period of deep hypothermic circulatory arrest (DHCA). A 1-mm diameter brain temperature probe was implanted randomly in the left or right posterior lateral cerebral hemisphere through a small burr-hole incision. Precautions were taken to ensure that the temperature probe was consistently placed 3 cm from the midline and 2 cm deep in the parietal cortex in each animal. Esophageal and rectal temperatures were monitored simultaneously throughout the entire experiment. A pair of near-infrared spectroscopic (NIRS) fiber-optic optodes were secured to the head with collodion over the frontal lobes, with an interoptode distance of 3 cm. Baseline electroencephalographic and NIRS tracings were recorded during 10 minutes before surgical instrumentation while the animal was maintained at an esophageal temperature of 37.0° to 37.5°C.

All surgical procedures were performed under sterile conditions. Arterial blood pressure was monitored before the operation and for 24 hours after the operation by cannulation of a superficial branch of the left femoral artery. The right femoral artery was then exposed in preparation for CPB arterial cannulation. A right anterolateral thoracotomy was performed in the third intercostal space to prepare the right atrium for venous cannulation. After systemic heparinization (300 IU/kg), an 8F arterial cannula (Medtronic Bio-Medicus, Minneapolis, Minn) and 24F venous cannula (Bard, Inc, USCI Division, Billerica, Mass) were inserted into the right femoral artery and right atrium, respectively. All animals underwent 30 minutes of cooling to 15°C and 100 minutes of DHCA, followed by 40 minutes of reperfusion. The extent of rewarming was determined according to the protocol assigned in a random fashion. Intravenous protamine (5 mg/kg) was administered after rewarming and weaning from CPB. After decannulation and closure of all incisions, all animals were mechanically ventilated for 24 hours, fully sedated, and par-

alyzed while the core temperature was regulated by a warming-cooling blanket, room temperature, a heating lamp, or all 3 to achieve the desired cerebral temperature determined by the experimental protocol.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH publication No 86-23, revised 1985).

Experimental groups. Fifteen piglets ($n = 5$ animals/group) were randomly assigned to 3 groups. In group I the brain temperature was maintained at 34°C, in group II at 37°C, and in group III at 40°C after CPB and for 24 hours after the operation.

CPB. The CPB circuit consisted of a roller pump (Cardiovascular Instrument Corp, Wakefield, Mass), sterile tubing (Oslo Medical Sales, Inc, Ashland, Mass) with a 40-µm arterial filter (Pediatric extracorporeal blood filter; PALL Biomedical, Inc, East Hills, NY), and a membrane oxygenator (VPCML plus; COBE Cardiovascular, Inc, Arvada, Colo). The priming solution was identical in all 3 groups and consisted of fresh heparinized blood obtained from a donor animal harvested on the same day of operation and diluted with crystalloid solution (Normosol, pH 7.4) to achieve a hematocrit value of 25%. Cefazolin sodium (25 mg/kg), methylprednisolone sodium succinate (30 mg/kg), furosemide (0.25 mg/kg), and sodium bicarbonate (10 mL) were added to the prime. After baseline recording of all parameters was completed, systemic heparinization, cannulation, and connection of the CPB circuit were carried out. CPB was initiated at a flow rate of 100 mL/kg/min with the pH-stat strategy. Esophageal temperature was cooled to 15°C during 30 minutes before establishment of CPB.

Furosemide (0.2 mg/kg), mannitol (0.5 g/kg), and sodium bicarbonate (10 mL) were administered into the pump immediately on reperfusion. Each animal was warmed during 40 minutes at a flow rate of 100 mL/kg/min to achieve a brain temperature determined by the protocol. The heart was defibrillated as necessary at 25°C, and blood was transfused to keep the hematocrit value at least 25% in all groups. Mechanical ventilation was restarted 10 minutes before weaning from CPB with 100% inspired oxygen fraction. When hemodynamic stability was confirmed, each animal was taken off CPB and decannulated, and intravenous protamine was administered. All incisions were closed under sterile conditions. Continuous NIRS and electroencephalographic data were recorded for 3 hours and for 48 hours, respectively, after the operation.

Postoperative management. All animals were monitored hemodynamically and remained fully sedated, paralyzed, and mechanically ventilated for the first 24 hours after the operation, at which time chest tubes were removed and the animals were weaned and extubated. Maintenance intravenous fluid was administered through the first postoperative day (POD), and additional fluid was given to keep the hematocrit value above 25%.

Table I. Experimental conditions

	Group I (mean $\pm$ SD)	Group II (mean $\pm$ SD)	Group III (mean $\pm$ SD)	P values (I vs II)	P values (I vs III)	P values (II vs III)
Preoperative body weight (kg)	9.0 $\pm$ 1.1	9.5 $\pm$ 1.4	8.7 $\pm$ 1.7	.56	.76	.38
Hematocrit (%)						
On CPB	25.0 $\pm$ 1.6	25.0 $\pm$ 2.2	25.6 $\pm$ 2.1	1.00	.64	.64
Rewarming	26.8 $\pm$ 2.8	25.8 $\pm$ 2.3	26.8 $\pm$ 2.5	.88	.56	.47
3 h off CPB	26.8 $\pm$ 2.8	26.6 $\pm$ 1.1	25.2 $\pm$ 1.6	.88	.22	.28
24 h off CPB	26.2 $\pm$ 1.3	29.0 $\pm$ 2.6	29.6 $\pm$ 3.9	.14	.08	.74
Esophageal temperature ($^{\circ}$ C)						
Baseline	37.3 $\pm$ 0.7	37.0 $\pm$ 0.7	37.5 $\pm$ 1.4	.67	.78	.48
DHCA	16.0 $\pm$ 1.5	16.0 $\pm$ 1.7	15.2 $\pm$ 2.3	.99	.53	.52
40 min rewarming	33.3 $\pm$ 1.6	36.0 $\pm$ 0.8	37.5 $\pm$ 1.1	.004*	.0001*	.07
3 h off CPB	32.8 $\pm$ 0.9	35.9 $\pm$ 1.0	37.6 $\pm$ 1.3	.0006*	.0001*	.03
24 h off CPB	35.6 $\pm$ 1.3	36.2 $\pm$ 0.3	38.8 $\pm$ 0.4	.21	.0001*	.0003*
Rectal temperature ($^{\circ}$ C)						
Baseline	36.6 $\pm$ 1.1	36.6 $\pm$ 0.8	37.6 $\pm$ 1.0	.97	.15	.14
DHCA	20.3 $\pm$ 3.8	18.4 $\pm$ 1.1	19.6 $\pm$ 1.8	.25	.66	.47
40 min rewarming	29.9 $\pm$ 3.2	34.1 $\pm$ 2.3	34.5 $\pm$ 2.3	.02	.016*	.82
3 h off CPB	32.1 $\pm$ 1.2	35.2 $\pm$ 1.0	37.5 $\pm$ 1.6	.002*	.0001*	.16
24 h off CPB	34.3 $\pm$ 1.9	35.1 $\pm$ 1.0	38.0 $\pm$ 0.9	.38	.0009*	.0048*
Brain temperature ($^{\circ}$ C)						
Baseline	38.3 $\pm$ 0.7	37.8 $\pm$ 0.8	38.5 $\pm$ 0.9	.32	.68	.17
DHCA	16.6 $\pm$ 2.0	15.9 $\pm$ 1.9	17.9 $\pm$ 0.5	.51	.23	.08
40 min rewarming	34.7 $\pm$ 0.6	36.9 $\pm$ 1.2	37.6 $\pm$ 2.3	.04	.01*	.49
3 h off CPB	34.0 $\pm$ 0.5	36.8 $\pm$ 0.3	38.9 $\pm$ 1.2	.002*	.0001*	.001*
24 h off CPB	36.0 $\pm$ 2.1	37.9 $\pm$ 0.9	40.0 $\pm$ 0.6	.05	.0006*	.03
Blood pressure (mm Hg)						
On CPB	67.2 $\pm$ 17.0	63.6 $\pm$ 23.0	61.0 $\pm$ 6.0	.74	.57	.81
40 min rewarming	82.2 $\pm$ 23.1	90.4 $\pm$ 11.7	79.8 $\pm$ 22.6	.53	.85	.41
3 h off CPB	91.4 $\pm$ 11.4	95.4 $\pm$ 14.1	88.6 $\pm$ 20.9	.70	.79	.51
24 h off CPB	78.6 $\pm$ 11.7	77.8 $\pm$ 19.1	79.0 $\pm$ 7.2	.93	.96	.89
Heart rate (beats/min)						
Baseline	154.8 $\pm$ 36.7	144.2 $\pm$ 15.8	154.4 $\pm$ 20.8	.53	.55	.98
3 h off CPB	131.4 $\pm$ 12.3	126.4 $\pm$ 19.2	146.8 $\pm$ 38.7	.77	.37	.24
24 h off CPB	135.4 $\pm$ 15.7	163.6 $\pm$ 22.9	161.6 $\pm$ 23.4	.06	.07	.08

* $P < .0167$ is statistically significant by ANOVA and Bonferroni.**Data collection**

Body weight. Baseline body weight was recorded before the operation. Weight measurements were repeated 3 hours, 24 hours, and 4 days after the operation.

Bioelectric impedance index. The total body water content (TBWC) was estimated by the bioelectric impedance (BEI), where $TBWC \propto Height^2/BEI$ was calculated by the following equation: $BEI = (Resistance^2 + Reactance^2)^{1/2}$. BEI (resistance) has a reciprocal relation with TBWC because of higher conductivity of water in the biologic system. The resistance and reactance were measured immediately before and repeated at 3 hours, 24 hours, and 4 days after the operation.

Blood analysis. Blood samples were collected before the operation and 24 hours after the operation. Complete blood cell count and biochemical tests for electrolytes, aspartate transaminase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphate, creatine kinase, total bilirubin, and blood urea nitrogen were measured.

Electroencephalographic analysis. A baseline electroen-

cephalogram was recorded 10 minutes before the operation and for 48 hours after the operation. The amplitude and frequency at 14 and 48 hours, as well as seizure activity, were evaluated and compared between groups by a trained electroencephalographer. Seizures were defined by the presence of increased amplitude ($>15 \mu V$), frequency (>30 Hz), and morphologic evolution of the electroencephalographic tracing, as well as the absence of movement artifact or voluntary motor activities on the monitor screen that lasted longer than 10 seconds.

Near-infrared spectroscopy. Techniques and details of spectroscopic analysis have been established from previous studies and described elsewhere.¹⁰ In brief, NIRS scanning measures relative changes in tissue chromophore concentration with a noninvasive optical method. With the use of appropriate wavelengths, NIRS scanning provides information on the relative concentrations of oxygenated and deoxygenated hemoglobin, as well as the redox state of cytochrome aa₃, which is the terminal enzyme of the electron transport chain.

Table II. Blood analysis

	Group I (mean ± SD)	Group II (mean ± SD)	Group III (mean ± SD)	P values (ANOVA)
AST (U/L)				
Preoperative level	47.2 ± 10.8	56.8 ± 23.4	51.2 ± 22.3	.75
Postoperative level	129.8 ± 48.0	137.4 ± 43.1	163.4 ± 38.5	.46
ALT (U/L)				
Preoperative level	28.4 ± 7.6	35.8 ± 6.5	31.2 ± 14.1	.52
Postoperative level	26.2 ± 4.1	30.6 ± 11.9	23.6 ± 15.8	.64
LDH (U/L)				
Preoperative level	789.0 ± 168.8	821.2 ± 235.4	876.0 ± 362.3	.88
Postoperative level	1233.2 ± 218.7	1128.2 ± 212.0	1114.0 ± 508.8	.84
ALP (U/L)				
Preoperative level	185.6 ± 71.2	215.0 ± 51.0	197.0 ± 68.8	.77
Postoperative level	205.4 ± 33.6	213.4 ± 37.0	226.0 ± 62.5	.78
CK (U/L)				
Preoperative level	847.2 ± 538.5	1280.8 ± 912.2	763.4 ± 392.0	.43
Postoperative level	3433.0 ± 1033.3	3212.8 ± 1252.3	2899.2 ± 1757.3	.83
Total bilirubin (mg/dL)				
Preoperative level	0.2 ± 0.0	0.3 ± 0.1	0.3 ± 0.2	.38
Postoperative level	0.6 ± 0.1	0.6 ± 0.2	0.4 ± 0.2	.10
BUN (mg/dL)				
Preoperative level	11.8 ± 4.1	11.0 ± 3.5	11.0 ± 1.2	.90
Postoperative level	14.6 ± 2.3	13.0 ± 4.5	14.8 ± 5.6	.78
Venous lactate				
Baseline	1.8 ± 0.9	2.2 ± 1.5	1.3 ± 0.3	.46
1 h off CPB	6.6 ± 2.0	7.0 ± 2.9	8.3 ± 4.5	.70
WBC				
Preoperative level	18.4 ± 2.5	17.0 ± 5.7	18.8 ± 5.7	.84
Postoperative level	28.2 ± 10.9	22.3 ± 6.7	32.7 ± 9.1	.23
Platelet (%)				
Preoperative level	665.6 ± 287.1	585.6 ± 239.5	583.4 ± 162.3	.82
Postoperative level	548.4 ± 173.8	417.2 ± 99.7	373.6 ± 66.5	.10

AST, Aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; CK, creatine kinase; BUN, blood urea nitrogen; WBC, white blood cell count.

Neurobehavioral assessment. Neurologic deficit score (NDS; 500, brain death; 0, normal) and overall performance category (OPC; 5, brain death; 1, normal) were used for evaluation of neurologic and behavioral deficits and were carried out by a veterinarian in a blinded fashion. Details of the method have been described elsewhere.⁹ The evaluation was performed on PODs 2, 3, and 4.

Neurohistologic evaluation. Four days after the operation all animals were killed and their brains were fixed in situ with 4% paraformaldehyde. Histologic scoring (0, normal; 5+, necrosis) was performed by a neuropathologist blinded to the experimental protocol.

Statistical analysis. All results are expressed as mean or percentage ± standard deviation (SD) and analyzed by a statistical analysis software package (StatView version 4.5; Abacus Concepts, Berkeley, Calif). Analysis of variance (ANOVA) and Bonferroni correction for multiple comparisons were used to analyze continuous data. Nonparametric Mann-Whitney *U* test was used for data analysis when continuous or normal distribution could not be assumed. With Bonferroni correction, a *P* value lower than .0167 was

required to reach statistical significance between individual groups.

Results

Experimental conditions. The experimental conditions for each group were similar throughout CPB (Table I). There were no statistically significant differences with respect to animal size; brain, esophageal, and rectal temperatures; and hemodynamic parameters before and after CPB among groups. The different brain temperatures in each group corresponded to esophageal temperatures of 33°C, 36°C, and 38.5°C.

Operative results. One animal assigned to group I had severe hypoxia develop before extubation and died 36 hours after the operation. Autopsy revealed severe bilateral pneumonia and pleural effusions, likely caused by aspiration. Another animal in group III was extremely anemic before the operation and died within 6 hours of the operation of persistent hypotension. All

Fig 1. Representative electroencephalographic tracing of seizure in a group III hyperthermic animal.

data from these 2 animals were excluded from analysis. All other 15 animals randomly assigned to the 3 experimental groups survived and were subsequently extubated uneventfully. In 1 animal in group III severe neurologic injury developed; the animal's condition progressively deteriorated, and it died after POD 3. Data from this animal were included in the analysis.

Changes in body weight. There were no differences with respect to the preoperative body weight among the 3 groups. Subsequent changes in body weight are expressed as percentage of baseline $\pm$ SD. At 3 hours after discontinuation of CPB, the changes in percentage body weight were not statistically significant (group I $112.1\% \pm 4.6\%$, group II $113.1\% \pm 4.6\%$, group III $114.9\% \pm 3.5\%$; $P = 0.59$ by ANOVA). At 24 hours after the operation, however, there was a significant change in body weight among groups, with group III animals having a significant increase in body weight compared with group I (group I $109.3\% \pm 1.7\%$, group II $113.6\% \pm 6.3\%$, and group III $117.9\% \pm 3.4\%$; I vs II, $P = .13$; I vs III, $P = .01$; II vs III, $P = .14$ by ANOVA and Bonferroni correction). The differences in body weight decreased with time, and by POD 4 there were no differences between groups. Indeed, group III animals tended to have lower percentage body weight before being killed (group I $104.1\% \pm 1.1\%$; group II $104.8\% \pm 4.3\%$, and group III $102.3\% \pm 5.6\%$; $P = .62$ by ANOVA).

Total body water content. The results are expressed as percentage of baseline $\pm$ SD. There were no differences in BEI among the groups before the operation and 3 hours after CPB (group I $88.3\% \pm 13.9\%$, group II $88.0\% \pm 4.8\%$, and group III $88.4\% \pm 10.2\%$; $P = 0.99$ by ANOVA). At 24 hours group III had a significantly lower BEI than did group I, signifying a higher TBWC (group I $83.9\% \pm 12.5\%$, group II $74.0\% \pm 9.6\%$, and group III $62.9\% \pm 10.8\%$; I vs II, $P = .18$; I vs III, $P = .01$; II vs III, $P = .14$ by ANOVA and

Bonferroni correction). This difference gradually diminished with time, and by POD 4 no differences were seen among groups (group I $82.4\% \pm 21.8\%$, group II $94.8\% \pm 31.9\%$, and group III $96.1\% \pm 21.8\%$; $P = 0.68$ by ANOVA).

Blood analysis. Levels of alanine aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatine kinase, alkaline phosphatase, total bilirubin, and blood urea nitrogen were not significantly different among the 3 experimental groups at baseline and 24 hours after the operation (Table II). Electrolytes, platelet count, and white blood cell count were not statistically different among groups, although there was a tendency toward a higher white blood cell count in groups I and III. No clinical evidence of infection was seen in any of these experimental animals throughout the duration of the study. The hematocrit levels tended to be higher in groups II and III (hematocrit 29.0%) 24 hours after the operation, despite additional fluid administration to maintain hematocrit level in the 26% to 27% range. Nevertheless, no significant differences were observed among the 3 groups.

Electroencephalographic analysis. The baseline electroencephalographic morphologic and other characteristics were similar in all groups, and there were isoelectric brain activities during DHCA (Figs 1 and 2). One animal in hyperthermic group III had 2 episodes of seizure activity about 10 hours after the operation (Fig 1). No animals in other groups had electroencephalographic evidence of seizure. In addition, there was a remarkable delay in the recovery of neuroelectric activity in group III, such that the electroencephalographic amplitude was significantly lower at 14 hours after DHCA (Fig 2). Nevertheless, none of the animals had resumed normal baseline electroencephalographic patterns by 48 hours after the operation. There were no differences in electroencephalographic frequency among the 3 groups before and after DHCA.

Near-infrared spectroscopic analysis. The NIRS patterns (oxyhemoglobin, deoxyhemoglobin, cytochrome aa_3) were similar in all 3 groups during cooling, DHCA, and rewarming from CPB (Figs 3, 4, and 5). In brief, the relative oxyhemoglobin concentration increased during the cooling period and rapidly decreased during DHCA. On reperfusion there was a progressive increase in the oxyhemoglobin signal toward a steady level (Fig 3). Reciprocal changes were observed in the deoxyhemoglobin signals in all 3 groups (Fig 4). The cytochrome aa_3 signal briefly decreased immediately on initiation of CPB and cooling but rapidly declined to a plateau from the onset of DHCA (Fig 5). During rewarming cytochrome aa_3 signals recovered

Fig 2. Mean electroencephalographic amplitude at baseline and at 14 and 48 hours after the operation. * $P < .05$, group I versus group III.

Fig 3. Results of cerebral oxyhemoglobin level by NIRS examination. *DPF*, Differential path length factor. * $P < .05$, group I versus group III.

toward a steady state. No significant differences were observed between groups with respect to the NIRS signals during CPB. After discontinuation of CPB, however, animals in the hypothermic group I had a significantly better recovery of oxyhemoglobin, deoxyhemoglobin, and cytochrome aa_3 levels for at least 3 hours ($P = .02$, $P = .003$, and $P = .01$, respectively, by repeated-measures ANOVA). After correction with Bonferroni test, group I had significantly better preservation of all NIRS parameters than did group III. In contrast to the other 2 groups, the recovery of oxyhemoglobin and cytochrome aa_3 signals in group III remained below baseline levels, whereas deoxyhemoglobin values stayed above baseline

levels.

Neurobehavioral assessment (Figs 6 and 7)

Neurologic deficit score. The NDS was highest (worst) on the first examination at POD 2 and subsequently improved in all groups. An exception was the hyperthermic animal in group III that had neurologic deterioration and died after POD 3; for statistical purposes the highest possible NDS score was assigned to this animal on the last day of the study. The NDS was significantly different among groups on PODs 2 and 3, but the difference was only marginally significant on POD 4 because of the large SD attributable to the single death in group III ($P = .003$, $P = .04$, and $P = .051$,

Fig 4. Results of cerebral deoxyhemoglobin level by NIRS examination. *DPF*, Differential path length factor. * $P < .05$, group I versus group III.

Fig 5. Results of cytochrome aa_3 level by NIRS examination. *DPF*, Differential path length factor. * $P < .05$, group I versus group III.

respectively, by ANOVA). Specifically, hypothermic group I animals had a significantly better neurologic outcome ($P = .001$ and $P = .013$ by Bonferroni correction) than did animals in group III.

Overall performance category. The OPC scoring was worst on POD 2 but progressively recovered toward normal in groups I and II. In group III the OPC remained unchanged or deteriorated with time for all animals. The OPC scores were significantly different among groups on PODs 3 and 4 ($P = .01$ and $P = .01$, respectively, by ANOVA). Specifically, hypothermic group I had a better OPC score than did hyperthermic group III at 3 and 4 days after the operation ($P = .004$ and $P = .005$, respectively, by Bonferroni correction).

Neurohistologic evaluation. Neuropathologic injury was evaluated as in previous studies (Fig 8).⁹ Evidence of hypoxic-ischemic injury was indicated by the presence of hypereosinophilic shrunken neurons with karyorrhectic nuclei. Only the hemisphere contralateral to the site of temperature probe insertion was scored histologically, however, because the ipsilateral hemisphere may have had potentially traumatic damage related to the probe. Two sham-treated animals were subjected to the insertion of a brain temperature probe followed by full heparinization that lasted for the duration of experimental protocol. These 2 animals had completely normal neurobehavioral scores and no histologic injury found in the contralateral hemisphere after 4 days.

Fig 6. NDS on PODs 2, 3, and 4. * $P < .05$, group I versus group III.

Fig 7. OPC on PODs 2, 3, and 4. * $P < .05$, group I versus group III.

The hypoxic-ischemic histologic injury was mild in groups I and II, and no statistically significant differences were seen between these 2 groups. Histologic scores were significantly worse in the cortical area between group I versus group III ($P = .04$ by Mann-Whitney U test); in the hippocampus between group I versus group III and group II versus group III ($P = .01$ and $P = .01$, respectively); and in the dentate gyrus area between group I versus group III ($P = .047$).

Discussion

This study examined the effects of various postischemic cerebral temperature strategies after a period of

DHCA in a survival piglet model. Postischemic hyperthermia caused significantly worse recovery of cerebral hemoglobin oxygenation and the redox state of cytochrome aa_3 . Hyperthermia was associated with persistent deterioration of neurobehavioral outcome. Fourteen hours after the operation, the electroencephalographic amplitude in hyperthermic animals was significantly lower than in the other 2 groups. Electroencephalographic seizures were seen only in the hyperthermic group. Histologic assessment confirmed the adverse effects of fever and demonstrated severe injury in the cortical and hippocampal areas. Gains in body weight and TBWC were significantly greater in ani-

Fig 8. Histologic scores for neocortex, hippocampus, dentate gyrus, and caudate nucleus. * $P < .05$, group I versus group III. # $P < .05$, group II versus group III.

mals subjected to hyperthermia after operation, suggesting diffuse body edema formation. The decreasing body weight of the group III animals by POD 4 probably reflected the severity of neurologic impairment that most of these hyperthermic animals had, which prevented them from drinking.

Postischemic hypothermia (brain temperature 34°C) resulted in a significantly improved outcome relative to hyperthermia but not relative to a brain temperature of 37°C. There was, however, a consistent trend toward improved neurobehavioral and histologic outcomes with hypothermia. Also, it should be noted that esophageal temperature tended to be 1°C less than brain temperature and rectal temperature 2°C less than brain temperature.

In the experimental animals the distribution of injury occurred primarily in the frontal and parietal cortex, with less damage in the occipital and temporal cortices, hippocampus, dentate gyrus, and caudate nucleus. This neuropathologic pattern of neocortical damage was consistently observed in our laboratory and other studies with a large-animal model, in contrast to many other studies in which the hippocampal CA1 region was reported to be most sensitive to ischemic injury.¹¹ This discrepancy may be attributed to the fact that most CA1 data were observed in rodent models in which deep hypothermia and CPB were not used.

The findings of this study have considerable clinical significance because aggressive surface rewarming has evolved as a cornerstone of management in stabilizing neonatal condition in the delivery room and neonatal

intensive care unit, including after cardiac operations. Furthermore, fever is commonly seen after CPB and is often left untreated during the early postoperative period. The findings presented here suggest that these strategies may exacerbate cerebral injury.

Although actual brain temperature after a global cerebral hypoxic-ischemic insult has not been thoroughly investigated in human beings, there have been a number of laboratory studies that suggest that hypoxia-ischemia may alter brain thermal regulation after an insult, to the detriment of neuronal recovery. Colbourne, Nurse, and Corbett¹ showed in a gerbil model that brain temperature recorded after transient ischemia was significantly higher than the median preischemic level, despite maintenance of constant ambient temperature. Others have noted similar postischemic hyperthermia in experimental animals.^{2,12} A recent study from our own laboratory that demonstrated the neuroprotective effect of oligosaccharide Sialyl Lewis^x analog CY-1503 with a survival piglet model also showed by direct measurement that brain temperature was higher in control animals after POD 1 (unpublished data). The mechanism of postischemic cerebral hyperthermia remains unclear. There is some evidence that certain proinflammatory cytokines are elevated after hypoxia-ischemia.¹³ These cytokines may affect the hypothalamic neurons that regulate temperature by elevating the thermal set-point.

The implications of this study for the management of patients not undergoing DHCA remain unclear, although suggestions of the potential deleterious effect of cerebral hyperthermia after CPB in the adult population have

recently been reported.¹⁴ In a randomized prospective study of 150 adult patients undergoing coronary artery bypass grafting, there was a tendency toward worse neuropsychologic outcome among patients who were weaned from CPB at a warmer nasopharyngeal temperature.¹⁵ These authors reported significantly worse visual reproduction subset of the Weschler memory scale at 3 months if the core temperature was rewarmed above 38°C during weaning from CPB.

Hyperthermia increases cerebral metabolic demands. If this occurs in the early postischemic period, when neurons are particularly vulnerable, it may precipitate neuronal cell death. The NIRS result in this study supports a hypothesis of early postischemic hypoxic stress. During the post-CPB phase, the oxyhemoglobin level was significantly lower and there was a concomitant increase in deoxyhemoglobin signal in hyperthermic group III animals. Also, the cytochrome aa₃ level was significantly reduced during the first 3 hours after CPB in the hyperthermic group with respect to the other 2 groups. The correlation of brain energy levels determined by magnetic resonance spectroscopy with cytochrome aa₃ measured by NIRS scanning and their correlation with neurologic outcome have been demonstrated previously in our laboratory.¹⁰

Previous studies have suggested mechanisms other than hypoxic stress through which hyperthermia exacerbates ischemic brain injury. Blood-brain barrier permeability is increased by normothermic or hyperthermic brain temperature after brain ischemia.¹⁶ The significant increase in body weight and TBWC may also reflect the potential for severe brain edema in the hyperthermic group.

Protective effects of mild hypothermia. Many investigators have demonstrated a significant reduction in histologic injury in the hippocampal CA1 area with mild (2°-3°C) postischemic hypothermia in survival rodent models. Chopp and associates¹⁷ found significant CA1 preservation after 8 minutes of ischemia in rats by immediate postischemic cooling for 2 hours to 34°C. Carroll and Beek¹⁸ were able to reduce CA1 loss after ischemia in gerbils at 4 days' survival by hypothermia applied either immediately or 1 hour after the insult but not 3 hours after the insult. Coimbra and Wieloch¹⁹ found significant CA1 preservation at 7 days in rats given 5 hours of delayed postischemic hypothermia at 33°C. These authors also showed that a 3.5-hour cooling period was much less effective than 5 hours, and 30 minutes was completely ineffective when started 2 hours after the insult. Although the optimal hypothermic therapy is not evident from these studies,

it is probable that the neuroprotective effect depends on the duration of the ischemic insult, the extent and duration of postischemic hypothermia, and the delay in initiation after the injury. Mild hypothermia is preferable because the side effects of cooling became more prevalent when the temperature drops below 30°C.

Optimal duration and timing of postischemic hypothermia. Colbourne and Corbett⁵ have shown that increasing the duration of postischemic hypothermia at 32°C from 12 hours to 24 hours produced greater neuroprotection. Nurse and Corbett²⁰ have also demonstrated neurohistologic protection after several days of mild hypothermia induced by a pharmacologic agent.

The timing of initiation of hypothermia is also critical. A number of animal studies have examined the effect of different intervals of postischemic normothermic recirculation before initiation of hypothermia. These studies demonstrated that postischemic hypothermia is of greatest benefit in attenuating the extent of brain injury when initiated shortly after injury and that efficacy decreases with increasing delay of initiation.⁵⁻⁷ Colbourne and Corbett⁵ have demonstrated a 90% preservation of CA1 neurons and reduced neurologic deficits after 30 days when 24 hours of hypothermia at 32°C was initiated 1 hour after ischemia, an insult that produced more than 95% cell loss without intervention. They further demonstrated in a similar study that such intervention provided persistent neuroprotection after 6 months, although the protection was less effective than that at 3 months.²¹ In studies with a repetitive cerebral ischemic gerbil model, Shuaib and coworkers⁶ also suggested that to be effective hypothermia must be initiated as soon as possible after the insult, because cooling at ½ hour or longer after repetitive injury produced no protection compared with control subjects.

Mechanisms of postischemic hypothermic neuroprotection. Indirect evidence indicates that modest hypothermia (core temperature 30°-31°C) exerts a protective effect on the development of ischemic edema and decreases the early postischemic elevation in leukotriene B₄, an arachidonate metabolite related to the development of edema.²² Ischemia has also been implicated in the inhibition of calcium ion-regulated enzyme systems such as calcium-calmodulin-dependent protein kinase II and protein kinase C, which are integrally involved in mediating neuronal excitability and neurotransmitter synthesis and release. Hyperthermia potentiates the reduction in protein kinase C and calcium-calmodulin-dependent protein kinase II, whereas modest hypothermia attenuates ischemia-induced inhibition of these important enzyme systems.^{23,24}

The quantitative relationship between brain temperature and energy use rate was demonstrated in vivo by Laptook and associates²⁵ with phosphorus 31 and proton nuclear magnetic resonance spectroscopy. They showed that brain temperature correlated inversely with phosphocreatine and intracellular pH, such that higher cerebral temperature reduces phosphocreatine and intracellular pH under nonischemic conditions. Brain temperature and energy use rate were directly correlated in a linear fashion. A reduction of brain temperature by 1°C was associated with a decline in energy use rate of 5.3%, which suggests a potential mechanism for the contribution of modest hypothermia to neuroprotection in this study. Thoresen and coworkers²⁶ further substantiated this hypothesis with phosphorus 31 nuclear magnetic resonance spectroscopy by showing that postischemic hypothermia significantly attenuated delayed energy failure for 3 days in piglets subjected to ischemic injury of the brain. Hypothermia thus reduces both the cerebral demand needed to sustain electrophysiologic and synaptic activity and the energy requirement necessary for intrinsic cellular support and membrane homeostasis.

Free radical-mediated cell damage represents another potential mechanism of reperfusion cell injury, although direct measurement of free radicals is difficult. Karibe and colleagues²⁷ showed a greater reduction of the endogenous antioxidants ascorbate and glutathione in rat cortex subjected to normothermic than hypothermic injury. This suggests higher free radical activity in the normothermic group.

Conclusions

This study demonstrates the dangers of postinsult hyperthermia and suggests possible beneficial effects of mild hypothermia. In light of these findings, the routine practice of aggressive rewarming and tolerance of fever in neonates after an insult such as a cardiac arrest or DHCA should be reconsidered. Maintenance of a controlled degree of mild hypothermia for as long as 24 hours after any hypoxic-ischemic cerebral insult may be beneficial for the infant at risk for brain injury.

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Discussion

Dr Julie A. Swain (*Lexington, Ky*). I congratulate you on another in a series of investigations answering fundamental questions in cardiac surgery. You have correlated anatomic, physiologic, and behavioral parameters in an elegant study.

As Professor Taylor emphasized earlier at this meeting, most patients undergoing CPB have demonstrated brain abnormalities. Those of us performing research on circulatory arrest models view circulatory arrest as a worst-case subset of brain injury after cardiac operations. Your study illustrates how we can use DHCA experiments to help us in all our cardiac operations.

You have emphasized that the operation is not over when the bandages are on. We can profoundly influence the ultimate course of patients with modifications of the care in the intensive care unit. It is well known that there is an ischemic penumbra (border zone) in the brain and spinal cord that is vulnerable for some time after the operation. There is no question that the border zone exists; the question is how long we have the opportunity to modify the environment.

I have 3 questions. Current investigations question whether postevent hypothermia simply delays the appearance of injury. You studied the animals for 4 days, during 1 of which the animals were hypothermic. Do you think that you might

have missed further injury? Many studies show that apoptosis occurs as long as 10 days after ischemia.

My second question asks how the results of this study have changed the daily practice of clinical medicine in your institution. Do you keep the patients hypothermic for 24 hours? If so, at what temperature?

My final question is whether you have considered reanalyzing the Boston Children's Study data for the effect of postoperative systemic temperature on the ultimate neurologic outcome? Because this study contains a wealth of carefully collected data, these retrospective results might be interesting.

Again, I congratulate you on an excellent study that will have wide-ranging implications for the postoperative care of patients.

Dr Shum-Tim. Your first question was whether postischemic hypothermia actually provided permanent protection or just delayed neurologic injury. I think, as you mentioned, that this question creates a difficult logistic problem because of the expense and the duration of the study and the question of how to define long-term results in the animals. I can quote you some of the data available from rodents in which the gerbil model was studied for as long 6 months and both neurobehavioral and pathologic protection were seen in the rodents exposed to postischemic hypothermia compared to the control group. However, it is important to emphasize, even in the rodent model, that although the 6-month result was significantly better than that in the control group there was still significant deterioration between 3 months and 6 months. Furthermore, even if in the worst case hypothermia does not provide permanent protection but simply delays cerebral injury, this may nevertheless provide a window of opportunity for some other resuscitative agents that could be applied, such as a pharmacologic agent.

Your second question was about what we do clinically. This study has certainly sensitized my own experience. Since I went back to Montreal a couple of months ago, we have alerted our intensive care nurses to pay strict attention to the rectal temperature, especially because the brain temperature is actually much higher than the esophageal or rectal temperature and we therefore tend to underestimate the degree of hyperthermia. In my experience at Boston Children's we also did that clinically, and I remember that it is almost an institutional protocol that none of our patient's rectal temperature is allowed to go above 38°C immediately after the operation. Particularly with patients who were in hemodynamically unstable condition or who had a cardiac arrest and were put on extracorporeal membrane oxygenation, we made an effort to perfuse these patients under extracorporeal membrane oxygenation at the relatively lower temperature of 35° to 36°C. This is my personal experience working with Dr Jonas at Boston Children's, and I am sure that investigation will greatly influence my own practice, and I hope that of my institution.

In response to the last question, we have not gone back to retrospectively analyze temperature data from the cohort of patients that Dr Jonas and Dr Newburger described in the *New England Journal of Medicine*. I agree that this is an interesting question.

Dr David A. Murphy (*Halifax, Nova Scotia, Canada*). It is a number of years since I qualified in veterinary medicine, in 1956, to be exact, but at that time we were taught that the normal pig temperature was 39°C (102.2°F). In your group III you have said that these piglets were kept at 39°C and designated them as hyperthermic, but if things have not changed since 1956 with respect to the normal pig temperature, would that influence your interpretation of your results? In other words, are all the pigs in groups I and II hypothermic and are the group III pigs actually normothermic?

Dr Shum-Tim. If I remember correctly, a temperature as high as 39°C is acceptable for the lamb. I do not recall in any of our animal models, at least for the past 3 years that I have worked with Dr Jonas in the laboratory, a regular temperature in our piglets as high as 39°C.

Dr Shunji Sano (*Okayama, Japan*). I think that brain protection is the major issue in the next century, and I think that better protection of the brain is to perfuse the brain during arch repair. For this reason, not only am I but also some of the Japanese younger surgeons are now using brain perfusion during arch repair, such as coarctation complex and hypoplastic aortic arch repairs, so that we can avoid circulatory arrest to the brain in older patients. I have done procedures on more than 20 patients, and we have had no neurologic insult so far.

My question is whether you checked the electroencephalographic and also neurologic examination results in the patient with mild to moderate hypothermia, no use of deep hypothermia, and circulatory arrest? For such a patient, do you still think that it is worthwhile to put the patient in mild hypothermia, not normothermia, after the operation?

Dr Shum-Tim. First I would like to emphasize that, as Dr Swain emphasized earlier, that our model uses the worst possible insult by creating a long DHCA; however, I am not sure whether CPB alone can create this kind of injury.

In my own experience, 2 of our patients operated on in the intensive care unit last week had no circulatory arrest for tetralogy of Fallot repair at 3 months old and for multiple ventricular septal defect closure at 3 years old. By the time

we operated on our second patient, we were called by the intensive care unit to tell us that the temperature had gone up to 40°C, even though there was not any circulatory arrest. What is the significance of that for the brain? Does it have the same implication as after DHCA? I do not know. Even if you use retrograde cerebral perfusion or other cerebral protection, I am not sure that we are completely immune from this kind of a problem.

In our experimental model, in the first 2 groups the electroencephalographic and the neurobehavioral recoveries were not perfect, particularly in the first 2 days. In view of the fact that they were in severe DHCA for 100 minutes, I would not expect them to have normal values; however, I would expect recoveries to be better than in the hyperthermic group.

Dr Sano. My cerebral perfusion is not retrograde. I do perfuse from the innominate artery and use antegrade perfusion all the time, and I do the whole operation between 25° and 30°C, because the electroencephalographic result is always normal.

Dr Shum-Tim. In the example I gave of my 2 clinical patients who had CPB alone, they also had antegrade perfusion, but they also had a temperature of 40°C. I do not know how we explain that, and I cannot say at this point whether it has any relationship to DHCA.

Dr Thomas L. Spray (*Philadelphia, Pa*). This is not by any means an area of my expertise, but it strikes me that you really have a model of injury here and that, with a flow rate of 100 mL/kg/min and warming to 39°C from 25°C, much of the ischemic damage to the brain may be occurring because of inadequate flow at high temperatures during the rewarming period. If you look at your graphs on cytochrome aa₃ and the deoxyhemoglobin curves, much of the changes that were seen late were already apparent at the end of the rewarming period and then were relatively stable after that. How do you know that there is actually ongoing damage after the period of rewarming?

Dr Shum-Tim. Your point is valid. Hyperthermia may exacerbate ischemia-reperfusion injury. Unfortunately, we do not have any practical method to separate these issues. Some clinical reports in the adult literature have shown a relatively better neurologic score 3 months down the line in a group of patients who were warmed less aggressively.