SURGERY FOR CONGENITAL HEART DISEASE

pH-STAT COOLING IMPROVES CEREBRAL METABOLIC RECOVERY AFTER CIRCULATORY ARREST IN A PIGLET MODEL OF AORTOPULMONARY COLLATERALS

Cardiopulmonary bypass with deep hypothermic circulatory arrest increases the risk of neurologic injury in patients with aortopulmonary collaterals. Experimental studies have demonstrated that such collaterals decrease the rate of cerebral cooling before arrest and cerebral metabolic recovery after circulatory arrest. Use of pH-stat blood gas management has been shown to increase cerebral blood flow during cooling. The current study was designed to test whether cooling with pH-stat blood gas management can decrease the cerebral metabolic impact of aortopulmonary collaterals. Twenty 4- to 6-week-old piglets underwent placement of a shunt between the left subclavian artery and main pulmonary artery. In control animals ($n = 10$) the shunts were immediately ligated, whereas in the shunt animals ($n = 10$) the shunts were left patent. All animals were supported with cardiopulmonary bypass, cooled to 18° C by means of either alpha-stat (five control and five shunt animals) or pH-stat (five control and five shunt animals) blood gas management, subjected to circulatory arrest for 90 minutes, and rewarmed to 37° C. The cerebral metabolic rate of oxygen consumption (a marker for neurologic function) was significantly lower after circulatory arrest in the shunt animals cooled with alpha-stat blood gas management than in the control animals subjected to alpha-stat management (1.2 ± 0.2 vs 2.3 ± 0.2 ml oxygen per 100 gm/min, $p < 0.05$). By contrast, there was no difference between the pH-stat shunt animals and either control group (2.1 ± 0.2 vs 2.3 ± 0.2 [alpha-stat] and 2.0 ± 0.3 [pH-stat] ml oxygen per 100 gm/min, $p =$ not significant). pH-Stat cooling protected the brain from shunt-related injury. When circulatory arrest is used in the presence of aortopulmonary collaterals, the use of pH-stat blood gas management during cooling results in better cerebral protection than alpha-stat blood gas management. (J THORAC CARDIOVASC SURG 1996;111:147-57)

Paul M. Kirshbom, MD^a (by invitation), Lynne R. Skaryak, MD^a (by invitation), Louis R. DiBernardo, MD^a (by invitation), Frank H. Kern, MD^b (by invitation), William J. Greeley, MD^b (by invitation), J. William Gaynor, MD^a (by invitation), and Ross M. Ungerleider, MD,^a Durham, N.C.

The use of cardiopulmonary bypass (CPB) with or without deep hypothermic circulatory arrest (DHCA) for the repair of congenital cardiac defects has been associated with postoperative neurologic

events of variable severity in up to 25% of cases.¹ Severe choreoathetosis can be one of the most devastating neurologic complications and causes significant morbidity and mortality.^{2,3} The development of postoperative choreoathetosis has been associated with the presence of large aortopulmonary collaterals, particularly collaterals arising from the head and neck vessels.³ The increased neurologic risk associated with aortopulmonary collaterals is likely the result of pulmonary runoff causing an effective reduction in cerebral perfusion. Whether this runoff causes primary cerebral ischemia or impairs cerebral cooling before arrest has not been determined.

From the Departments of Surgery^a and Anesthesiology,^b Duke University Medical Center, Durham, N.C.

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Address for reprints: Ross M. Ungerleider, MD, Duke University Medical Center, PO Box 3178, Durham, NC 27710.

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Fig. 1. Position of aortopulmonary shunt: Polytetrafluoroethylene (4 mm) shunt placed between the left subclavian artery and the main pulmonary artery.

Hypothermia is the most important mechanism used to protect the brain during DHCA; thus any factor that impairs cerebral cooling before arrest increases the likelihood of cerebral injury. Studies of CPB and DHCA in piglets have demonstrated that aortopulmonary collaterals can decrease cerebral perfusion and the rate of cerebral cooling during both surface and core cooling.^{4,5} More importantly, aortopulmonary collaterals have been shown to significantly impair cerebral metabolic recovery after DHCA.⁶

In this study, a piglet model of aortopulmonary collaterals was used to examine the effects of different blood gas management strategies during cooling on cerebral perfusion and metabolic recovery after DHCA. The alpha-stat protocol, in which blood gases are measured at 37° C with no correction for patient temperature, is the most commonly used protocol clinically. In the pH-stat protocol, blood

gases are corrected to the patient's core body temperature and the oxygenator carbon dioxide flow is manipulated to maintain a normal corrected pH and arterial carbon dioxide tension during hypothermia. Alpha-stat blood gas management is more commonly used clinically at this time because cerebral metabolism/perfusion linkage and both intracellular and tissue pH have been shown to be preserved by means of this approach.⁷ pH-Stat blood gas management, on the other hand, markedly increases the arterial carbon dioxide tension, which results in cerebral vasodilatation, increased cerebral blood flow (CBF), and changes in regional CBF distribution.^{8,9} This study was designed to test the hypothesis that the use of pH-stat blood gas management during cooling before DHCA would increase CBF, improve cerebral cooling, and thereby decrease the cerebral injury associated with aortopulmonary collaterals.

Materials and methods

Anesthesia. Twenty 4- to 6-week old DeKalb piglets weighing 9 to 13 kg were premedicated with intramuscular ketamine (20 mg/kg) and acepromazine (1 mg/kg), intubated, and supported with a mechanical ventilator (Sechrist Infant Ventilator, model IV-100B, Sechrist Industries, Inc., Anaheim, Calif.). The piglets were anesthetized and paralyzed with intravenous fentanyl (100 µg/kg bolus and 50 µg/kg per hour infusion) and pancuronium (0.3 mg/kg). The ventilator was set with a positive inspiratory pressure of 25 mm Hg and positive end-expiratory pressure of 3 mm Hg. Respiratory rate and inspired oxygen fraction were titrated to maintain an arterial carbon dioxide tension of 35 to 45 mm Hg and an oxygen tension of 200 to 300 mm Hg. Sodium bicarbonate (8.5%) was used to maintain a base excess between -3 and 3 mmol/L. All animals received methylprednisolone (25 mg/kg intravenously) before the operation.

All experiments were conducted with the approval of the Animal Care and Use Committee of Duke University Medical Center. 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. 85-23, revised 1985).

Shunt placement and instrumentation. A femoral arterial cannula was placed for blood pressure and arterial blood gas monitoring. A left thoracotomy was then performed through the fourth intercostal space. Intravenous heparin (500 U/kg) was administered and a 4 mm polytetrafluoroethylene graft was placed between the subclavian artery and the main pulmonary artery (Fig. 1). All shunts had a palpable thrill and caused a decrease in mean arterial pressure. The animals were then randomized to either the control group, in which the shunts were imme-

Table I. Arterial blood gases and systemic arterial pressures

Group	MAP (mm Hg)	pH	PCO ₂ (mm Hg)	PO ₂ (mm Hg)	Hematocrit (%)
Warm pre-DHCA					
Control-aS	87 ± 12	7.36 ± 0.03	46 ± 2	319 ± 24	19 ± 2
Control-pHS	63 ± 7	7.36 ± 0.02	45 ± 2	300 ± 26	16 ± 1
Shunt-aS	57 ± 5	7.44 ± 0.03	36 ± 3*	377 ± 6	17 ± 1
Shunt-pHS	43 ± 1*	7.42 ± 0.03	37 ± 2*	361 ± 10	17 ± 1
Cold pre-DHCA					
Control-aS	108 ± 5	7.42 ± 0.02	37 ± 2	621 ± 23	19 ± 1
Control-pHS	82 ± 2*	7.11 ± 0.01*	95 ± 2*	540 ± 14	17 ± 1
Shunt-aS	55 ± 5*	7.37 ± 0.03	37 ± 3	708 ± 62	18 ± 1
Shunt-pHS	42 ± 3*	7.02 ± 0.02*	104 ± 7*	701 ± 19	18 ± 1
Warm post-DHCA					
Control-aS	90 ± 7	7.34 ± 0.02	42 ± 2	289 ± 18	21 ± 1
Control-pHS	61 ± 6*	7.35 ± 0.01	43 ± 1	276 ± 6	18 ± 1
Shunt-aS	57 ± 5*	7.39 ± 0.01	35 ± 1*	340 ± 6	20 ± 0.4
Shunt-pHS	47 ± 2*	7.40 ± 0.02	35 ± 2*	312 ± 14	19 ± 1

MAP, Mean arterial pressure; PCO₂, carbon dioxide tension; PO₂, oxygen tension; DHCA, deep hypothermic circulatory arrest; aS, alpha-stat; pHS, pH-stat.
**p* < 0.05 versus control-aS.

diately ligated, or the shunt group, in which the shunts were allowed to remain patent throughout the experiment.

The animals were placed in the supine position and a median sternotomy was performed. Nasopharyngeal (Yellow Springs Instruments, Yellow Springs, Ohio, YSI-400), cortical, and deep brain temperature probes (Shiley Inc., Irvine, Calif., 15 mm and 30 mm myocardial probes) were placed. The cerebral temperature probes were placed 3 to 4 mm lateral to the sagittal suture and anterior to the transverse suture.

CPB and circulatory arrest. Size 10F aortic, 28F right atrial, and 22F left atrial cannulas were placed for CPB and venting of the left atrium in all animals. Left atrial venting was required to prevent left ventricular distention and pulmonary edema in the shunt animals when the heart fibrillated during cooling. The CPB circuit consisted of two Stöckert Shiley roller pumps (Shiley Inc., Irvine, Calif., model 10-10-00) for CPB and venting of the left atrium, a Cobe membrane oxygenator (Cobe Laboratory, Lakewood, Colo.), and a Bio-cal 370 heat exchanger (Medtronic Bio-Medicus, Minneapolis, Minn.). The pump was primed with whole donor blood and normal saline solution at 36° C to maintain a CPB hematocrit value between 18% and 20%. Oxygen and carbon dioxide flows were used to maintain blood gases within the preset limits.

All animals were supported with CPB at a rate of 100 ml/kg per minute and cooled to a nasopharyngeal temperature of 18° C over 20 minutes. The animals were randomized to be cooled with either alpha-stat or pH-stat blood gas management, with five animals in each group. Alpha-stat animals were maintained with an arterial carbon dioxide tension of 35 to 45 mm Hg uncorrected for body temperature, whereas pH-stat animals received supplemental carbon dioxide in the oxygenator gas mixture to maintain the temperature-corrected arterial carbon dioxide tension in the same range. No topical hypothermia was used. After cooling, all of the animals were subjected to circulatory arrest for 90 minutes and then rewarmed to

37° C over 30 minutes. Alpha-stat blood gas management was used during rewarming in all animals. The ventilator was set at a rate of 6 breaths/min during CPB.

Data collection. Data were collected at three time points: warm during CPB before cooling (warm pre-DHCA), at the end of the cooling period (cold pre-DHCA), and during CPB after rewarming (warm post-DHCA). Data collected included arterial and sagittal sinus blood gases, nasopharyngeal, cortical, and basilar brain temperatures, and mean arterial blood pressure. Radioactive microspheres (3 × 10⁶ microspheres, 10 μm, in 1 ml of 10% dextran and 0.01% polysorbates [Tween]) were injected into the aortic cannula at each time point (gadolinium 153, tin 113, ruthenium 103, niobium 95, and scandium 46 in random order; NEN Research Products, DuPont, Wilmington, Del.). During each injection an arterial reference sample was withdrawn at a rate of 7 ml/min over 120 seconds starting 10 seconds before the injection (Continuous Infusion/Withdrawal Device, model 4400-001, Harvard Apparatus Co., Inc., South Natick, Mass.).

The animals were euthanized after the last data point and the brain and lungs were harvested. The brain was subdivided into the cortex, basal ganglia, cerebellum, and brain stem. All tissue and arterial reference samples were counted in a gamma counter (Minaxi Auto-gamma Counter, 5000 Series, Packard Instrument Co., Meriden, Conn.), and individual nuclide activity was calculated (Compusphere Microsphere Multinuclide Analysis Software, Packard Instrument Co.).

Cardiac output was determined by means of the reference organ technique¹⁰ and tissue blood flows were calculated by means of the following equation:¹¹

$$\text{Flow}_T = \text{Flow}_R \times (\text{CPM}_T / \text{CPM}_R)$$

in which Flow_T = tissue blood flow, Flow_R = arterial reference sample withdrawal rate, CPM_T = tissue counts per minute, and CPM_R = arterial reference sample

Fig. 2A. Nasopharyngeal (NP) temperatures during cooling over 20 minutes before circulatory arrest.

counts per minute. Cerebral metabolic rate of oxygen consumption ($CMRO_2$) was calculated from the global CBF and the arterial-sagittal sinus oxygen difference. Tissue blood flow is expressed as milliliters per 100 gm/min and $CMRO_2$ as milliliters of oxygen per 100 gm/min.

The systemic/pulmonary flow ratio was calculated by means of microsphere-derived flows from the first time point as described by Mavroudis and colleagues.⁴

Statistical analysis. Analysis of variance was used to compare data between groups with pair-wise comparison adjusted with the Scheffe method followed by unpaired *t* tests. Comparisons within groups were made by means of paired *t* tests, with correction for repeated measures yielding a *p* value less than 0.025 considered significant. Data are presented as means $\pm$ standard error of the mean.

Results

Table I displays the arterial blood gas values and mean arterial pressures in the four groups at the three time points. The mean arterial pressures of the shunt animals were significantly lower than those of control animals at all time points. No significant differences were noted between the shunt animals. The normothermic arterial carbon dioxide tension was significantly lower in the shunt animals because of the continued pulmonary blood flow and ventilation. Again, there was no difference between the shunt groups.

In control animals, 3% of the injected micro-

spheres were trapped in the lungs. These microspheres represent bronchial flow, systemic-pulmonary collateral flow, and recirculation of microspheres that were not trapped in the systemic capillary beds. This result is similar to the 5% figure reported by Mavroudis and colleagues.⁴ The pulmonary/systemic flow ratio in the shunt groups was $2.0 \pm 0.3:1$ and was not significantly different between the two groups.

Nasopharyngeal and cerebral temperatures. All animals were cooled to a nasopharyngeal temperature of 18° C over 20 minutes. Nasopharyngeal, cortical, and basilar brain temperatures during cooling are displayed in Figs. 2A, 2B, and 2C. The rate of cooling in all regions was slower in the shunt animals than in the control animals, but the nasopharyngeal temperature was not significantly different among the four groups by the end of the cooling period. Although the shunt groups were not distinguishable with regard to nasopharyngeal temperature, the brains of the pH-stat shunt animals cooled more quickly than those of the alpha-stat shunt animals. By the end of the cooling period, there was a trend toward lower temperatures in the cortex and basilar brains of the pH-stat shunt animals than in the brains of the alpha-stat shunt animals. The temperature difference in the basilar brain ap-

Fig. 2B. Cortical temperatures during cooling over 20 minutes before circulatory arrest.

Fig. 2C. Basilar brain temperatures during cooling over 20 minutes before circulatory arrest.

proached statistical significance with a p value of 0.023 by two-tailed unpaired t test. Nasopharyngeal, cortical, and basilar brain temperatures at the end of the cooling period are summarized in Table II.

By the end of the circulatory arrest period, the differences in cerebral temperatures between the shunt groups was even more marked, as displayed in Fig. 3. The cortex of the alpha-stat shunt animals

Fig. 3. Cortical and basilar brain temperature at the end of circulatory arrest in animals with systemic-pulmonary shunts.

Table II. Nasopharyngeal, cortical, and basal brain temperatures after 20 minutes of cooling

	Temperatures (°C)		
	Nasopharyngeal	Cortical	Basal brain
Control-aS	18.1 ± 0.3	20.0 ± 0.4	19.6 ± 0.4
Control-pHS	17.8 ± 0.3	19.6 ± 0.3	19.0 ± 0.3
Shunt-aS	18.5 ± 0.8	21.0 ± 0.6	20.0 ± 0.5
Shunt-pHS	18.1 ± 0.8	19.4 ± 0.6	18.2 ± 0.5

No significant differences between groups by analysis of variance. aS, Alpha-stat; pHS, pH-stat.

was significantly warmer than that of the pH-stat shunt animals ($24.1^{\circ} \pm 0.5^{\circ}$ vs $22.5^{\circ} \pm 0.2^{\circ}$ C, respectively, $p = 0.012$, unpaired t test).

CBF and CMRO₂. Global CBF and CMRO₂ for the three time points are graphically displayed in Fig. 4, A and B. The shunt animals started out with significantly lower CBFs than the control animals. CBF was decreased in all groups after DHCA; however, the pH-stat-treated shunt animals had a smaller decrease in CBF than did the alpha-stat-treated shunt animals. Thus the CBF in the pH-stat shunt group was not different from that of the control animals after DHCA. By contrast, CBF in

the alpha-stat shunt group remained significantly lower than that in the control animals. CMRO₂ followed a similar pattern, with the alpha-stat-treated shunt animals recovering to a significantly lower level than the control animals; by contrast, the CMRO₂ of the pH-stat-treated shunt animals was not different from that of the control animals.

During the cooling period, the use of pH-stat management resulted in significantly higher CBFs in the control animals. In the shunt animals, pH-stat did not result in a significant increase in global CBF compared with that of the group cooled with alpha-stat. The CMRO₂ of all four groups was suppressed to 13% to 18% of baseline before arrest. Cerebral oxygen extraction tended to be higher in the shunt animals, but this difference did not achieve statistical significance at any point and is not shown.

Regional CBFs during CPB before and after DHCA are summarized in Table III. The region that was most significantly affected by DHCA in all groups was the cortex. Blood flow to the cortex of the control pH-stat animals was markedly decreased (63 ± 3 to 28 ± 7 ml/100 gm/min, $p = 0.02$ by paired t test); the control alpha-stat animals had a relatively

Fig. 4. CBF (A) and CMRO₂ (B) warm during CPB before DHCA, after cooling before DHCA, and warm during CPB after DHCA. *aS*, Alpha-stat; *pHS*, pH-stat.

Table III. Regional and global CBF

Time point Groups	CBF (ml/100 gm/min)				
	Cortex	Cerebellum	Basal ganglia	Brain stem	Global
Warm pre-DHCA					
Control-aS	69 ± 6	73 ± 8	67 ± 8	53 ± 5	68 ± 6
Control-pHS	63 ± 3	73 ± 5	68 ± 3	60 ± 4	65 ± 3
Shunt-aS	44 ± 4*	52 ± 6	49 ± 3	39 ± 2	46 ± 4*
Shunt-pHS	46 ± 3*	49 ± 3	49 ± 3	43 ± 4	47 ± 2*
Warm post-DHCA					
Control-aS	42 ± 7	76 ± 7	62 ± 4	56 ± 6	50 ± 5
Control-pHS	28 ± 7†	75 ± 14	63 ± 6	72 ± 13	41 ± 6†
Shunt-aS	16 ± 3†	37 ± 9	43 ± 3*	40 ± 3	23 ± 4*†
Shunt-pHS	33 ± 5†	54 ± 4	43 ± 3*	41 ± 3	37 ± 4†

aS, Alpha-stat; pHS, pH-stat.

* $p < 0.05$ versus control-aS (analysis of variance).† $p < 0.025$ versus warm pre-DHCA (two-tailed paired t test).

smaller decrease (69 ± 6 to 42 ± 7 ml/100 gm/min, $p = 0.04$, paired t test).

Discussion

This study examined the effects of using different blood gas management strategies during cooling on CBF and cerebral metabolic recovery after CPB and DHCA in the presence of aortopulmonary collateral flow. A systemic-pulmonary shunt was found to decrease global CBF, with the largest changes occurring in the cerebral hemispheres. If alpha-stat blood gas management was used during cooling, cerebral metabolic recovery was more impaired in shunt animals than in control animals; however, this shunt-related injury was eliminated if pH-stat blood gas management was used.

Aortopulmonary collaterals have been correlated with an increased risk for postoperative choreoathetosis in children undergoing repair of congenital cardiac defects.³ These children have subsequently been shown to have cortical and subcortical defects by single photon emission computed tomography (SPECT).¹² Animal studies have shown that aortopulmonary collaterals can alter CBF during surface⁴ and core⁵ cooling, and CMRO₂ recovery after DHCA has also been shown to be impaired in a piglet model of aortopulmonary collaterals.⁶ These findings suggest that patients with large aortopulmonary collaterals may be at particular risk for neurologic injury and might benefit from alternative cerebral protection strategies.

One technical aspect of CPB that has elicited much controversy during the past 20 years is blood gas management during hypothermia. The pH-stat strategy has been shown to increase CBF relative to

the alpha-stat strategy in normal animals.⁸ This increased perfusion is believed by some to be advantageous in that it may decrease the possibility of local ischemia and improve cerebral cooling; others maintain that it merely increases the risk of microembolism.¹³ The alpha-stat strategy is believed by many to be advantageous because cerebral metabolism/blood flow coupling is maintained,⁷ so that the brain is allowed to optimize regional CBF to meet metabolic needs. Although numerous studies comparing the physiologic effects of these two strategies, primarily in normal animals, have been published, the question of whether one strategy is superior for patients who are at particular risk for neurologic injury remains unanswered. Given the clinical and experimental data suggesting that aortopulmonary collaterals increase neurologic risk during CPB and DHCA, an animal model of aortopulmonary collaterals was chosen to investigate this question.

This study was designed to test three hypotheses. The first was that the use of pH-stat blood gas management during cooling would increase CBF. This hypothesis was supported in the control animals, but no significant increase in CBF relative to alpha-stat management was observed in the shunt animals. The second hypothesis was that the rate of cerebral cooling would be increased through the use of pH-stat blood gas management. Despite the lack of a significant increase in CBF, there was a trend toward more rapid cerebral cooling in the pH-stat shunt animals. This trend progressed through the circulatory arrest period and resulted in a significantly colder brain in the pH-stat shunt animals by the end of arrest. Finally, the hypothesis that the use of pH-stat blood gas management during cooling

would improve neurologic protection in animals with a systemic-pulmonary shunt was supported by this study.

As with any animal model, interpretation of the results must be tempered by the differences from the clinical scenario. No topical hypothermia was used in this study, and clearly the cerebral warming observed during circulatory arrest would have been decreased had topical cooling been used. Also, the effects of blood gas management on blood flow and cooling rates might not be as great in the clinical setting, because vasodilators such as phentolamine are often used clinically. Although the CPB flow rate of 100 ml/kg per minute was lower than the rate that is typically used in human infants, it was in the physiologic range of normal for piglets of this age. Thus the CPB pump flow equaled or exceeded the baseline cardiac output of the control animals.

The results of this study are interesting in that they support the use of both alpha-stat and pH-stat blood gas management, but in different groups of patients. pH-Stat management was clearly advantageous in the presence of large aortopulmonary collaterals. Despite nearly identical nasopharyngeal cooling in the shunt animals, the brains of the pH-stat shunt animals cooled more rapidly than those of the alpha-stat shunt animals. This discrepancy resulted in a nonsignificant trend toward a colder brain in the pH-stat shunt animals at the end of the cooling period and a significantly colder brain by the end of circulatory arrest. After circulatory arrest, the CBF and CMRO₂ of the pH-stat shunt animals was not different from those values in the control animals; by contrast, the alpha-stat shunt animals had a significantly greater decrease in CBF and CMRO₂ than the control group.

Comparing the two strategies in the control animals, on the other hand, pH-stat did not confer any advantage and, in fact, may have been detrimental. Although the number of animals was too small to achieve statistical significance, there was a trend toward a persistent brain stem hyperemia in the pH-stat animals, with a concomitant decrease in cortical flow. This suggests an intracerebral "steal" phenomenon that theoretically could prove injurious. Because both control groups cooled quickly, the control animals derived no benefit from the use of pH-stat with regard to cerebral cooling.

In conclusion, this study supports the use of pH-stat blood gas management in patients who are at particular risk for cerebral ischemia during CPB and DHCA. These patients would likely benefit

from any strategy that maintains CBF at or above normal levels, thus maximizing cerebral cooling and protection during DHCA. These data also confirm that the use of pH-stat blood gas management changes regional control of CBF in relatively normal animals, which may be disadvantageous for patients with normal baseline cerebral perfusion.

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Discussion

Dr. Richard A. Jonas (*Boston, Mass.*). The authors have demonstrated using their piglet model of DHCA that if a communication is present between the systemic arterial circulation and the pulmonary arterial circulation, then the pH-stat strategy used during core cooling to deep hypothermia can importantly influence cerebral outcome. Like many other centers, we at Children's Hospital in the mid-1980s changed our pH strategy for hypothermic bypass from the more acidotic pH-stat strategy to the more alkalotic alpha-stat strategy.

When we reviewed the cognitive development of children who underwent hypothermic circulatory arrest in this time frame, we found that the alpha-stat strategy was associated with a worse developmental outcome. In addition, beginning in the mid 1980s, we experienced several cases of choreoathetosis. Between 1982 and 1986 there were no cases of choreoathetosis at Children's Hospital, but between 1986 and 1990 there were 11 cases with four deaths. All but one of the 11 children in whom choreoathetosis developed had undergone circulatory arrest and had pulmonary blood flow derived either from large collateral vessels or a systemic-pulmonary arterial shunt. We subsequently studied this issue in the laboratory, also in a piglet model of hypothermic circulatory arrest. Using magnetic resonance spectroscopy, we demonstrated that the pH-stat strategy was associated with more rapid recovery of high-energy phosphates. Like the authors, we were able to demonstrate that the pH-stat strategy is associated with greater cerebral blood flow during the cooling phase relative to the alpha-stat strategy. We were also able to demonstrate redistribution of CBF during cooling when the pH-stat strategy was used. We noted that there was increased CBF to deep subcortical structures such as the basal ganglia relative to the cerebral cortex. Perhaps in some way this may explain the lower risk of choreoathetosis with the pH-stat strategy.

I have two questions. Although you did not demonstrate greater CBF in the pH-stat animals with a shunt relative to the alpha-stat animals with a shunt, the brain temperature was lower. Can you speculate on a possible mechanism for the temperature difference? Second, inasmuch as cerebral metabolic rate is highly temperature-dependent and you observed lower brain temperatures in the pH-stat animals, can you speculate as to why the CMRO₂ was not lower in the pH-stat animals?

Dr. Kirshbom. You asked our opinion on why there was a temperature difference when we did not see a significant increase in CBF in the pH-stat-treated animals. There are a couple of possibilities. First, there was a small but not significant increase in CBF, and that small increase in CBF, cumulative over the entire cooling period, may have cumulatively decreased the temperature. The other explanation, which I tend to favor, is that pH-stat blood gas management may result in a more homogeneously cooled brain. Even though CBF may not be globally increased, the blood flow may be distributed in such a way as to cool the brain more effectively. This theory is supported somewhat by the fact that the temperature differences between the alpha-stat and pH-stat animals were more marked after circulatory arrest, perhaps suggesting that the pH-stat-treated animals were more homogeneously cooled,

whereas the alpha-stat-treated animals tended to redistribute the temperature and rewarm more quickly.

Regarding the second question, I assume you referred to the CMRO₂ at the end of the cooling period. Why CMRO₂ was not further suppressed I cannot answer. In all of these animals, CMRO₂ was suppressed to 10% to 15% of baseline, and in my experience we have not been able to depress CMRO₂ below that level. Although a 1° to 2° temperature decrease in the pH-stat-treated animals may have been protective in that the animals did not rewarm as much during circulatory arrest, perhaps it was not enough to decrease CMRO₂ further below that threshold.

Mr. Marc R. de Leval (*London, England*). I have no doubt of the importance of the pH strategy during cooling on the cerebral metabolism. I wonder whether air embolization could not be a mechanism of cerebral dysfunction in the subset of patients in whom you are interested: those with pulmonary atresia with ventricular septal defect and multifocal blood supply. Those patients may have large communications between the central pulmonary arteries and the systemic collateral arteries so that the opening of the central pulmonary arteries can allow air to travel from the collateral arteries to the cerebral vessels. I wonder whether you would not consider opening the pulmonary artery of your animals during the period of total circulatory arrest.

Dr. Kirshbom: I am not entirely sure that I understand your question. In this experimental model all the animals were treated identically in that the shunt was placed in the control animals as well as the shunt animals.

Mr. de Leval. I postulate that the choreoathetosis described by the Boston group some years ago, after the placement of right ventricle-pulmonary arterial conduits in patients with pulmonary atresia, ventricular septal defect, and multifocal blood supply, using total circulatory arrest, could possibly be related to air emboli. If the large systemic collateral arteries communicate with the central pulmonary arteries, the opening of the former would allow blood to reach the cerebral vessels through those communications. It is, in a way, like leaving a ductus arteriosus open during a period of total circulatory arrest with the pulmonary artery open.

Dr. Kirshbom. I cannot offer a clinical explanation. However, the clinical results of the Boston group would tend to argue against that, given that the change in pH-stat strategy with no presumable change in their method of repair in their children has apparently decreased their incidence of choreoathetosis.

I should emphasize that this is not really a model for choreoathetosis; none of these animals were studied after the operation. This is more a model of animals with decreased CBF and higher risk of neurologic injury. There may not be a direct correlation between this group and the choreoathetosis group observed clinically.

Dr. Jonas. I am not sure that I understand Mr. de Leval's question. If you open the pulmonary arteries but remain on bypass . . . or are you suggesting that under conditions of circulatory arrest this might allow air to enter the arterial circulation?

Mr. de Leval. Yes, exactly. I think if you use circulatory arrest and leave the ductus open, there is a risk of air

emboli, and this is what you create in this subset of patients. You open the pulmonary artery, which communicates with large collateral arteries arising from the systemic circulation. I believe that the risk of air embolism is very similar to the one you have during total circulatory arrest with the ductus arteriosus open.

Dr. Bradley S. Allen (*Chicago, Ill.*). I do not have a problem with your conclusions, but I do have a question concerning the method you used to determine CBF in the presence of a shunt. I am concerned about injecting microspheres into the aorta very close to a shunt. How do you determine that there was good mixing of the microspheres so as to avoid large clumps being lost through the shunt, thus causing the calculated flows to be incorrect. Specifically, where was your reference catheter, and how far away from the shunt were you injecting the microspheres to allow adequate mixing? Inadequate mixing certainly could explain why the flows were not different in the shunt animals, and yet they got colder.

Dr. Kirshbom. That is a very important point and has been well documented by Dr. Buckberg and colleagues in their studies on the microsphere technique. We are injecting the microspheres at least 12 inches away from the tip of the aortic cannula. Our reference cannula is in the distal aorta via the right femoral artery. Also, as an internal control, we compared left hemisphere versus right hemisphere, assuming that if the microspheres were not properly mixed, they would not distribute evenly within the cerebral circulation. There was never a significant difference in any animal between one side and the other. Therefore I believe we did have adequate mixing of the microspheres, but that is an important point, they do have to be properly handled.

Dr. Serafin Y. DeLeon (*Maywood, Ill.*). I know Dr. Jonas knows about this. When we published our paper, we also had an epidemic of choreoathetosis between 1986 and 1989, but we attributed that more to the change in the heat exchanger with the Teruomo oxygenator. If you are not careful, although the desired rectal temperature may only be 25° to 28° C, the esophageal or blood temperature, because the Teruomo oxygenator has a very effective cooling system, can go down to 10° to 15° C. Choreoathetosis developed in eight of 800 patients undergoing cardiac operation at that time. We believed that the deep hypothermia caused the injury to the brain, which, in contrast to most organs, is 90% lipids. Since then we have changed our strategy. In most of our patients, we lower the bladder temperature to 28° C. If circulatory arrest is going to be used, the flow is reduced significantly during cooling. Since then, we have not encountered any more cases of choreoathetosis.

I would caution you that adding carbon dioxide during cooling causes cerebral vasodilation and may be injurious. Doty and colleagues reported that before circulatory arrest, they would give carbon dioxide and increase the flow, so that the brain would be thoroughly cold. They had a high incidence of choreoathetosis.

Dr. Kirshbom. I cannot speak to the clinical issues of choreoathetosis with or without circulatory arrest. We did not have trouble with cooling the animals too much. It was more the other way around. We also moved away from the use of rectal temperatures, because we thought they were entirely inaccurate. We used nasopharyngeal temperatures throughout with intracerebral temperature probes and never measured temperatures below 18° C. I do not believe this is a hypothermia/freezing problem.

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