

## Hyperglycemia during Hypothermic Canine Cardiopulmonary Bypass Increases Cerebral Lactate

Alan E. Feerick, F.F.A.R.C.S.I.,\* William E. Johnston, M.D.,† Larry W. Jenkins, Ph.D.,‡ Cheng Y. Lin, Ph.D.,§ Jonathan H. Mackay, F.R.C.A.,\* Donald S. Prough, M.D.||

**Background:** Hyperglycemia frequently occurs during cardiopulmonary bypass (CPB), although its direct effects on cerebral perfusion and metabolism are not known. Using a canine model of hypothermic CPB, we tested whether hyperglycemia alters cerebral blood flow and metabolism and cerebral energy charge.

**Methods:** Twenty anesthetized dogs were randomized into hyperglycemic ( $n = 10$ ) and normoglycemic ( $n = 10$ ) groups. The hyperglycemic group received an infusion of D<sub>50</sub>W, and the normoglycemic animals received an equal volume of 0.9% NaCl. Both groups underwent 120 min of hypothermic (28°C) CPB using membrane oxygenators, followed by rewarming and termination of CPB. Cerebral blood flow (radioactive microspheres) and the cerebral metabolic rate for oxygen were measured intermittently during the experiment and brain tissue metabolites were obtained after bypass.

**Results:** Before CPB, the glucose-treated animals had higher serum glucose levels ( $534 \pm 12$  mg/dL; mean  $\pm$  SE) than controls ( $103 \pm 4$  mg/dL;  $P < 0.05$ ), and this difference was maintained throughout the study. Cerebral blood flow and metabolism did not differ between groups at any time during the experiment. Sagittal sinus pressure was comparable between groups throughout CPB. Tissue high-energy phosphates and water contents were similar after CPB, although cerebral lactate levels were greater in hyperglycemic ( $37.2 \pm 5.7$   $\mu$ mol/g) than normoglycemic animals ( $19.7 \pm 3.7$   $\mu$ mol/g;  $P < 0.05$ ). After CPB, pH values of cerebrospinal fluid for normoglycemic

( $7.33 \pm 0.01$ ) and hyperglycemic ( $7.34 \pm 0.01$ ) groups were similar.

**Conclusions:** Hyperglycemia during CPB significantly increases cerebral lactate levels without adversely affecting cerebral blood flow and metabolism, cerebrospinal fluid pH, or cerebral energy charge. (Key words: Cardiopulmonary bypass. Cerebral blood flow. Cerebral metabolism. Hyperglycemia.)

HYPERGLYCEMIA occurs frequently in patients undergoing cardiopulmonary bypass (CPB). Possible causes include reduced insulin secretion and peripheral glucose utilization secondary to hypothermia<sup>1,2</sup> and nonpulsatile blood flow, causing pancreatic hypoperfusion.<sup>3</sup> In addition, surgical stress can elicit a generalized sympathoadrenal response, with increased plasma levels of glucagon, epinephrine, norepinephrine, growth hormone, and cortisol,<sup>4</sup> all of which antagonize insulin and increase blood glucose. Consequently, blood glucose levels during CPB conducted with a nonglucose prime solution range from 180 to 385 mg/dL in nondiabetic patients and from 275 to 520 mg/dL in diabetic patients.<sup>1,5</sup> With glucose-containing CPB priming solution, blood glucose levels are increased to  $836 \pm 99$  mg/dL.<sup>6</sup>

The appropriate management of hyperglycemia during CPB and whether hyperglycemia adversely affects neurologic outcome remain controversial.<sup>6,7</sup> One strategy for maintaining normoglycemia throughout CPB is based primarily on studies of cerebral ischemia in experimental animals.<sup>7</sup> Yet clinical studies of hyperglycemia during CPB have not found impaired neurologic<sup>6</sup> or psychometric<sup>8</sup> outcomes. Preischemic hyperglycemia can exacerbate the extent of neurologic injury and potentiate regional lactic acidosis in brain tissue,<sup>9-11</sup> as has been shown with glucose loading in experimental animals before circulatory arrest during CPB.<sup>12</sup> Hyperglycemia can reduce cerebral blood flow,<sup>13</sup> particularly during reperfusion.<sup>14-17</sup> Further, if cerebral ischemia occurs during routine CPB, hyperglycemia could increase intracranial pressure<sup>16</sup> more

\* Visiting Assistant Professor.

† Professor and James F. Arens Chair.

‡ Associate Professor.

§ Research Associate.

|| Professor and Rebecca Terry White Chair.

Received from the Department of Anesthesiology, The University of Texas Medical Branch at Galveston, Galveston, Texas. Submitted for publication May 23, 1994. Accepted for publication October 11, 1994. Presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, California, October 15-19, 1994. Supported in part by National Institutes of Health grant R01-44944.

Address correspondence to Dr. Johnston: Department of Anesthesiology, The University of Texas Medical Branch at Galveston, Suite 2A John Sealy, 301 University Boulevard, Galveston, Texas 77555-0591.



## HYPERGLYCEMIA DURING CARDIOPULMONARY BYPASS

than the increment reported with CPB alone<sup>18</sup> and thereby reduce cerebral perfusion pressure. If these detrimental effects of hyperglycemia during CPB were confirmed, then aggressive therapy would be justified to correct and maintain normoglycemia.

The direct effects of hyperglycemia on cerebral blood flow and metabolism during CPB have not been studied, particularly where other factors affecting cerebral perfusion could be controlled. Using a canine model of hypothermic CPB, we tested the hypothesis that hyperglycemia reduces cerebral blood flow and adversely affects cerebral metabolism to a greater extent than normoglycemia.

## Materials and Methods

### Animal Preparation

The studies were conducted after approval by the institutional Animal Care and Use Committee. General anesthesia was induced with 20 mg/kg intravenous thiamylal sodium in 23 fasted, microfilaria-free mongrel dogs of either sex weighing  $24.1 \pm 1.1$  kg. After tracheal intubation, the lungs of each animal were ventilated with a tidal volume of 18 ml/kg using a volume-cycled ventilator (model 607, Harvard Apparatus, Natick, MA). The respiratory rate was adjusted to maintain normocarbida, and the  $\text{FiO}_2$  was adjusted to keep the  $\text{PaO}_2$  greater than 100 mmHg. Anesthesia was continued with 25  $\mu\text{g}/\text{kg}$  fentanyl and 0.5 mg/kg diazepam given as an initial bolus and maintained with a continuous infusion of 20  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  fentanyl and 0.25 mg  $\cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  diazepam (model AS40A infusion pump, Baxter, Santa Ana, CA). Supplemental increments of fentanyl (10  $\mu\text{g}/\text{kg}$ ) and diazepam (0.15 mg/kg) were given as necessary to maintain a suitable level of anesthesia. The total dose of each anesthetic used was recorded. Temporary muscle paralysis for sternotomy was provided by 0.15 mg/kg vecuronium bromide, with repeat boluses as necessary to control shivering.

Our experimental model of CPB has been described in detail previously.<sup>18-20</sup> Catheters were inserted into the right brachial artery for microsphere reference sampling and into the right brachial vein for fluid administration. Core temperature was measured with a precalibrated thermistor (Yellow Springs Instruments, Yellow Springs, OH) placed in the distal esophagus. A pulmonary artery catheter was inserted through the right external jugular vein to measure thermodilution cardiac output before and after CPB. The dog was

turned prone, and both temporalis muscles were dissected free from the overlying cranium. Near the junction of the frontal and parietal sutures in the middle of the skull, a 2-mm hole was drilled to expose the dorsal sagittal sinus, which was cannulated with a 22-G catheter. The catheter was secured with dental acrylic glue, and both temporalis muscles were reapproximated. Each dog received 4 mg/kg sodium heparin intravenously, with supplements of 1–1.5 mg/kg every hour, to maintain the activated clotting time greater than 400 s.

After median sternotomy, a 14-Fr vent (Sarns, Ann Arbor, MI) was inserted into the left ventricle *via* a branch of the right superior pulmonary vein. A triple lumen catheter was inserted through another side branch of the right superior pulmonary vein and guided into the left ventricle, with the proximal lumen remaining in the left atrium for microsphere administration. Pressure transducers (MPC 500, Millar Instruments, Houston, TX) were placed in the aorta and superior vena cava *via* the right internal mammary artery and vein, respectively. After incising and tenting the pericardium, a 20-Fr arterial inflow cannula was placed in the ascending aortic arch. A two-stage 40-Fr venous drainage cannula was introduced through the right atrial appendage and manually guided into the inferior vena cava. After aortic cannulation, 500 ml of autologous blood was collected in a heparinized storage bag for later administration.

The bypass pump was primed with 1,000 ml of electrolyte solution (Plasmalyte, Baxter Healthcare, Deerfield, IL) and 500 ml of Hespan (Dupont Pharmaceuticals, Wilmington, DE). A 40- $\mu\text{m}$  arterial blood filter and bubble trap (model SP3840, Pall Biomedical Products, East Hills, NY) was inserted in the arterial infusion line, and a membrane oxygenator and reservoir unit (model VPCML, Cobe Medical Products, Arvada, CO) was used. Nonpulsatile perfusion was initiated using roller pump (model 700, Sarns) at a constant pump flow rate of 100 ml  $\cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  throughout CPB. Proximal superior vena caval pressure was measured to confirm adequate drainage of the cerebral venous circulation. The  $\text{PaO}_2$  was maintained greater than 200 mmHg during bypass by adjusting the air/oxygen mixture. The gas flow rate was adjusted to maintain the  $\text{PaCO}_2$  at 40 mmHg (temperature-uncorrected method).

### Protocol

The animals were randomized into hyperglycemic or normoglycemic groups, and baseline hemodynamic



measurements and blood flow (microspheres) measurements were obtained. The hyperglycemic group ( $n = 10$ ) received a constant infusion of 50% glucose to maintain the serum glucose greater than 500 mg/dL; the normoglycemic group ( $n = 11$ ) received a comparable volume of 0.9% saline. After obtaining repeated hemodynamic and microsphere measurements, total CPB was instituted, and the left ventricle was emptied of blood. After 30 min of warm CPB and repeated measurements, the animals were cooled to an esophageal temperature of 28°C using a thermostatically controlled water bath. Hemodynamic measurements were again acquired at 1 h of hypothermia. After 2 h of hypothermia, the animals were rewarmed to 37°C and, after stabilizing for 30 min, hemodynamic and blood flow measurements were repeated. During cooling and rewarming, the temperature gradient between the water bath and esophageal probes did not exceed 10°C. Next, the left ventricular vent was clamped to allow ventricular filling, and the animal was separated from CPB. Thirty minutes after discontinuing CPB, final hemodynamic and blood flow measurements were obtained.

To examine the effects of hyperglycemia alone without CPB, two control animals were instrumented and received D<sub>50</sub>W infusion to maintain serum glucose greater than 500 mg/dL. These hyperglycemic animals had hemodynamic and blood flow measurements acquired at time intervals similar to those in the CPB groups.

#### Measurements

All intravascular pressures were measured by transducer-tipped catheters connected to a Gould ES2000 electrostatic recorder (Valley View, OH). Mean cardiac output before and after CPB was determined by thermodilution averaged from three injections of 5 ml iced saline after an initial cold flush. Blood gas analysis was performed on arterial and sagittal sinus samples (model 1304 Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA), and oxygen content and hematocrit were measured (CO-Oximeter model 282, Instrumentation Laboratory), with adjustments for canine hemoglobin. Serum osmolality was measured using a vapor pressure osmometer (Wescor, Logan, UT), and serum glucose was determined by a glucometer (Lifescan, Milpitas, CA).

Cerebral blood flow ( $\text{ml} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ ) was measured by injecting 1–2 million microspheres ( $15 \pm 3 \mu\text{m}$  in diameter) labeled with strontium 85, chromium

51, cerium 141, niobium 95, or tin 113. The dose of microspheres was chosen to ensure that all tissue samples contained more than 400 microspheres.<sup>18</sup> Each microsphere group was sonicated for 30 min, mixed with 3 ml of saline solution, vortexed, and injected over 15 s. Microspheres were injected through the left atrial catheter during spontaneous circulation and through the aortic cannula during CPB. Microspheres injected through the aortic cannula during CPB are completely mixed, with total entrapment within the cerebral circulation.<sup>18</sup> Reference sampling from the brachial artery began 10 s before the injection of microspheres, and blood was collected in separate tared vials at 6.5 ml/min over 4 min. Radioactivity in tissue samples was counted using a gamma counter (Packard Gamma Counter, Meriden, CT), with appropriate corrections for tissue sample height and overlap. Tissue blood flow ( $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ) was calculated using the formula:

$$Q_t = ((Q_r \cdot C_t) / (C_r \cdot W_t)) \cdot 100,$$

where  $Q_t$  = tissue blood flow,  $Q_r$  = reference sample flow,  $C_t$  and  $C_r$  = radioactivity in tissue and reference samples, respectively, and  $W_t$  = weight of tissue sample. Cerebral blood flow was determined from the total number of gamma counts using both entire cerebral hemispheres. Cerebral metabolic rate for oxygen ( $\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ) was calculated as [(arterial oxygen content – sagittal sinus oxygen content) (cerebral blood flow)] ÷ 100. In addition, radioactivity of the cerebellum, hippocampus, caudal brainstem, and the right and left kidneys was counted.

#### Brain Tissue Analysis

At the end of each experiment, the animal was turned prone, and a sample of cerebrospinal fluid was aspirated from the cisterna magna for pH measurement while simultaneous arterial and sagittal sinus blood samples were obtained. Next, a 2 × 3-cm hole was made through the right parietal bone. Bleeding was controlled using bone wax, and the overlying dura was excised. The dorsal cerebral cortex was biopsied near the boundary zone between the middle and anterior cerebral arteries using a high-speed suction device, which deposited 150–250 mg of tissue into liquid nitrogen within 0.5 s.<sup>19</sup>

After the cortical biopsy was obtained, the heart was arrested using a saturated potassium solution. The entire brain was quickly removed and covered with a moist towel to prevent drying. Biopsy samples from



each hemisphere were placed into tared vials, weighed, and dried in a convection oven at 85°C for at least 5 days until a stable dry weight had been obtained. Percent water content was calculated as  $[1 - (\text{dry weight}/\text{wet weight}) \times 100]$ . All of the remaining brain tissue was counted for radioactivity.

Cortical biopsy samples remained frozen at -76°C until subsequent analysis, when each sample was homogenized in liquid nitrogen, extracted with ice-cold 1N perchloric acid, and centrifuged at 10,000 g for 10 min.<sup>21</sup> The tissue pellet was analyzed for protein content using the Lowry modification of the Folin phenol reagent method.<sup>22</sup> The supernatant was filtered and analyzed for high-energy phosphates, lactate, and glucose. ATP, ADP, and AMP concentrations were measured by reverse-phase high-performance liquid chromatography. Lactate and glucose concentrations were enzymatically determined using a spectrophotometer.<sup>23</sup> All concentrations are expressed as  $\mu\text{mol/g}$  protein. The energy state of each tissue sample was calculated as adenylate energy charge, where

$$\text{energy charge} = \frac{(\text{ATP} + 0.5 \text{ ADP})}{(\text{ATP} + \text{ADP} + \text{AMP})}.$$

#### Statistical Analysis

Criteria for inclusion in the study were successful completion of the protocol and separation from CPB with stable hemodynamic parameters. Hemodynamic and blood flow data were analyzed using a two-factor analysis of variance with time as a repeated-measures factor. Fisher's least-significant difference procedure with Bonferroni adjustment was employed for all multiple comparisons. Unpaired *t* tests were used to compare the two treatment groups for high-energy phosphates, water content, and tissue metabolites. Data are presented as mean  $\pm$  SE; a *P* value less than 0.05 was considered statistically significant.

## Results

The study was successfully completed in 22 animals. One animal was eliminated from the study before bypass because of technical problems cannulating the sagittal sinus. Hyperglycemic animals required  $207 \pm 12$  g (range 150–250 g) of glucose throughout the study to maintain serum glucose levels greater than 500 mg/dL. Anesthetic requirements for fentanyl and diazepam were similar for both groups. The duration

of CPB was  $226 \pm 3$  min in normoglycemic animals and  $232 \pm 4$  min in hyperglycemic animals (*P* = NS).

Hemodynamic and blood gas data acquired before, during, and after CPB are shown in table 1. Mean aortic blood pressure decreased in both groups at the warm CPB period but returned to baseline level in the normoglycemic group. In contrast, aortic pressure in the hyperglycemic animals remained significantly lower than in normoglycemic animals after rewarming and termination of CPB. Systemic vascular resistance was comparable between groups throughout the experimental protocol but was lower in hyperglycemic animals after CPB. Values for pH,  $\text{PaO}_2$ ,  $\text{PaCO}_2$ , and serum hemoglobin remained comparable in both groups. Esophageal temperature decreased significantly in both groups during hypothermic CPB and was slightly but significantly greater in the hyperglycemic group after rewarming and termination of CPB. At all periods except baseline, serum glucose and osmolality were significantly greater in hyperglycemic animals. Of particular interest, sagittal sinus pressure did not differ between groups during the experimental procedure. Sagittal sinus pressure decreased during CPB with slight, albeit statistically significant, increases in both groups during rewarming and termination of CPB.

Adequate microsphere mixing during the study was confirmed by comparing regional blood flow in the cerebral hemispheres (left cerebral blood flow =  $[1.01]$  [right cerebral blood flow] -  $0.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ;  $r = 0.98$ ;  $P < 0.05$ ) as well as in the kidneys (left renal blood flow =  $[0.94]$  [right renal blood flow] +  $17.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ g}^{-1}$ ;  $r = 0.97$ ;  $P < 0.05$ ). Blood flow to the cerebral hemispheres, cerebellum, brainstem, and hippocampus was similar between groups at baseline and after glucose/saline administration (table 2). Blood flows to these regions increased on CPB and remained comparable between groups after rewarming. After CPB was terminated, blood flows decreased when compared with rewarm values although they were similar between groups and similar to baseline values in each group. The cerebral metabolic rate for oxygen did not differ between groups at any period, including after rewarming and termination of CPB.

Data from the cortical biopsies are shown in table 3. Brain tissue glucose was greater in the hyperglycemic group by nearly sixfold. Although high-energy phosphate levels did not differ between groups, brain lactate levels were nearly twice as great in hyperglycemic as in normoglycemic animals ( $P < 0.05$ ). After CPB was terminated, pH values in the sagittal sinus ( $P = 0.769$ )



Table 1. Hemodynamic and Oxygenation Variables during the Experimental Procedure

Variable	Group	Baseline	After Glucose/ Saline	Cardiopulmonary Bypass			
				Warm	Cold	Rewarm	Off CPB
Mean aortic pressure (mmHg)	N	93 ± 2	93 ± 4	75 ± 2*	80 ± 4	89 ± 3	94 ± 3
	H	90 ± 2	99 ± 2	73 ± 2*	76 ± 3	76 ± 3†	76 ± 3†‡§
Flow (ml/min)	N	2,764 ± 207	2,755 ± 252	2,480 ± 182	2,314 ± 167	2,406 ± 180	2,773 ± 153
	H	2,496 ± 158	3,081 ± 186	2,461 ± 111	2,453 ± 137	2,556 ± 132	3,798 ± 271
Systemic vascular resistance (dyne · s · cm <sup>-5</sup> )	N	2,817 ± 196	2,826 ± 193	2,519 ± 169	2,853 ± 195	3,047 ± 182	2,765 ± 166
	H	2,947 ± 173	2,626 ± 127	2,389 ± 108	2,535 ± 166	2,407 ± 121	1,667 ± 133*†‡§
Sagittal sinus pressure (mmHg)	N	8 ± 0.5	7 ± 0.4	4 ± 0.3*	4 ± 0.3	5 ± 0.5*	8 ± 0.7*†
	H	9 ± 0.3	8 ± 0.5	5 ± 0.4*	4 ± 0.3	5 ± 0.2*	9 ± 0.4*†
pH	N	7.38 ± 0.01	7.37 ± 0.01	7.38 ± 0.01	7.40 ± 0.01	7.37 ± 0.01	7.4 ± 0.01
	H	7.39 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.39 ± 0.01
PaO <sub>2</sub> (mmHg)	N	288 ± 14	258 ± 21	201 ± 24	248 ± 31	223 ± 16	286 ± 38
	H	263 ± 21	248 ± 21	232 ± 23	312 ± 36	168 ± 21	315 ± 32
PaCO <sub>2</sub> (mmHg)	N	37.8 ± 0.90	38.5 ± 1.0	37.4 ± 0.90	35.4 ± 0.5*	36.4 ± 0.9	37.1 ± 1.1
	H	37.4 ± 0.50	39.5 ± 0.60	39.6 ± 0.70	36.5 ± 1.1*	38.0 ± 1.3	38.8 ± 1.1
Serum glucose (mg/dl)	N	103 ± 3	103 ± 4	106 ± 5	109 ± 5	111 ± 9	91 ± 6
	H	96 ± 3	534 ± 12*†	508 ± 14†	525 ± 9†	578 ± 9*†	556 ± 15†§
Serum osmolality (mOsm/L)	N	300 ± 2	301 ± 1	303 ± 2	305 ± 2	308 ± 1	310 ± 2†§
	H	302 ± 2	323 ± 2*†	325 ± 2†	327 ± 2†	331 ± 2†	334 ± 2†‡§
Hemoglobin (mg/dl)	N	12.3 ± 0.6	12.5 ± 0.6	7.9 ± 0.7*	8.2 ± 0.6	8.8 ± 0.6	9.1 ± 0.5*†§
	H	12.9 ± 0.6	11.4 ± 0.4*	7.2 ± 0.5*	7.0 ± 0.5	8.5 ± 0.4	8.9 ± 0.4†§
Esophageal temperature (°C)	N	37.4 ± 0.2	37.2 ± 0.1	37.3 ± 0.1	27.9 ± 0.1*	37.4 ± 0.1*	36.4 ± 0.2*†‡§
	H	37.6 ± 0.2	37.2 ± 0.1	37.5 ± 0.1	28.0 ± 0.1*	37.6 ± 0.1*	37.1 ± 0.2*†

Values are mean ± SEM. CPB = cardiopulmonary bypass.  
N = normoglycemic group; H = hyperglycemic group.  
\* *P* < 0.05 versus previous value.  
† *P* < 0.05 versus normoglycemic group.  
‡ *P* < 0.05 versus glucose/saline value.  
§ *P* < 0.05 versus baseline value.

Table 2. Cerebral Blood Flow and Metabolic Rate Data for Normoglycemic (Group N) and Hyperglycemic (Group H) Animals

	Group	Baseline	After Dextrose/ Saline	Cardiopulmonary Bypass		Off CPB
				Warm	Rewarm	
Blood flow (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )						
Cerebrum	N	48 ± 4	53 ± 5	72 ± 7*	68 ± 8	53 ± 6*
	H	50 ± 3	56 ± 4	85 ± 4*	67 ± 6	48 ± 4*
Cerebellum	N	51 ± 3	56 ± 6	87 ± 10*	66 ± 7*	50 ± 6*
	H	57 ± 4	67 ± 4	99 ± 6*	75 ± 7*	50 ± 4*
Brainstem	N	40 ± 3	43 ± 4	64 ± 7*	53 ± 7*	40 ± 4*
	H	40 ± 2	47 ± 4	75 ± 6*	56 ± 6*	37 ± 3*
Hippocampus	N	49 ± 4	59 ± 7	94 ± 15*	80 ± 8	55 ± 6*
	H	54 ± 5	60 ± 6	99 ± 6*	77 ± 6	48 ± 4*
Cerebral metabolic rate for oxygen (ml · min <sup>-1</sup> · 100 g <sup>-1</sup> )	N	3.4 ± 0.3	4.1 ± 0.5	3.6 ± 0.4	3.9 ± 0.3	3.4 ± 0.4
	H	3.8 ± 0.4	3.6 ± 0.4	3.7 ± 0.3	4.2 ± 0.4	3.6 ± 0.3

Values are mean ± SEM.  
CPB = cardiopulmonary bypass.  
\* *P* < 0.05 versus previous values.



## HYPERGLYCEMIA DURING CARDIOPULMONARY BYPASS

**Table 3. Cortical Tissue Metabolites and Water Contents after Cardiopulmonary Bypass**

Variable	Normoglycemic	Hyperglycemic
ATP ( $\mu\text{mol/g}$ )	$21.3 \pm 0.7$	$20.1 \pm 1.1$
ADP ( $\mu\text{mol/g}$ )	$3.9 \pm 0.2$	$3.9 \pm 0.5$
AMP ( $\mu\text{mol/g}$ )	$0.6 \pm 0.1$	$0.8 \pm 0.2$
Water content (%)	$76.1 \pm 0.4$	$75.5 \pm 0.4$
Energy charge	$0.90 \pm 0.01$	$0.89 \pm 0.02$
Glucose ( $\mu\text{mol/g}$ )	$16.0 \pm 2.4$	$98.3 \pm 9.2^*$
Lactate ( $\mu\text{mol/g}$ )	$19.7 \pm 3.7$	$37.2 \pm 5.7^*$

Values are mean  $\pm$  SEM.

ATP = adenosine triphosphate; ADP = adenosine diphosphate; AMP = adenosine monophosphate.

\*  $P < 0.05$  versus normoglycemic group.

and cerebrospinal fluid ( $P = 0.558$ ) were similar in normoglycemic and hyperglycemic groups (table 4). Brain water content values were similar between normoglycemic ( $76.1 \pm 0.4\%$ ) and hyperglycemic ( $75.5 \pm 0.4\%$ ) animals.

In two hyperglycemic control animals that did not undergo CPB, serum glucose was maintained between  $567 \pm 9$  mg/dL (start) and  $542 \pm 29$  mg/dL (end) without adversely affecting cerebral blood flow ( $56 \pm 8$  and  $48 \pm 5$  ml  $\cdot$  min $^{-1} \cdot 100$  g $^{-1}$ , respectively) or sagittal sinus pressure ( $8 \pm 0.5$  and  $7 \pm 0.2$  mmHg, respectively). Cortical metabolic data from biopsies taken at the end of the experiments were: AMP  $0.7 \pm 0.5$   $\mu\text{mol/g}$ ; ADP  $3.2 \pm 0.6$   $\mu\text{mol/g}$ ; ATP  $24.6 \pm 4.9$   $\mu\text{mol/g}$ ; glucose  $93.2 \pm 6.9$   $\mu\text{mol/g}$ ; lactate  $21.8 \pm 0.3$   $\mu\text{mol/g}$ ; and energy charge  $0.92 \pm 0.01$ .

## Discussion

Hyperglycemia, with serum glucose levels exceeding 500 mg/dL throughout hypothermic CPB and rewarming, did not alter global cerebral blood flow or metabolism as compared with normoglycemia. Although brain tissue glucose was sixfold higher in hyperglycemic animals, there was no evidence of high-energy phosphate depletion in the brain or acidosis in the cerebrospinal fluid or sagittal sinus after CPB. Sagittal sinus pressures and brain water content values were similar in both groups, which indicates that hyperglycemia *per se* did not alter or potentiate edema formation in the brain. However, cortical lactate levels in hyperglycemic animals were nearly twice those in normoglycemic animals. The cause of the increased cortical lactate level in hyperglycemic animals after CPB is un-

clear, but possible explanations include brain ischemia (either global or focal), with resolving anaerobic metabolism, or a primary alteration in cerebral metabolism during CPB. Each of these possible explanations will be discussed further.

Nearly all animal studies demonstrating a neurotoxic effect associated with hyperglycemia have used models of global cerebral ischemia or hypoxia. Under these conditions, preischemic glucose loading has resulted in greater neuronal damage,<sup>7,17</sup> presumably secondary to lactate accumulation in the brain and tissue acidosis.<sup>10</sup> Any reduction in brain oxygen delivery to less than the critical level necessary for mitochondrial oxidative phosphorylation causes accelerated glycolysis, with pyruvate being converted to lactate rather than being dephosphorylated to form acetyl CoA. The level of brain lactate, therefore, is assumed to be a marker of inadequate oxygen supply to the brain.<sup>24</sup> Gaseous and particulate embolization frequently occurs during CPB,<sup>19</sup> and under these conditions, hyperglycemia during CPB could potentiate the extent of ischemic damage. Further, hyperglycemia could worsen any ongoing oxygen supply/demand mismatch in the brain, either by reducing cerebral blood flow<sup>13</sup> or by attenuating reperfusion,<sup>14,15</sup> possibly secondary to endothelial cell swelling.<sup>25</sup> In addition, hyperglycemia could increase intracranial pressure,<sup>16</sup> particularly after ischemia,<sup>17</sup> and reduce cerebral perfusion pressure.

In the current study, hyperglycemia did not alter cerebral perfusion or metabolism during or after hypothermic CPB. Although acute hyperglycemia has been found in rats to reduce cerebral perfusion,<sup>13</sup> prebypass glucose loading in the current study did not decrease cerebral blood flow (table 2). Likewise, Sieber *et al.* found that hyperglycemia did not alter cerebral blood flow,<sup>26</sup> although it is not clear why any discrepancy exists. Further, neither sagittal sinus pressure (as an indicator of intracranial pressure) nor brain water content differed between groups, supporting the concept

**Table 4. pH Values for Arterial, Sagittal Sinus, and Cerebrospinal Fluid Samples Obtained 30 min after Terminating Cardiopulmonary Bypass**

Sample	Normoglycemic	Hyperglycemic
Arterial	$7.43 \pm 0.01$	$7.42 \pm 0.02$
Sagittal sinus	$7.33 \pm 0.01$	$7.33 \pm 0.01$
Cerebrospinal fluid	$7.33 \pm 0.01$	$7.34 \pm 0.01$

Values are mean  $\pm$  SEM.



that vasogenic edema secondary to an altered blood-brain barrier is not produced by hypothermic CPB.<sup>20</sup> Consequently, hyperglycemia during CPB does not appear to cause global cerebral hypoperfusion nor induce global cerebral flow-metabolism mismatch, although focal areas of ischemic injury could have been missed. An inherent problem in using microspheres is the inability to accurately delineate flow defects in very small tissue regions.

During progressive cerebral hypoxia, lactate is produced by brain cells before degradation of pyridine nucleotides.<sup>27-29</sup> Mild focal ischemia severe enough to cause lactate production but not severe enough to stimulate ATP hydrolysis could have occurred in the hyperglycemic animals during CPB. However, the lactate levels found in the brains of hyperglycemic animals after CPB exceed those associated with tissue damage by acidosis from anaerobic ATP hydrolysis during severe cerebral ischemia.<sup>9,30</sup> Alternatively, because high-energy phosphates are restored more rapidly during reperfusion than lactate degradation,<sup>31</sup> our findings could indicate mild, resolving ischemic injury after termination of CPB. However, based on experimental studies of cerebral ischemia, the marked elevation of brain lactate seen in hyperglycemic animals after CPB should have been sufficient to produce significant acidosis<sup>9,30</sup> and impair restitution of adenylate energy charge during reperfusion.<sup>32</sup> In addition, cerebral oxygen metabolism after CPB was unaffected, which argues against a significant ischemic insult.<sup>33</sup> Finally, pH values obtained from the sagittal sinus and cerebrospinal fluid immediately before cortical biopsy did not indicate cerebral anaerobic metabolism. With global cerebral ischemia, cisternal cerebrospinal fluid pH parallels changes in brain intracellular pH,<sup>27</sup> although any effect of CPB on this relationship is not known. Direct measurement of brain pH, which was not performed in our study, would be necessary to confirm these findings.

Another possible explanation of our data is a primary alteration in cerebral metabolism, specifically, accelerated glycolysis relative to oxidative metabolism. Nonpulsatile CPB leads to flow-metabolism uncoupling in the brain whereby cerebral metabolism is reduced independent of cerebral perfusion.<sup>34</sup> The presence of brain lactate does not exclusively signify anaerobic metabolism, as neuronal activation alone can produce lactate by aerobic glycolysis<sup>35,36</sup> or a lactate shuttle with aerobic metabolism of glucose.<sup>37</sup> The availability of large amounts of glucose as a substrate could lead to accelerated glycolysis, particularly before CPB, with

the accumulation of pyruvate in brain cells. Normally, pyruvate would enter the citric acid cycle and undergo oxidative metabolism. This process, however, may be considerably slowed by hypothermic bypass, causing the buildup of pyruvate and, consequently, lactate. Further study of the activity of the metabolic enzymes during hypothermic CPB is necessary to support this hypothesis, as neither hypothermia<sup>38</sup> nor hyperglycemia<sup>33</sup> alone increases brain lactate levels. Nevertheless, our data support a gradual accumulation of brain lactate in hyperglycemic animals during CPB without pyridine nucleotide hydrolysis so that tissue buffers could bind available protons without changing tissue pH.<sup>30,39</sup> Although an increase in brain lactate could be secondary to diffusion from the blood, blood pH values were similar in both groups (table 1), and animal studies of lactate infusions have shown no<sup>40</sup> or minimal<sup>41</sup> transport of lactate from the blood into the brain.

Although cerebral blood flow was unchanged after terminating CPB when compared to baseline, it should have been substantially greater because of effects from hemodilution. The exact etiology of this finding is not clear but has been noted previously.<sup>19</sup> Further, data from the current study indicate that hyperglycemia during CPB does not worsen or exacerbate this process. Another consideration is whether the use of glucose-containing solutions during CPB decreases perioperative fluid requirements and postoperative fluid retention.<sup>6</sup> These parameters were not evaluated in the current study, although brain water content and serum hemoglobin values were similar between normoglycemic and hyperglycemic animals. In our study, hemodynamic parameters appeared comparable between groups except for a reduction in systemic vascular resistance in hyperglycemic animals after CPB, which may reflect a higher body temperature (table 1).

Several potentially confounding influences should be discussed. The current study targeted serum glucose in the hyperglycemic group at 500 mg/dL, and any detrimental effect from higher levels is unknown. However, this level exceeds that generally found in patients undergoing cardiac surgery,<sup>1,5</sup> and the adverse effects of glucose in cerebral ischemia appear to be dose-dependent, with a plateau at 650 mg/dL.<sup>30</sup> Second, our experimental animals did not have overt, co-existing cerebral ischemia, and under those conditions, hyperglycemia could be anticipated to potentiate ischemic consequences with lactic acidosis. Such conditions may exist during hypothermic circulatory arrest,



## HYPERGLYCEMIA DURING CARDIOPULMONARY BYPASS

in which hyperglycemia has been shown to reduce brain intracellular pH.<sup>12</sup> Third, our CPB experiments were performed under hypothermic conditions; extrapolation to normothermic CPB should not be inferred. Although hyperglycemia potentiated neural ischemic injury in rats by worsening blood-brain barrier breakdown, hypothermia (30°C) attenuated any alteration in cerebrovascular permeability.<sup>42</sup> Finally, any effect of subsequent cerebral ischemia in brain tissue having a preexisting elevated lactate level is unknown. Hyperglycemia during CPB could increase the brain's susceptibility to ischemia in the postbypass period by reducing the buffer capacity of the extracellular space. Depletion of tissue buffers as a result of prior utilization could predispose the brain to more severe ischemic consequences from any subsequent oxygen supply/demand mismatch.

We conclude that hyperglycemia begun before and continued throughout the course of hypothermic CPB does not adversely affect cerebral blood flow or oxygen metabolism, sagittal sinus pressure, or brain water content. Although brain tissue glucose was markedly elevated, levels of high-energy phosphates were similar to those found in normoglycemic CPB animals as well as in hyperglycemic control animals. However, brain lactate was elevated twofold, which could be interpreted as mild resolving cerebral ischemia, although this possibility seems less likely in our CPB model. Rather, lactate accumulation in the brain during CPB could occur secondary to an alteration in cerebral glucose metabolism resulting from accelerated glycolysis relative to ongoing oxidative metabolism.

The authors thank Tatsuo Uchida, M.S., for statistical analysis, Kimberly Jackson and Mitra Madani, for manuscript preparation, Faith McLellan, for editorial review, and Karen Inners-McBride and Gregory Asimakis, Ph.D., for brain tissue analysis.

## References

- Lehot JJ, Piriz H, Villard J, Cohen R, Guidollet J: Glucose homeostasis: Comparison between hypothermic and normothermic cardiopulmonary bypass. *Chest* 102:106-111, 1992
- Kuntschen FR, Galletti PM, Hahn C: Glucose-insulin interactions during cardiopulmonary bypass: Hypothermia versus normothermia. *J Thorac Cardiovasc Surg* 91:451-459, 1986
- Nagaoka H, Innami R, Watanabe M, Satoh M, Murayama F, Funakoshi N: Preservation of pancreatic beta cell function with pulsatile cardiopulmonary bypass. *Ann Thorac Surg* 48:798-802, 1989
- Kuntschen FR, Galletti PM, Hahn C, Arnulf JJ, Isetta C, Dor V: Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. *J Thorac Cardiovasc Surg* 89:97-106, 1985
- Mills NL, Beaudet RL, Isom OW, Spencer FC: Hyperglycemia during cardiopulmonary bypass. *Ann Surg* 177:203-205, 1973
- Metz S, Keats AS: Benefits of a glucose-containing priming solution for cardiopulmonary bypass. *Anesth Analg* 72:428-434, 1991
- Lanier WL: Glucose management during cardiopulmonary bypass: Cardiovascular and neurologic implications (editorial). *Anesth Analg* 72:423-427, 1991
- Frasco P, Croughwell N, Blumenthal J, Will C, Leone B, White W, Goodman D, Reves JG: Association between blood glucose level during cardiopulmonary bypass and neuropsychiatric outcome (abstract). *ANESTHESIOLOGY* 75:A55, 1991
- Plum F, Kraig RP, Pulsinelli WA: Compartmentation of acid-base balance in brain during complete ischemia. *Neurochem Pathol* 9:139-144, 1988
- Nakakimura K, Fleischer JE, Drummond JC, Scheller MS, Zornow MH, Grafe MR, Shapiro HM: Glucose administration before cardiac arrest worsens neurologic outcome in cats. *ANESTHESIOLOGY* 72:1005-1011, 1990
- Chopp M, Welch KMA, Tidwell CD, Helpert JA: Global cerebral ischemia and intracellular pH during hyperglycemia and hypoglycemia in cats. *Stroke* 19:1383-1387, 1988
- Anderson RV, Siegman MG, Balaban RS, Ceckler TL, Swain JA: Hyperglycemia increases cerebral intracellular acidosis during circulatory arrest. *Ann Thorac Surg* 54:1126-1130, 1992
- Duckrow RB, Beard DC, Brennan RW: Regional cerebral blood flow decreases during hyperglycemia. *Ann Neurol* 17:267-272, 1985
- Ginsberg MD, Welsh FA, Budd WW: Deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat: I. Local cerebral blood flow and glucose utilization. *Stroke* 11:347-354, 1980
- Kagstrom E, Smith M-L, Siesjö BK: Recirculation in the rat brain following incomplete ischemia. *J Cereb Blood Flow Metab* 3:183-192, 1983
- Fishman RA: Effects of isotonic intravenous solutions on normal and increased intracranial pressure. *Arch Neurol Psychiatr* 70:350-360, 1953
- Natale JE, Stante SM, D'Alecy LG: Elevated brain lactate accumulation and increased neurologic deficit are associated with modest hyperglycemia in global brain ischemia. *Resuscitation* 19:271-289, 1990
- Johnston WE, Vinten-Johansen J, DeWitt DS, O'Steen WK, Stump DA, Prough DS: Cerebral perfusion during canine hypothermic cardiopulmonary bypass: effect of arterial carbon dioxide tension. *Ann Thorac Surg* 52:479-489, 1991
- Johnston WE, Stump DA, DeWitt DS, Vinten-Johansen J, O'Steen WK, James RL, Prough DS: Significance of gaseous microemboli in the cerebral circulation during cardiopulmonary bypass in dogs. *Circulation* 88:319-329, 1993
- Johnston WE, DeWitt DS, Vinten-Johansen J, Stump DA, Prough DS: Phenylephrine does not reduce cerebral perfusion during canine cardiopulmonary bypass. *Anesth Analg* 79:14-18, 1994
- Asimakis GK, Sandhu GS, Conti VR, Sordahl LA, Zwischenberger JB: Intermittent ischemia produces a cumulative depletion of mitochondrial adenine nucleotides in the isolated perfused rat heart. *Circ Res* 66:302-310, 1990
- Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with the folin phenol reagent. *J Biol Chem* 193:265-275, 1951
- Asimakis GK, Zwischenberger JB, Inners-McBride K, Sordahl LA, Conti VR: Postischemic recovery of mitochondrial adenine nucleotides in the heart. *Circulation* 85:2212-2220, 1992



24. Paschen W, Djuricic B, Mies G, Schmidt-Kastner R, Linn F: Lactate and pH in the brain: Association and dissociation in different pathophysiological states. *J Neurochem* 48:154-159, 1987
25. Paljarvi L, Rehncrona S, Soderfeldt B, Olsson Y, Kalimo H: Brain lactic acidosis and ischemic cell damage: Quantitative ultrastructural changes in capillaries of rat cerebral cortex. *Acta Neuropathol* 60:232-240, 1983
26. Sieber FE, Brown PR, Wu Y, Koehler RC, Traystman RJ: Cerebral blood flow responsivity to CO<sub>2</sub> in anesthetized chronically diabetic dogs. *Am J Physiol* 264:H1069-H1075, 1993
27. Siesjö BK, Zwetnow NN: The effect of hypovolemic hypotension on extra- and intracellular acid-base parameters and energy metabolites in the rat brain. *Acta Physiol Scand* 79:114-124, 1970
28. Siesjö BK, Nilsson L: The influence of arterial hypoxia upon labile phosphates and upon extracellular and intracellular lactate and pyruvate concentrations in the rat brain. *Scand J Clin Lab Invest* 27(suppl):83-96, 1971
29. LeBlanc MH, Huang M, Vig V, Patel D, Smith EE: Glucose affects the severity of hypoxic-ischemic brain injury in newborn pigs. *Stroke* 24:1055-1062, 1993
30. Combs DJ, Dempsey RJ, Maley M, Donaldson DL, Smith C: Relationship between plasma glucose, brain lactate, and intracellular pH during cerebral ischemia in gerbils. *Stroke* 21:936-942, 1990
31. Ljunggren B, Ratcheson RA, Siesjö BK: Cerebral metabolic state following complete compression ischemia. *Brain Res* 73:291-307, 1974
32. Rehncrona S, Rosen I, Siesjö BK: Brain lactic acidosis and ischemic cell damage: I. Biochemistry and neurophysiology. *J Cereb Blood Flow Metab* 1:297-311, 1981
33. Siemkowicz E, Gjedde A: Post-ischemic coma in rat: Effect of different pre-ischemic blood glucose levels on cerebral metabolic recovery after ischemia. *Acta Neurol Scand* 110:225-232, 1980
34. Andersen K, Waaben J, Husum B, Voldby B, Bodker A, Hansen AJ, Gjedde A: Nonpulsatile cardiopulmonary bypass disrupts the flow-metabolism couple in the brain. *J Thorac Cardiovasc Surg* 90:570-579, 1985
35. Korf J, De Boer J: Lactography as an approach to monitor glucose metabolism on-line in brain and muscle. *Int J Biochem* 22:1371-1378, 1990
36. Kuhr WG, Korf J: Extracellular lactic acid as an indicator of brain metabolism: Continuous on-line measurement in conscious freely moving rats with intrastriatal dialysis. *J Cereb Blood Flow Metab* 8:130-137, 1988
37. Brooks GA: Lactate production under fully aerobic conditions. The lactate shuttle during rest and exercise. *Fed Proc* 45:2924-2929, 1986
38. Siesjö BK: *Brain Energy Metabolism*. New York, John Wiley & Sons, 1978
39. Buchalter SE, Crain MR, Kreisberg R: Regulation of lactate metabolism in vivo. *Diabetes Metab Rev* 5:379-391, 1989
40. Alexander SC, Workman RD, Lamberstein CJ: Hyperthermia, lactic acid infusion, and the composition of arterial blood and cerebrospinal fluid. *Am J Physiol* 202:1049-1054, 1962
41. Dager SR, Marro KI, Richards TL, Metzger GD: MRS detection of whole brain lactate rise during 1M sodium lactate infusion in rats. *Biol Psychiatry* 32:913-921, 1992
42. Dietrich WD, Alonso O, Busto R: Moderate hyperglycemia worsens acute blood-brain barrier injury after forebrain ischemia in rats. *Stroke* 24:111-116, 1993