BLOOD GAS MANAGEMENT AND DEGREE OF COOLING: EFFECTS ON CEREBRAL METABOLISM BEFORE AND AFTER CIRCULATORY ARREST

This study investigated the effects of different cooling strategies on cerebral metabolic response to circulatory arrest. In particular, it examined the impact of blood gas management and degree of cooling on cerebral metabolism before and after deep hypothermic circulatory arrest. Sixty-nine 1-week-old piglets (2 to 3 kg) were placed on cardiopulmonary bypass (37° C) at 100 ml/kg per minute. Animals were cooled to 18° or 14° C as follows: alpha-stat strategy to 18° C ($n = 9$) or 14° C ($n = 6$), pH-stat strategy to 18° C ($n = 9$) or 14° C ($n = 7$), or pH-stat strategy for 18 minutes followed by a switch to alpha-stat strategy for the last 5 minutes of cooling to 18° C ($n = 12$) or 14° C ($n = 10$). Animals underwent 60 minutes of circulatory arrest followed by rewarming with alpha-stat strategy to 36° C. Control animals were cooled with alpha-stat strategy to 18° C ($n = 10$) or 14° C ($n = 3$) and then maintained on cold cardiopulmonary bypass (100 ml/kg per minute) for 60 minutes. Three animals were excluded (see text). With the use of xenon 133 clearance methods, cerebral blood flow was measured at the following points: point I, cardiopulmonary bypass (37° C); point II, cardiopulmonary bypass before circulatory arrest or control flow (18° or 14° C); and point III, cardiopulmonary bypass after rewarming (36° C). Cerebral metabolic rate of oxygen consumption was calculated for each point. At point II, cerebral metabolism was more suppressed at 14° C compared with that at 18° C. At any given temperature (18° or 14° C), pH-stat strategy provided the greatest suppression of cerebral metabolism. In control animals, cerebral metabolic oxygen consumption at point III returned to baseline values after 60 minutes of cold bypass. Sixty minutes of circulatory arrest resulted in a significant reduction in cerebral metabolic oxygen consumption at point III compared with that at point I regardless of cooling temperature or blood gas strategy. The amount of cerebral metabolic recovery was significantly reduced in the pH-stat 14° C group compared with that in the pH-stat 18° C group at point III. The use of pH-stat strategy followed by a switch to alpha-stat at 14° C provided better cerebral metabolic recovery compared with either strategy used alone. The use of pH-stat strategy during initial cooling may provide the animal with maximal cerebral metabolic suppression. The cerebral acidosis produced with pH-stat cooling may worsen cerebral metabolic injury from circulatory arrest, but this effect is eliminated with the use of alpha-stat just before the period of circulatory arrest. (J THORAC CARDIOVASC SURG 1995;110:1649-57)

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Deep hypothermic circulatory arrest (DHCA) is often used during the repair of complex congenital heart disease in neonates. Transient and permanent neuropsychologic injury may be observed after DHCA.¹⁻³ The optimal goal during active cooling before a period of DHCA is to uniformly deliver cold perfusate to the brain so that there is a homogeneous reduction in temperature and metabolic activity. The reduction of cerebral metabolic rate of oxygen consumption (CMRO₂) at the start of DHCA is crucial for maintenance of energy stores and organ protection.⁴

Strategies during the cooling phase that would result in the lowest CMRO₂ before DHCA may provide the best cerebral protection. Two such strategies are the use of more profound hypothermia and the use of pH-stat blood gas management. Because CMRO₂ is exponentially related to temperature during hypothermic cardiopulmonary bypass (CPB),⁵ the use of more profound hypothermia during cooling may provide better global suppression of CMRO₂ before DHCA. Alpha-stat and pH-stat are blood gas management strategies used to regulate arterial carbon dioxide tension (Paco₂) during hypothermia. Alpha-stat strategy maintains a Paco₂ level of 40 mm Hg when measured by the gas analyzer at 37° C (temperature uncorrected). The pH-stat strategy uses the addition of carbon dioxide to the oxygenator gas flow during cooling to achieve a Paco₂ level of 40 mm Hg when corrected to the patient's core temperature (temperature corrected). This addition of carbon dioxide causes increased cerebral blood flow (CBF) during hypothermic CPB.⁶⁻⁹ The advantages of the use of alpha-stat when compared with pH-stat management are more optimal buffering capacity and enzymatic function,¹⁰ preservation of flow metabolism coupling,⁶ and reduction in progressive tissue acidosis during and after a period of DHCA.¹¹ The advantages of alpha-stat strategy may be outweighed by less effective cooling of the brain and therefore less suppression of cerebral metabolism at the start of ischemia.

This study examined the effects of blood gas management (alpha-stat and pH-stat) and degree of cooling (14° and 18° C) on cerebral metabolism before and after a 60-minute period of DHCA. The techniques used in this investigation were designed to duplicate those used in the clinical setting.

Methods

Animal preparation. Sixty-nine 1-week-old piglets weighing 2 to 3 kg were studied with approval of the institution's

Animal Care and Use Committee and in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985). Animals were premedicated with intramuscular ketamine (20 mg/kg) and intubated and the lungs mechanically ventilated (infant ventilator; Sechrist Industries, Anaheim, Calif.). Methylprednisolone (40 mg/kg) was given intravenously. After a bolus of intravenous fentanyl (100 µg) and pancuronium (0.1 mg/kg), anesthesia was maintained with continuous fentanyl infusion (50 µg · kg⁻¹ · hr⁻¹). A femoral artery catheter was placed for measurement of mean arterial pressure and arterial blood gas sampling. Temperature probes were placed in the nasopharynx and cortical region of the brain and a median sternotomy was performed. A burr hole was made in the skull at the crus of the sagittal and coronal sutures to allow sagittal sinus blood sampling.

Method of CBF measurement. Hemispheric CBF was measured by the xenon (¹³³Xe) clearance technique previously described by this group and others.^{12,13} Two extracranial 16 mm cadmium telluride gamma emission detectors were placed over the right and left temporal lobes. Radioactive xenon (1.5 mCi in 2 ml of normal saline solution) was injected into the aortic cannula and radioactive decay recorded from each hemisphere over a 5-minute period. With use of a modification of the initial slope index method, CBF was determined.¹⁴ By this method, CBF = (slope)(λ)(100), where slope is the natural logarithm of the ¹³³Xe clearance 1 minute after the peak of the curve, λ is the tissue-blood partition coefficient for xenon corrected for hematocrit and temperature,¹⁵ and 100 converts milliliters times grams⁻¹ times minutes⁻¹ to milliliters times 100 gm⁻¹ times minutes⁻¹. Global CBF was determined from the average of the individually calculated hemispheric blood flow values. The baseline ¹³³Xe value was measured before each determination and subtracted to correct curves for residual xenon. This method has recently been validated during hypothermic CPB.¹³

Perfusion technique. A Stöckert-Shiley (Irvine, Calif.) Computer Assisted Perfusion System nonpulsatile roller pump and a Cobe VP-CML (Denver, Colo.) membrane oxygenator with venous reservoir comprised the CPB circuit. Circuit blood gas values were monitored with a CDI-300 (CDI; 3M Healthcare, Irvine, Calif.) continuous in-line blood gas analyzer. The circuit was primed with fresh heparinized donor pig whole blood with a hematocrit value of 26% ± 0.3%. After animals were heparinized (500 U/kg), an 8F arterial and a 14F venous cannula were inserted in the ascending aorta and right atrium, respectively, and CPB initiated. Pump flow was maintained at a constant flow rate of 100 ml · kg⁻¹ · min⁻¹ throughout the duration of CPB. Pharmacologic agents were not administered to control blood pressure during CPB. Sodium bicarbonate was given to maintain a base excess between -3 and 3 mmol/L. The Paco₂ was maintained at a predetermined level according to the study protocol by adjusting the gas flow rate in the oxygenator with the addition of 5% CO₂ as necessary during the period of hypothermic CPB.

Study protocol. A schematic diagram of the experimental protocol and data collection sequence is shown in Fig. 1. After instrumentation, animals were placed on CPB

($37.2^\circ \pm 0.1^\circ \text{C}$) at 100 ml/kg per minute and baseline measurements (point I) were obtained. Animals were cooled to $18.4^\circ \pm 0.1^\circ \text{C}$ or $14.0^\circ \pm 0.2^\circ \text{C}$ over 23 minutes and data (point II) were obtained. The experimental groups were cooled as follows: the $\alpha(18^\circ \text{C})$ group received alpha-stat strategy to 18°C ($n = 9$); the pH(18°C) group received pH-stat strategy to 18°C ($n = 9$); the pH $\rightarrow\alpha(18^\circ \text{C})$ group received pH-stat strategy for 18 minutes followed by a switch to alpha-stat strategy for the last 5 minutes of cooling to 18°C ($n = 12$); the $\alpha(14^\circ \text{C})$ group received alpha-stat strategy to 14°C ($n = 6$); the pH(14°C) group received pH-stat strategy to 14°C ($n = 7$); and the pH $\rightarrow\alpha(14^\circ \text{C})$ group received pH-stat strategy for 18 minutes followed by a switch to alpha-stat strategy for the last 5 minutes of cooling to 14°C ($n = 10$). Alpha-stat strategy was defined as the maintenance of Paco_2 at 40 ± 5 mm Hg, temperature uncorrected, and pH-stat as maintenance of Paco_2 at 40 ± 5 mm Hg, temperature corrected. Animals underwent 60 minutes of DHCA followed by rewarming with alpha-stat strategy to $36.4^\circ \pm 0.1^\circ \text{C}$ over 26 ± 1 minutes and final measurements were obtained during CPB (point III). Not shown in this schematic are control animals that were cooled with alpha-stat strategy to 18°C (group CTL[18°C], $n = 10$) or 14°C (group CTL[14°C], $n = 3$) followed by 60 minutes of deep hypothermic CPB at 100 ml/kg per minute. The duration of CPB for animals undergoing DHCA was 84 ± 1 minutes and 149 ± 3 minutes for those undergoing deep hypothermic CPB.

Nasopharyngeal and cortical brain temperatures, mean arterial pressure, arterial and sagittal sinus blood gas values, hemoglobin concentration, and CBF were measured at each stage. The cerebral arteriovenous oxygen content difference (cCa-vO_2) was then calculated as $\text{CaO}_2 - \text{CvSO}_2$, where CaO_2 is the arterial oxygen content and CvSO_2 is the sagittal sinus oxygen content. A GEM-STAT blood gas/electrolyte monitor (Mallinckrodt, Ann Arbor, Mich.) was used to measure blood gas values. Oxygen saturation and hemoglobin were measured by an IL482 Co-Oximeter system (Instrumentation Laboratory, Lexington, Mass.). Cerebral metabolism (CMRO_2), cerebral oxygen delivery ($\text{cD} \cdot \text{O}_2$), and cerebral oxygen extraction ratio (CO_2ER) were calculated as follows:

$$\text{CMRO}_2(\text{ml} \cdot 100 \text{ gm brain}^{-1} \cdot \text{min}^{-1}) = (\text{cCa-vO}_2)(\text{CBF})$$

$$\text{cD} \cdot \text{O}_2(\text{ml O}_2 \cdot 100 \text{ gm brain}^{-1} \cdot \text{min}^{-1}) = (\text{CaO}_2)(\text{CBF})$$

$$\text{CO}_2\text{ER}(\%) = \text{CMRO}_2/\text{cD} \cdot \text{O}_2$$

Statistical analysis. Data were analyzed by the Student's paired t test to compare results within each group. The unpaired t test and analysis of variance were used to compare results between groups. All results are expressed as means plus or minus the standard errors. Significance was defined as $p < 0.05$.

Results

The study was successfully completed in 66 of the 69 animals. Three animals were excluded, two be-

Fig. 1. Experimental protocol and data collection sequence. After instrumentation, animals were placed on CPB at 100 ml/kg per minute and 37°C and baseline measurements (I) were obtained. Animals were cooled to 18° or 14°C over 23 minutes and data (II) were obtained. Experimental groups were cooled as follows: $\alpha(18^\circ \text{C})$, alpha-stat strategy to 18°C ($n = 9$); pH(18°C), pH-stat strategy to 18°C ($n = 9$); pH $\rightarrow\alpha(18^\circ \text{C})$, pH-stat strategy for 18 minutes followed by switch to alpha-stat strategy for last 5 minutes of cooling to 18°C ($n = 12$); $\alpha(14^\circ \text{C})$, alpha-stat strategy to 14°C ($n = 6$); pH(14°C), pH-stat strategy to 14°C ($n = 7$); pH $\rightarrow\alpha(14^\circ \text{C})$, pH-stat strategy for 18 minutes followed by switch to alpha-stat strategy for last 5 minutes of cooling to 14°C ($n = 10$). Animals underwent 60 minutes of DHCA followed by rewarming to 36°C over 26-minute period. Final measurements were obtained at this time (III). Not shown in this schematic are control animals, which were cooled with alpha-stat strategy to 18°C (CTL[18°C], $n = 10$) or 14°C (CTL[14°C], $n = 3$) followed by 60 minutes of deep hypothermic CPB (100 ml/kg per minute).

cause of markedly abnormal baseline CMRO_2 values (groups pH[18°C] and α [14°C]) and one because of the inability to adequately rewarm to a nasopharyngeal temperature of 36°C within 30 minutes after reinstitution of CPB (group pH[18°C]).

Summary data for all animals are shown in Tables I through IV. For simplicity, statistical significance is designated in tables only for selected variables.

Control data. There were no significant differences in arterial or sagittal sinus pH or Pco_2 values, mean arterial pressure, nasopharyngeal temperature, or cerebral oxygen extraction ratio between stage I and stage III. In the CTL(18°C) animals after rewarming after 60 minutes of deep hypothermic CPB (stage III) there was a significant decrease in CBF compared with that in stage I. CMRO_2 returned to baseline values in all animals regardless

Table I. Summary data for all animals

	18° C				14° C			
	CTL	α	pH	pH $\rightarrow\alpha$	CTL	α	pH	pH $\rightarrow\alpha$
NPT (°C)								
I	37.4 $\pm$ 0.1	37.5 $\pm$ 0.2	37.0 $\pm$ 0.2	37.2 $\pm$ 0.2	37.4 $\pm$ 0.6	36.8 $\pm$ 0.2	37.1 $\pm$ 0.2	37.4 $\pm$ 0.3
II	18.4 $\pm$ 0.3	18.6 $\pm$ 0.2	18.4 $\pm$ 0.2	18.1 $\pm$ 0.1	14.5 $\pm$ 0.3	13.6 $\pm$ 0.3	13.6 $\pm$ 0.3	14.3 $\pm$ 0.3
III	36.9 $\pm$ 0.3	36.7 $\pm$ 0.3	36.6 $\pm$ 0.3	35.9 $\pm$ 0.3	35.8 $\pm$ 0.1	37.0 $\pm$ 0.0	36.1 $\pm$ 0.1	36.4 $\pm$ 0.2
Brain T (°C)								
I	36.8 $\pm$ 0.3	37.1 $\pm$ 0.5	34.9 $\pm$ 0.4*†	37.1 $\pm$ 0.3‡	37.9 $\pm$ 0.5	35.3 $\pm$ 0.5*†	36.3 $\pm$ 0.6	37.4 $\pm$ 0.4
II	21.2 $\pm$ 0.5	21.2 $\pm$ 0.6	21.6 $\pm$ 0.6	19.3 $\pm$ 0.4*†‡	17.1 $\pm$ 0.6	17.8 $\pm$ 1.2	16.5 $\pm$ 0.8	17.6 $\pm$ 1.1
III	34.4 $\pm$ 0.4§	33.8 $\pm$ 0.8§	31.7 $\pm$ 0.6*†§	32.9 $\pm$ 0.6§	33.6 $\pm$ 1.2	33.5 $\pm$ 0.7	33.2 $\pm$ 1.0§	33.4 $\pm$ 0.9§
MAP (mm Hg)								
I	62 $\pm$ 8	55 $\pm$ 5	46 $\pm$ 6	38 $\pm$ 2	33 $\pm$ 1	45 $\pm$ 6	46 $\pm$ 2	45 $\pm$ 4
II	83 $\pm$ 6	69 $\pm$ 5	66 $\pm$ 6	61 $\pm$ 4	57 $\pm$ 1	65 $\pm$ 8	63 $\pm$ 4	57 $\pm$ 4
III	70 $\pm$ 9	55 $\pm$ 7	53 $\pm$ 8	49 $\pm$ 3	45 $\pm$ 5	58 $\pm$ 9	57 $\pm$ 4	58 $\pm$ 6
HCT (%)								
I	26 $\pm$ 1	26 $\pm$ 1	27 $\pm$ 1	26 $\pm$ 1	25 $\pm$ 1	26 $\pm$ 1	27 $\pm$ 2	27 $\pm$ 0
II	26 $\pm$ 1	25 $\pm$ 1	27 $\pm$ 1	26 $\pm$ 1	25 $\pm$ 2	25 $\pm$ 1	27 $\pm$ 2	27 $\pm$ 1
III	33 $\pm$ 2§	27 $\pm$ 1*	28 $\pm$ 1*	27 $\pm$ 1*	30 $\pm$ 1	27 $\pm$ 1	26 $\pm$ 2	28 $\pm$ 1

Values given as mean plus or minus standard error. CTL, Control; α , alpha-stat; pH, pH-stat; pH $\rightarrow\alpha$, pH-stat switched to alpha-stat; I, CPB (37° C); II, CPB (18° or 14° C); III, CPB (36° C); NPT, nasopharyngeal temp; Brain T, cortical temp; MAP, mean arterial pressure; HCT, hematocrit.

* $p < 0.05$, all groups versus control.

† $p < 0.05$, all groups versus α (18° C).

‡ $p < 0.05$, all groups versus pH(18° C).

§ $p < 0.05$, stage III versus stage I.

Table II. Arterial and sagittal sinus blood gas data for animals cooled to 18° C

	CTL	α	pH	pH $\rightarrow\alpha$
apH				
I	7.40 $\pm$ 0.01	7.39 $\pm$ 0.15	7.41 $\pm$ 0.01	7.40 $\pm$ 0.01
II	7.38 $\pm$ 0.02	7.34 $\pm$ 0.13	7.13 $\pm$ 0.02*†‡ (7.40 $\pm$ 0.02)	7.09 $\pm$ 0.01*† (7.37 $\pm$ 0.01) $\rightarrow$ 7.35 $\pm$ 0.01
III	7.41 $\pm$ 0.01	7.38 $\pm$ 0.01	7.40 $\pm$ 0.01	7.39 $\pm$ 0.01
Paco ₂ (mm Hg)				
I	38 $\pm$ 1	37 $\pm$ 1	38 $\pm$ 1	38 $\pm$ 1
II	40 $\pm$ 2	44 $\pm$ 2	83 $\pm$ 7*†‡ (36 $\pm$ 2)	93 $\pm$ 3*† (37 $\pm$ 1) $\rightarrow$ 42 $\pm$ 1
III	38 $\pm$ 1	37 $\pm$ 1	37 $\pm$ 0	39 $\pm$ 1
sspH				
I	7.29 $\pm$ 0.01	7.27 $\pm$ 0.01	7.27 $\pm$ 0.02	7.27 $\pm$ 0.01
II	7.30 $\pm$ 0.02	7.25 $\pm$ 0.01	7.08 $\pm$ 0.01*†‡	7.05 $\pm$ 0.01 $\rightarrow$ 7.27 $\pm$ 0.01§
III	7.32 $\pm$ 0.02	7.27 $\pm$ 0.02	7.23 $\pm$ 0.02	7.25 $\pm$ 0.02
PssCO ₂ (mm Hg)				
I	55 $\pm$ 2	55 $\pm$ 1	56 $\pm$ 2	56 $\pm$ 1
II	50 $\pm$ 2	56 $\pm$ 2	95 $\pm$ 2*†‡	102 $\pm$ 2 $\rightarrow$ 53 $\pm$ 1§
III	52 $\pm$ 2	56 $\pm$ 5	60 $\pm$ 3	57 $\pm$ 2

Values given as mean plus or minus standard error. Temperature-uncorrected values given with temperature-corrected values in parentheses. CTL, Control (60 minutes deep hypothermic CPB); α , alpha-stat; pH, pH-stat; pH $\rightarrow\alpha$, pH-stat switched to alpha-stat; I, CPB (37° C); II, CPB (18° or 14° C); III, CPB (36° C); apH, arterial pH; sspH, sagittal sinus pH; PssCO₂, sagittal sinus carbon dioxide tension.

* $p < 0.05$, all groups versus control.

† $p < 0.05$, all groups versus α (18° C).

‡ $p < 0.05$, all groups versus α (14° C).

§ $p < 0.05$, all groups versus pH(18° C).

of final cooling temperature (18° or 14° C) after rewarming. It is also interesting to note that CMRO₂ returned to baseline values even though there was a significant decrease in cortical brain temperature in CTL(18° C) group animals at stage

III after rewarming compared with that in stage I. There was a significant increase in hematocrit concentration in the CTL(18° C) group at stage III compared with that at stage I; however, this increase was not believed to be large enough to account for

Table III. Arterial and sagittal sinus blood gas data for animals cooled to 14° C

	CTL	α	pH	pH→ α
apH				
I	7.38 ± 0.02	7.39 ± 0.02	7.40 ± 0.01	7.38 ± 0.01
II	7.40 ± 0.03	7.38 ± 0.01	6.95 ± 0.03*†‡§ (7.29 ± 0.01)	7.01 ± 0.01*‡ (7.35 ± 0.01)→7.38 ± 0.02
III	7.43 ± 0.02	7.40 ± 0.01	7.41 ± 0.02	7.42 ± 0.01
Paco ₂ (mm Hg)				
I	39 ± 3	40 ± 2	40 ± 1	39 ± 1
II	39 ± 4	42 ± 1	133 ± 8*†‡§ (43 ± 3)	123 ± 4*‡ (41 ± 1)→39 ± 2
III	37 ± 0	37 ± 1	39 ± 1	38 ± 1
sspH				
I	7.26 ± 0.02	7.23 ± 0.01	7.27 ± 0.01	7.28 ± 0.02
II	7.32 ± 0.02	7.30 ± 0.01	6.92 ± 0.03*†‡§	6.99 ± 0.01→7.27 ± 0.01
III	7.31 ± 0.03	7.27 ± 0.00	7.28 ± 0.02	7.29 ± 0.01
Pssco ₂ (mm Hg)				
I	61 ± 3	61 ± 1	56 ± 1	60 ± 1
II	50 ± 4	50 ± 2	131 ± 7*†‡§	123 ± 3→53 ± 2
III	54 ± 3	52 ± 2	56 ± 3	57 ± 3

Values given as mean plus or minus standard error. Temperature-uncorrected values given with temperature-corrected values in parentheses. CTL, Control (60 minutes deep hypothermic CPB); α , alpha-stat; pH, pH-stat; pH→ α , pH-stat switched to alpha-stat; I, CPB (37° C); II, CPB (18° or 14° C); III, CPB (36° C); apH, arterial pH; sspH, sagittal sinus pH; Pssco₂, sagittal sinus carbon dioxide tension.

*p < 0.05, all groups versus control.

†p < 0.05, all groups versus α (18° C).

‡p < 0.05, all groups versus α (14° C).

§p < 0.05, all groups versus pH(18° C).

||p < 0.05, all groups versus pH(14° C).

Table IV. Summary data for all animals

	18° C				14° C			
	CTL	α	pH	pH→ α	CTL	α	pH	pH→ α
CBF (ml/100 gm/min)								
I	38.8 ± 2.0	36.0 ± 2.3	32.1 ± 1.8*	30.4 ± 0.8*†	26.4 ± 1.0	32.4 ± 2.5	34.7 ± 1.1*	31.4 ± 1.4
II	35.8 ± 2.0	32.6 ± 2.7	27.4 ± 2.1	28.6 ± 1.0	26.0 ± 1.9	28.5 ± 3.2	33.7 ± 1.8*	26.5 ± 1.2
III	31.0 ± 3.4‡	30.2 ± 2.0‡	23.9 ± 1.0‡	24.0 ± 0.7*‡	22.1 ± 0.8	26.1 ± 1.5‡	25.9 ± 1.2‡	27.3 ± 1.1‡
CMRO ₂ (ml/100 gm/min)								
I	3.01 ± 0.13	3.06 ± 0.13	2.79 ± 0.12	2.65 ± 0.10*†	2.68 ± 0.18	2.52 ± 0.13†	2.74 ± 0.14	2.71 ± 0.10
II	1.19 ± 0.08	1.30 ± 0.30	1.05 ± 0.06†§	0.83 ± 0.05*	0.94 ± 0.17	0.80 ± 0.06†	0.56 ± 0.06*†§	0.75 ± 0.05¶
III	2.97 ± 0.21	2.30 ± 0.20*‡	2.26 ± 0.09*‡§	2.08 ± 0.11*‡	2.66 ± 0.14	1.91 ± 0.06*‡	1.91 ± 0.11*‡	2.35 ± 0.08‡§¶
co ₂ ER (%)								
I	64.7 ± 3.5	68.3 ± 2.1	67.7 ± 3.0	69.0 ± 2.2	82.3 ± 1.7	64.6 ± 4.9	62.3 ± 1.8	65.4 ± 1.1
II	25.9 ± 2.1	31.2 ± 2.9	25.9 ± 1.8	22.4 ± 1.5	27.3 ± 4.9	22.9 ± 3.2	12.5 ± 1.4*†§	20.7 ± 2.1¶
III	62.5 ± 4.6	66.2 ± 3.9	70.5 ± 3.1	65.7 ± 2.4	82.0 ± 1.6	58.4 ± 4.8	60.3 ± 4.8	62.8 ± 1.9

Values given as mean plus or minus standard error. CTL, Control; α , alpha-stat; pH, pH-stat; pH→ α , pH-stat switched to alpha-stat; I, CPB (37° C); II, CPB (18° or 14° C); III, CPB (36° C); co₂ER, cerebral oxygen extraction ratio.

*p < 0.05, all groups versus control.

†p < 0.05, all groups versus α (18° C).

‡p < 0.05, stage III versus stage I.

§p < 0.05, all groups versus α (14° C).

||p < 0.05, all groups versus pH(18° C).

¶p < 0.05, all groups versus pH(14° C).

the return of CMRO₂ to baseline levels in these animals.

Effects of cooling temperature on CMRO₂. Cortical brain temperatures were significantly lower in those groups of animals cooled to 14° C versus those cooled to 18° C. At stage II (Fig. 2), CMRO₂ was

significantly more suppressed at 14° C than at 18° C. Regardless of the final cooling temperature and the amount of cerebral metabolic suppression at stage II, 60 minutes of DHCA resulted in a significant reduction in CMRO₂ after rewarming compared with baseline values (Fig. 3).

Fig. 2. CMRO₂ measurements before DHCA at maximal cooling (18° or 14° C). CMRO₂ is more suppressed at 14° C compared with value at 18° C. At any given temperature (18° or 14° C), pH-stat strategy provides better suppression of CMRO₂. Mean data plus or minus standard error are shown. **p* < 0.05 versus all other groups at maximal cooling.

Effects of blood gas management (alpha-stat versus pH-stat) on CMRO₂. There were no significant differences in cortical brain temperatures at stage II between the α(18° C) and pH(18° C) or α(14° C) and pH(14° C) groups. At any given temperature (18° or 14° C), pH-stat strategy provided significantly better suppression of CMRO₂ at stage II compared with that with the use of alpha-stat strategy (Fig. 2). CBF decreased at stage III in groups α(18° C), pH(18° C), α(14° C), and pH(14° C) compared with that at stage I. Cerebral oxygen extraction ratio at stage III was significantly decreased in the group pH(14° C) animals compared with that in the α(18° C), pH(18° C), and α(14° C) groups.

Even though the use of pH-stat strategy provided the least amount of CMRO₂ at stage II, 60 minutes of DHCA resulted in a significant reduction of CMRO₂ after rewarming compared with baseline values in the pH(18° C) and pH(14° C) group animals and in the α(18° C) and α(14° C) groups (Fig. 3). There were no significant differences in the amount of cerebral metabolic recovery at stage III between the α(18° C) and pH(18° C) or α(14° C) and pH(14° C) groups. There was, however, a significant reduction in CMRO₂ at stage III in the α(14° C) and pH(14° C) groups compared with that in the pH(18° C) group (Fig. 3). This reduction in CMRO₂ at stage III was not seen when the α(18° C) and α(14° C) groups were compared. These reductions in CMRO₂ may be the result of the use of such profound hypothermia in those animals cooled to 14° C. There was a significant difference in sagittal sinus pH, venous carbon dioxide tension (PvCO₂),

Fig. 3. CMRO₂ measurements before and after deep hypothermic CPB or DHCA. Control (CTL) animals had almost complete return of CMRO₂ to baseline values after deep hypothermic CPB. There was significant decrease in CMRO₂ from stage I to stage III in all animals undergoing 60 minutes of DHCA. Mean data plus or minus standard error are shown. **p* < 0.05, stage III versus stage I; †*p* < 0.05, pH(14° C) versus pH(18° C); I, CPB (37° C); III, CPB (36° C) after rewarming.

and Paco₂ values in the pH(18° C) and pH(14° C) groups compared with those values in the α(18° C) and α(14° C) animals (Tables II and III). Animals in the pH-stat groups were profoundly acidotic with very low pH and high PvCO₂ values, especially those animals cooled to 14° C.

pH→α-stat data. There was a significant increase in sagittal sinus pH and a significant decrease in sagittal sinus PvCO₂ at stage II in the pH→α(18° C) and pH→α(14° C) animals compared with respective values in the pH(18° C) and pH(14° C) groups. The cortical brain temperature and CMRO₂ at stage II were significantly lower in the pH→α(18° C) group than these values in the α(18° C) and pH(18° C) group animals. These differences in cortical brain temperature and CMRO₂ at stage II did not occur in the pH→α(14° C) animals. CBF decreased at stage III in the pH→α(18° C) and pH→α(14° C) groups compared with values at stage I. CMRO₂ was significantly increased at stage III in the pH→α(14° C) animals compared with this value in the α(14° C) and pH(14° C) groups (Fig. 4). There was no significant difference in CMRO₂ at stage III in the pH→α(18° C) group compared with the value in the α(18° C) and pH(18° C) group animals. Again, 60 minutes of DHCA resulted in decreased CMRO₂ after rewarming compared with baseline values in both pH→α(18° C) and pH→α(14° C) groups.

The baseline cortical brain temperatures were significantly lower in the pH(18° C) and α(14° C)

groups; however, this was not believed to be of physiologic importance. The cortical brain temperatures at stage III decreased significantly in the $\alpha(18^\circ\text{C})$, pH(18 $^\circ\text{C}$), pH $\rightarrow\alpha(18^\circ\text{C})$, pH $\rightarrow\alpha(14^\circ\text{C})$, and pH(14 $^\circ\text{C}$) groups compared with those at stage I. A similar decrease in brain temperature after rewarming occurred in the CTL(18 $^\circ\text{C}$) animals, and this did not seem to affect the recovery of CMRO₂ to baseline values. Baseline CMRO₂ values in the pH $\rightarrow\alpha(18^\circ\text{C})$ and $\alpha(14^\circ\text{C})$ animals were significantly lower compared with those in the CTL(18 $^\circ\text{C}$) and $\alpha(18^\circ\text{C})$ groups and in the $\alpha(18^\circ\text{C})$ group, respectively. A strict study protocol was adhered to for each animal in regard to anesthesia and instrumentation, which makes these unlikely explanations for these differences. The data were analyzed with use of the raw change in CMRO₂ comparing stage I with stage III values within groups; therefore, these baseline differences should not interfere with data analysis.

Discussion

The prevalence of neuropsychologic injury occurring after DHCA for the repair of complex congenital heart defects may be as high as 25%.² The principal method of cerebral protection during DHCA is the use of hypothermia. Cerebral metabolism decreases exponentially with reductions in temperature.⁵ A reduction in CMRO₂ decreases the depletion rate of high-energy phosphate compounds and the development of intracellular acidosis that occurs during circulatory arrest.^{4, 16, 17} These findings emphasize the importance of the uniform delivery of cold perfusate to the brain so that a homogeneous reduction in cerebral temperature and CMRO₂ occurs at the start of DHCA. Cerebral metabolic recovery after DHCA may be enhanced by strategies that provide the least amount of cerebral metabolism before DHCA. The use of lower cooling temperatures and use of the cerebral vasodilator CO₂ (pH-stat blood gas strategy) are two strategies that by themselves or in combination may result in improved cerebral metabolic recovery after a period of DHCA.

This study demonstrates in this model of neonatal CPB that CMRO₂ is more suppressed at 14 $^\circ\text{C}$ than at 18 $^\circ\text{C}$. At any given temperature, 18 $^\circ$ or 14 $^\circ\text{C}$, CMRO₂ is better suppressed in those animals cooled with pH-stat blood gas management (Fig. 2). Exposure to 60 minutes of DHCA, however, resulted in a significant decrease in CMRO₂ from

Fig. 4. CMRO₂ measurements before and after DHCA in those animals cooled to 14 $^\circ\text{C}$. There was significant decrease in CMRO₂ from stage I to stage III in all animals. At stage III, there was significant decrease in CMRO₂ in alpha-stat and pH-stat groups compared with values in pH $\rightarrow\alpha$ -stat group animals. Mean data plus or minus standard error are given. * $p < 0.05$, stage III versus stage I; † $p < 0.05$, pH $\rightarrow\alpha$ -stat versus alpha-stat and pH-stat; I, CPB (37 $^\circ\text{C}$); III, CPB (36 $^\circ\text{C}$) after rewarming.

baseline values after rewarming regardless of blood gas strategy or final cooling temperature (Fig. 3).

Possible mechanisms for the impairment in cerebral metabolic recovery after DHCA include inadequate rewarming of the brain after profound hypothermia, continued consumption of oxygen by the brain during the arrest period, and further reductions in intracellular pH value during the arrest period. The almost 100% recovery of CMRO₂ seen in control animals after prolonged exposure to profound hypothermia (14 $^\circ$ or 18 $^\circ\text{C}$), measured at statistically similar rewarming temperatures to those in the experimental groups, makes inadequate rewarming of the brain an unlikely mechanism (Fig. 3).

This study demonstrates that even though the use of pH-stat at more profound hypothermic temperatures (14 $^\circ\text{C}$) provides the least amount of cerebral metabolism, the brain continues to consume oxygen before and during the period of DHCA. The presence of continued cerebral metabolism at the start of DHCA has been shown to occur clinically and in other experimental models of neonatal CPB^{5, 18, 19} and may in part explain the impairment in CMRO₂ after DHCA. Recent investigations have demonstrated that 1 hour of arrest, even at deep hypothermic temperatures, reduces the metabolic reserve of the brain. Strategies such as topical cooling of the brain, intermittent perfusion, and trickle flow may

help prevent further cerebral injury from occurring during the arrest time.^{12, 20}

Cerebral metabolic recovery was significantly reduced in those animals cooled with pH-stat to 14° C compared with that in the pH(18° C) group. This difference was not seen in those groups cooled with alpha-stat strategy. At the start of DHCA, the pH-stat animals were profoundly acidotic with very low arterial and sagittal sinus pH values and high PvCO₂ values, especially those cooled to 14° C (pH 6.95 ± 0.03, pH 6.92 ± 0.03, and 131 ± 7 mm Hg, respectively). This degree of acidosis preceding DHCA may make the brain less tolerant of prolonged ischemia despite the degree of metabolic suppression. A recent investigation has demonstrated that if a period of arrest is used in addition to pH-stat strategy, a further reduction occurs in intracellular pH.¹¹ The resultant severe cerebral acidosis may delay or prevent full brain recovery. Lower intracellular pH also results in an impairment in cellular enzymatic function.²¹

From the latter findings, a switch strategy was devised. pH-stat strategy would be used during initial cooling to provide maximal cerebral metabolic suppression. A switch to alpha-stat strategy would follow just before the period of arrest to decrease the severe acid debt that occurs at profound hypothermia with the use of pH-stat. The sagittal sinus pH and PvCO₂ values were not significantly different after the use of the switch strategy compared with those in the animals cooled to 14° C with alpha-stat strategy alone. The switch strategy provided significantly better recovery of cerebral metabolism after DHCA compared with recovery with either strategy used alone (pH-stat or alpha-stat) in those animals cooled to 14° C (Fig. 4). However, an impairment in cerebral metabolic recovery after 60 minutes of DHCA still occurred. When the switch strategy was used during cooling to 18° C, there was no difference in cerebral metabolic recovery after DHCA compared with the recovery with either strategy used alone. This latter finding may be explained by the fact that the acid debt accrued with the use of pH-stat at 18° C is not as large; therefore, the addition of a 60-minute period of DHCA may not be as deleterious.

There are several limitations to this study. The cerebral metabolic response patterns demonstrated in these animals are acute changes only. However, recent investigations have demonstrated that DHCA is associated with an impairment in long-term neurologic outcome that may be related to the

pattern of cerebral metabolic recovery seen in the immediate post-CPB period.²² The measurements of CBF are global and do not provide information about regional blood flow. However, this method of CBF measurement was chosen to parallel methods used in patients at this institution to make results produced in the laboratory setting clinically applicable. The brains were not examined histologically or on a molecular level. Further studies will need to be done to help understand these acute changes in cerebral metabolism on a molecular level.

In summary, this study demonstrates that CMRO₂ is more suppressed at 14° C than at 18° C. pH-stat strategy provides better suppression of cerebral metabolism at any given temperature (14° and 18° C). The use of pH-stat strategy during initial cooling to 14° C followed by a switch to alpha-stat strategy just before arrest results in better recovery of cerebral metabolism after DHCA compared with the recovery with either strategy used alone. Regardless of degree of cooling and blood gas strategy used, 60 minutes of DHCA results in an impairment in the recovery of cerebral metabolism after re-warming. The appropriateness of a blood gas strategy depends on many factors including the degree of hypothermia, pump flow rate, the use of DHCA, and the presence of anatomic variants (large aortopulmonary shunts). In situations in which inefficient cooling may occur because of anatomic variants or in which a prolonged use of DHCA is anticipated, the use of lower cooling temperatures and the cerebrovasodilation of CO₂ may be beneficial. Once the patient is cool, however, a switch to alpha-stat strategy may help preserve intracellular pH by reducing the amount of postarrest cerebral acidosis.

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