CEREBRAL OXYGENATION DURING CARDIOPULMONARY BYPASS IN CHILDREN

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Objective: Previous work has found cerebral oxygen extraction to decrease during hypothermic cardiopulmonary bypass in children. To elucidate cardiopulmonary bypass factors controlling cerebral oxygen extraction, we examined the effect of perfusate temperature, pump flow rate, and hematocrit value on cerebral hemoglobin-oxygen saturation as measured by near infrared spectroscopy. **Methods:** Forty children less than 7 years of age scheduled for cardiac operations with continuous cardiopulmonary bypass were randomly assigned to warm bypass, hypothermic bypass, hypothermic low-flow bypass, or hypothermic low-hematocrit bypass. For warm bypass, arterial perfusate was 37° C, hematocrit value 23%, and pump flow 150 ml/kg per minute. Hypothermic bypass differed from warm bypass only in initial perfusate temperature (22° C); hypothermic low-flow bypass and low-hematocrit bypass differed from hypothermic bypass only in pump flow (75 ml/kg per minute) and hematocrit value (16%), respectively. Cerebral oxygen saturation was recorded before bypass (baseline), during bypass, and for 15 minutes after bypass had been discontinued. **Results:** In the warm bypass group, cerebral oxygen saturation remained at baseline levels during and after bypass. In the hypothermic bypass group, cerebral oxygen saturation increased $20\% \pm 2\%$ during bypass cooling ($p < 0.001$), returned to baseline during bypass rewarming, and remained at baseline after bypass. In the hypothermic low-flow and hypothermic low-hematocrit bypass groups, cerebral oxygen saturation remained at baseline levels during bypass but increased $6\% \pm 2\%$ ($p = 0.05$) and $10\% \pm 2\%$ ($p < 0.03$), respectively, after bypass was discontinued. **Conclusions:** In children, cortical oxygen extraction is maintained during warm cardiopulmonary bypass at full flow and moderate hemodilution. Bypass cooling can decrease cortical oxygen extraction but requires a certain pump flow and hematocrit value to do so. Low-hematocrit hypothermic bypass and low-flow hypothermic bypass can also alter cortical oxygen extraction after discontinuation of cardiopulmonary bypass. (J Thorac Cardiovasc Surg 1997;113:71-9)

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Supported in part by National Institutes of Health grant NO1-NS-1-2315.

This research was presented in part at the 1995 annual meeting of the American Heart Association in Anaheim, Calif.

Received for publication April 2, 1996; revisions requested June 25, 1996; revisions received July 26, 1996; accepted for publication July 31, 1996.

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0022-5223/97 \$5.00 + 0 12/1/77143

Despite the technical advances in cardiovascular surgery over the years, children having open cardiac operations continue to have neurologic complications.¹⁻³ Some complications appear soon after the operation, such as seizures, stroke, and coma, whereas others appear long after the operation, such as cognitive deficits and psychomotor delay. Radiologic and pathologic studies have described a spectrum of brain lesions after pediatric cardiac surgery, located mainly in the neocortex, periventricular white matter, and basal ganglia, corresponding to the neurologic deficits seen clinically.^{4,5} The spectrum of lesions is consistent with hypoxic-ischemic injury. When this injury occurs—before, during, or after the operation—remains uncertain.

During cardiopulmonary bypass (CPB), there is clearly a risk of both global and focal ischemic brain injury. Focal injury results from bubbles or particulate matter (or both) originating from the CPB circuit, heart, or aorta that embolize to the cerebral arterial circulation. Global injury results from widespread deficiency in oxygen supply relative to demand in the brain, but especially in vulnerable regions such as neocortex, hippocampus, and periventricular white matter. When cerebral oxygen insufficiency occurs in relation to CPB in children is unclear. Several aspects of CPB are known to decrease cerebral oxygen supply and increase cerebral oxygen extraction, including the use of hemodilution and low pump flows. However, cerebral oxygen supply relative to demand and cerebral oxygen extraction may not change during hypothermic CPB because cerebral oxygen demand decreases with hypothermia.

Previous work investigating the cerebral oxygen supply/demand relationship in children during hypothermic CPB have found cerebral oxygen extraction to decrease, as indicated by increases in the ratio of cerebral blood flow to cerebral metabolic rate for oxygen ($CBF/CMRO_2$), cerebrovascular hemoglobin-oxygen saturation (ScO_2) as measured by near infrared spectroscopy (NIRS), or jugular bulb hemoglobin-oxygen saturation.⁶⁻¹¹ However, these studies did not identify which CPB factors—hemodilution, pump flow, hypothermia, or arterial oxygenation—decreased cerebral oxygen extraction. The purpose of the present study was to determine the effect of temperature, pump flow, and hematocrit value on cortical oxygen extraction in children during CPB. NIRS was used to monitor hemoglobin-oxygen saturation in the cortical circulation as the index of oxygen extraction.

Methods

Study population. Children less than 7 years of age with noncyanotic cardiovascular disease scheduled for surgical repair with continuous CPB were eligible for study. Children with hemodynamic instability or preexisting pulmonary or neurologic disease were not eligible. All studies were conducted at The Children's Hospital of Philadelphia and were approved by its Institutional Review Board.

Before entering the operating room, children were randomly assigned to one of four groups on the basis of the CPB technique to be used during the operation: (1) warm CPB, (2) hypothermic CPB, (3) hypothermic low-flow CPB, or (4) hypothermic low-hematocrit CPB. Anesthetic management was standardized. Preanesthetic medications included oral atropine (20 μ g/kg), pentobar-

bital (4 mg/kg), and meperidine (3 mg/kg). Anesthesia was induced by inhalation of halothane and nitrous oxide in oxygen. After insertion of an intravenous catheter, halothane and nitrous oxide were discontinued and fentanyl (20 μ g/kg), scopolamine (7 μ g/kg), and pancuronium (0.2 mg/kg) were administered intravenously. The trachea was intubated and the lungs were mechanically ventilated with isoflurane (0.5% to 1% inspired) in oxygen. Heparin (200 units/kg) was administered intravenously before CPB. During anesthetic induction and surgical preparation, patients were surface cooled to 33° to 35° C by exposure to a 15° C ambient operating room.

CPB technique was standardized as much as possible between study groups, except for pump flow, temperature, and hematocrit value. The duration of CPB varied among the patients depending on the surgical repair. The CPB circuit used a nonpulsatile pump (Sarns 7000; Sarns, 3M Health Care Cardiovascular Systems), heat exchanger (Homeotherm; Cincinnati Sub-zero), and bubble oxygenator (Bentley Bio-5; Baxter Healthcare Corp., Bentley Div.) receiving oxygen at a rate of 1 to 2 L/min. Arterial filters and carbon dioxide were not used. Systemic arterial perfusion was accomplished through a cannula placed in the proximal ascending aorta. Systemic venous return was achieved by direct cannulation of the right atrium. During repairs of atrial septal defects or pulmonary valves, ventricular fibrillation was induced by topical cooling of the heart with ice water. During aortic valve repairs, cardiac asystole was induced by coronary perfusion with cardioplegic solution. The pump prime contained heparin (1500 units), mannitol (0.5 gm/kg), cefazolin (25 mg/kg), furosemide (1 mg/kg), methylprednisolone (30 mg/kg), fentanyl (30 μ g/kg), and pancuronium (0.2 mg/kg). In the warm, hypothermic, and hypothermic low-flow CPB groups, electrolyte solution (Plasma-Lyte A; Travenol Laboratories) and whole blood were added to the pump. In the hypothermic low-hematocrit CPB group, electrolyte solution (Plasma-Lyte A) and albumin 5% (250 ml) were added to the pump (bloodless prime). When blood was used in the pump prime, calcium chloride (500 mg), sodium bicarbonate (25 mEq), and heparin (1500 units) were also added.

Management of CPB pump flow and perfusate temperature was as follows. In the warm CPB group, arterial perfusate temperature and pump flow were 37° C and 150 ml/kg per minute, respectively. In the hypothermic CPB group, pump flow was 150 ml/kg per minute and arterial perfusate temperature was 22° C until nasopharyngeal and esophageal temperatures reached 25° C to 28° C; then perfusate temperature was adjusted to this body temperature to maintain it for several minutes, the duration depending on the surgical repair. For rewarming, perfusate temperature was increased to 36° to 38° C. In the hypothermic low-flow CPB group, arterial perfusate temperature and pump flow rate were initially the same as in the hypothermic CPB group. When nasopharyngeal and esophageal temperatures reached 25° to 28° C, pump flow was decreased to 75 ml/kg per minute and perfusate temperature was adjusted to maintain this body temperature. For rewarming, pump flow was increased to 150 ml/kg per minute and perfusate temperature was increased to 36° to 38° C, as in the hypothermic CPB group.

In the hypothermic low-hematocrit CPB group, pump flow and arterial perfusate temperature were treated the same as in the hypothermic CPB group for cooling and rewarming.

CPB was discontinued after the cardiovascular lesion was repaired, hemodynamics and pulmonary function were acceptable, and esophageal and nasopharyngeal temperatures were greater than 35° C. Whole blood or red blood cells (concentrated from the CPB reservoir) and calcium gluconate (30 mg/kg) were infused intravenously as needed. Protamine (4 mg/kg) was administered intravenously after CPB had been discontinued. No other anesthetic or vasoactive drugs were administered during CPB.

NIRS methodology. NIRS is a noninvasive, optical technique that relies on the relative transparency of biologic tissues to near infrared light (700 to 1000 nm) where oxygenated and deoxygenated hemoglobin have distinct absorption spectra. By measuring the change in optical density at wavelengths where the extinctions of oxygenated and deoxygenated hemoglobin differ, it is possible to monitor ScO_2 or concentrations of oxyhemoglobin and deoxyhemoglobin, depending on the design of the NIRS instrument. NIRS differs from pulse oximetry in several respects. Pulse oximetry looks for a pulse-gated change in optical density in the tissue to determine arterial saturation, whereas NIRS looks at total optical density in the tissue and thereby monitors oxygen saturation in the tissue circulation (capillaries, arterioles, and venules). NIRS reflects oxygen extraction by the tissue and is influenced by tissue oxygen transport factors, such as CBF, $CMRO_2$, arterial hemoglobin concentration, arterial oxygen saturation, and hemoglobin binding affinity to oxygen. In contrast, pulse oximetry is influenced mainly by cardiopulmonary factors and reflects one component of tissue oxygen supply. At present, NIRS is limited to monitoring change in ScO_2 from baseline (ΔScO_2) because of uncertainties in optical path length and light scattering in tissue. Baseline ScO_2 is unknown.

The NIRS instrument used in this study (Run-man, NIM Incorporated, Philadelphia, Pa.) consisted of an optical probe that housed a light source and two photo diode detectors filtered for 760 nm and 850 nm light. The probe was connected by a 2 m wire bundle to a main unit housing the electronic hardware. The main unit sent the optical data via an analog-to-digital converter (Prairie Digital, Prairie du Sac, Wis.) to a laptop computer (Gateway, Fargo, N.D.) for storage and conversion to ΔScO_2 . Change in the optical density difference between 850 nm and 760 nm ($\Delta OD_{850-760}$) was converted to ΔScO_2 from an algorithm in the form of $\Delta ScO_2 = m\Delta OD_{850-760} + b$, where m and b are experimentally derived constants.¹² The optical probe was placed on the right frontal aspect of the forehead below the hairline and secured by means of a gauze wrap. The head and probe were then covered by a light-impermeable cloth. Previous work in animal models, infants, and young children indicate the probe in this position monitors ScO_2 located in the frontal cerebral cortex.^{13, 14}

Study protocol. Baseline ScO_2 was obtained after induction of anesthesia and before the onset of CPB when all patients were in hemodynamically stable condition.

Table I. Age, weight, and duration of CPB for the study groups

	wCPB (n = 10)	cCPB (n = 10)	clfCPB (n = 9)	clhCPB (n = 9)
Age (yr)	3.2 ± 0.6	3.9 ± 0.7	3.4 ± 0.5	3.8 ± 0.6
Weight (kg)	15 ± 2	16 ± 3	15 ± 1	16 ± 2
CPB (min)	18 ± 1	27 ± 4	22 ± 2	27 ± 4

Values are mean ± standard error of the mean. wCPB, Warm CPB; cCPB, hypothermic CPB. clfCPB, hypothermic low-flow CPB; clhCPB, hypothermic low-hematocrit CPB.

Changes in ScO_2 were recorded every 15 seconds thereafter until the operation was completed. For purposes of analysis, ΔScO_2 were noted at 10 minutes after the onset of CPB, when steady state conditions had been achieved, and at 15 minutes after CPB had been discontinued, when hemodynamics, ventilation, and hematocrit value were again at steady state. ScO_2 at each time point was the signal average over that minute. During the operation, anesthesiologists and surgeons were blinded to the NIRS recordings. Other physiologic data were also recorded at baseline, 10 minutes after the onset of CPB, and 15 minutes after CPB had been discontinued. Demographic data were also noted, including duration of CPB, cardiovascular lesion, and neurologic status for 2 days after the operation. Neurologic status was judged as normal or abnormal on the basis of physical examination by the intensive care physician of record. *Abnormal* was defined as the presence of seizures, stroke, or coma (prolonged loss of consciousness, lasting >24 hours after the operation).

Statistical analysis. Data are presented as mean ± standard error of the mean. Analysis of variance was used to compare data at baseline, during CPB, and after CPB. For significant F values, multiple means were compared by Tukey's test. Significance was defined as $p < 0.05$.

Results

Forty children were enrolled in the study. Two patients were removed from the study because of protocol violations, leaving 38 patients in whom data were analyzed. Table I presents the demographic features and duration of CPB in the study groups. There were no significant differences in age, weight, or duration of CPB between groups. The cardiovascular lesions included atrial septal defects ($n = 35$), aortic stenosis ($n = 2$), or pulmonary stenosis ($n = 1$). Postoperative neurologic status was normal in all patients.

Table II displays the physiologic data before (baseline), during, and after CPB in each group. No significant differences existed between groups in any of the variables during baseline. By study design, there were significant differences between groups during CPB in nasopharyngeal temperature, mean arterial pressure, and hematocrit value. Except for

Table II. Physiologic data before, during, and after CPB

	wCPB (n = 10)	cCPB (n = 10)	clfCPB (n = 9)	clhCPB (n = 9)
Before CPB				
pH	7.46 ± 0.08	7.50 ± 0.02	7.48 ± 0.03	7.52 ± 0.02
Pco ₂ (mm Hg)	29 ± 2	27 ± 1	28 ± 2	26 ± 2
Po ₂ (mm Hg)	426 ± 65	528 ± 53	443 ± 71	350 ± 77
Hct (%)	33 ± 1	30 ± 1	31 ± 1	33 ± 1
MAP (mm Hg)	77 ± 5	80 ± 5	76 ± 4	78 ± 3
T (°C)	34 ± 1	35 ± 1	35 ± 1	35 ± 1
During CPB				
pH	7.51 ± 0.06	7.54 ± 0.02†	7.47 ± 0.02	7.48 ± 0.02
Pco ₂ (mm Hg)	27 ± 1	24 ± 2	27 ± 2	25 ± 2
Po ₂ (mm Hg)	484 ± 46	400 ± 45	509 ± 48	342 ± 37‡
Hct (%)	23 ± 1	23 ± 1	22 ± 1	16 ± 1*
MAP (mm Hg)	48 ± 3	49 ± 2	32 ± 1*	49 ± 3
T (°C)	33 ± 1*	26 ± 2	27 ± 1	28 ± 1
After CPB				
pH	7.52 ± 0.02	7.57 ± 0.02	7.53 ± 0.03	7.51 ± 0.02
Pco ₂ (mm Hg)	29 ± 2§	25 ± 1	25 ± 1	28 ± 2
Po ₂ (mm Hg)	438 ± 59	553 ± 33	491 ± 47	425 ± 49
Hct (%)	35 ± 1	35 ± 1	33 ± 1	32 ± 1
MAP (mm Hg)	67 ± 4	67 ± 4	69 ± 4	70 ± 4
T (°C)	35 ± 1	36 ± 1	36 ± 1	36 ± 1

Values are mean ± standard error of the mean. wCPB, Warm CPB; cCPB, hypothermic CPB; clfCPB, hypothermic low-flow CPB; clhCPB, hypothermic low-hematocrit CPB; Pco₂, arterial carbon dioxide tension; Po₂, arterial oxygen tension; Hct, hematocrit value; MAP, mean arterial pressure; T, nasopharyngeal temperature.

**p* < 0.0001 versus other groups.

†*p* < 0.05 versus clfCPB and clhCPB.

‡*p* < 0.05 versus wCPB and clfCPB.

§*p* < 0.05 versus cCPB and clfCPB.

arterial pH, oxygen tension, and carbon dioxide tension, there were no other significant intergroup differences in physiologic data.

Fig. 1 illustrates a recording of Sco₂ during the study in a representative patient from each group and the time points from which ΔSco₂ was recorded. Fig. 2 summarizes the group changes in Sco₂ from baseline to the time points. In the warm CPB group, Sco₂ remained relatively constant during the study (Fig. 1, A), and there were no significant changes in Sco₂ during or after CPB (Fig. 2). In the hypothermic CPB group, Sco₂ increased during CPB cooling, then returned to baseline during CPB rewarming, and remained at baseline after CPB (Fig. 1, B). The increase in Sco₂ during CPB cooling (20% ± 2%) was highly significant (*p* < 0.0001) in the hypothermic CPB group (Fig. 2). In the hypothermic low-flow CPB group (Fig. 1, C), Sco₂ increased during CPB cooling at full pump flow. When pump flow was decreased, Sco₂ decreased, and after CPB was discontinued, Sco₂ increased above baseline, although in three of nine patients Sco₂ did not increase but instead remained at baseline. For the hypothermic low-flow CPB group (Fig. 2), Sco₂

during CPB was not significantly different from pre-CPB levels, although Sco₂ tended to be increased after CPB (ΔSco₂ 6% ± 3%, *p* = 0.056), reflecting the increase seen in six of nine patients. In the hypothermic low-hematocrit CPB group (Fig. 1, D), Sco₂ did not change during CPB. After CPB, however, Sco₂ increased above pre-CPB levels. For the hypothermic low-hematocrit CPB group (Fig. 2), the increase in Sco₂ (10% ± 2%) after CPB was significant (*p* < 0.03).

Discussion

Many factors influence cerebral oxygen extraction, including temperature, arterial blood gases, hematocrit value, perfusion pressure, and anesthetic drugs. During pediatric cardiac surgery, these factors are regulated mainly by the details of the CPB method, which often differ between institutions, as well as between operations in an institution. Our results indicate that CPB methods differing in temperature, hematocrit value, and pump flow can have different cortical oxygen extractions during CPB, as well as after CPB. For instance, Sco₂ remained unchanged in relation to warm CPB, reflecting a

Fig. 1. NIRS recordings from a representative patient in each group illustrating ΔScO_2 during and after CPB relative to baseline (before CPB). Arrows denote the points at which ΔScO_2 was noted for Fig. 2. Bars denote CPB interval. **A**, Warm CPB group. **B**, Hypothermic CPB group. **C**, Hypothermic low-flow CPB group. **D**, Hypothermic low-hematocrit CPB group.

maintenance of cortical oxygen extraction with this method of CPB. ScO_2 increased during hypothermic CPB but not during low-flow or low-hematocrit conditions, indicating that cooling can decrease cortical oxygen extraction but requires a certain pump flow and hematocrit to do so. Interestingly, after hypothermic low-flow or low-hematocrit CPB, ScO_2 increased above pre-CPB levels, suggesting that certain hematocrit and pump flows during CPB can alter the cortical oxygen extraction after CPB as well.

NIRS is a developing technology with potential clinical applicability to pediatric cardiac surgery.¹⁵ The spatial domain monitored by NIRS is unique and merits comment. It is useful to consider the optical probe illuminating a volume of tissue beneath it. Computer modeling describes this illuminated volume as “banana shaped,” where the light

emitter and detector in the optical probe define the ends of the banana, and the emitter-detector separation determines its length and thickness.^{16,17} For a 3 cm emitter-detector separation, the body of the banana lies 2 to 3 cm beneath the surface, indicating that our optical probe on the infant forehead illuminates frontal cerebral cortex.^{13,14,16} Within this spatial domain, NIRS is sensitive to oxyhemoglobin and deoxyhemoglobin. Because hemoglobin is located in capillaries, arteries, and veins, NIRS monitors a mixed vascular oxygen saturation, although it appears to be weighted to gas-exchanging vessels (capillaries, arterioles, and venules) rather than conductance vessels (large veins and arteries).^{7,18} A limitation of current NIRS technology is that it can only measure change in saturation from an unknown baseline rather than absolute saturation because of uncertainties in optical path length and light scat-

Fig. 2. Cerebral oxygen saturation relative to baseline (ΔScO_2) during CPB and after CPB in each group. *wCPB*, Warm CPB. *cCPB*, Hypothermic CPB. *clfCPB*, Hypothermic low-flow CPB. *clhCPB*, Hypothermic low-hematocrit CPB. By definition, $\Delta\text{ScO}_2 = 0$ at baseline. Values are mean $\pm$ standard error of the mean; $n = 9$ or 10 in each group. *Significantly different from baseline.

tering losses in tissue. However, absolute ScO_2 appears to be 60% to 75% during normoxic, normothermic conditions.¹⁹⁻²¹ In our study, baseline ScO_2 should have been in this range because all patients were well oxygenated and had normal arterial pressure and temperature.

Changes in ScO_2 correlate with changes in other indices of cerebral oxygen extraction, such as cerebral venous oxygen saturation, jugular bulb hemoglobin-oxygen saturation, and cerebral oxygen extraction ratio.^{13, 19, 21} The relationship between ScO_2 , intracellular oxygenation, and neurologic injury is not well defined. Although decreased ScO_2 indicates increased tissue oxygen extraction, it does not necessarily indicate intracellular hypoxia or cellular energy failure.^{22, 23} For instance, Nioka and associates²² found that intracellular high-energy phosphates did not decrease during mild to moderate desaturation (ΔScO_2 0% to -30%), but they did decrease during desaturation of greater severity. However, Levy, Levin, and Chance²⁴ observed neuronal dysfunction even during mild to moderate desaturation. The relationship between ScO_2 and intracellular energetics is less clear during deep hypothermia because of the changes in hemoglobin and cytochrome oxygen affinities and other enzymatic rate constants. No study, as yet, has distin-

guished whether the changes in cerebrovascular oxygen saturation during hypothermia represent pathologic or physiologic changes.

Previous studies in pediatric patients have found cerebral oxygen extraction to decrease during hypothermic CPB, as indexed by CBF/CMRO_2 ratio, NIRS, or jugular bulb hemoglobin-oxygen saturation. We reported ScO_2 to increase in neonates, infants, and children during CPB cooling to deep hypothermia before circulatory arrest.^{7, 8} Other investigators observed similar changes in NIRS, jugular bulb hemoglobin-oxygen saturation, or CBF/CMRO_2 during CPB cooling in infants and children.^{9, 10, 11, 25} However, none of these studies elucidated which patient or CPB factors influenced cerebral oxygen extraction, because each study included a variety of cardiovascular diseases (e.g., cyanotic and noncyanotic lesions) and CPB methods (e.g., temperatures and pump flows). The present study was conducted in a fairly homogeneous population of children in whom CPB perfusate temperature, pump flow, and hematocrit value were independently varied while other factors were controlled as much as possible. Our results show that hypothermia is the factor that decreases cerebral oxygen extraction, with hematocrit and pump flow as necessary cofactors.

Although cerebral oxygenation and hemodynamics may change during hypothermic CPB, existing data suggested that they return to pre-CPB levels when preoperative physiologic conditions have been restored.^{11,25} Our study also showed this to be the case for ScO_2 after hypothermic full-flow CPB, but not necessarily after hypothermic low-hematocrit or low-flow CPB, in which ScO_2 was increased after the operation. Increased ScO_2 indicates decreased cerebral oxygen extraction, although it cannot resolve whether this results from increased cerebral oxygen supply, decreased cerebral oxygen demand, or impaired oxygen flux from capillary to mitochondria and respiratory chain. After brief normothermic cardiac arrest, ScO_2 is increased as a result of increased cerebral blood flow ("reperfusion hyperemia") from the accumulation of hypoxic-ischemic vasodilator metabolites.²⁶ In our study, it is possible that the increased ScO_2 represented reperfusion hyperemia from anemic hypoxia during CPB in the hypothermic low-hematocrit CPB group, or incomplete ischemia during low-flow CPB in the hypothermic low-flow CPB group (in many but not all patients). Alternatively, cerebral oxygen metabolism is depressed after hypothermic circulatory arrest.⁸ It is also possible the increased ScO_2 in the hypothermic low-hematocrit and low-flow CPB groups represented depressed $CMRO_2$ after hypothermic low-flow or low-hematocrit CPB, whether it be from decreased demand or impaired oxygen flux.

Gaining popularity in recent years is the use of a bloodless prime for CPB, followed by hemoconcentration and transfusion of blood remaining in the reservoir after CPB. This CPB method can eliminate heterologous transfusion, with its risk of blood-borne infection, and was used in the hypothermic low-hematocrit CPB group in our study. For small children and those with preoperative anemia, very low hematocrit values during CPB can occur. Although the optimum hematocrit value for the brain during CPB is unknown, recent work in adults indicates worse neurologic outcome with lower hematocrit values.^{27,28} Combined with our observations in the hypothermic low-hematocrit CPB group, the relationship between CPB hematocrit and neurologic outcome deserves further examination in pediatric patients having cardiac operations.

Low-flow hypothermic CPB is commonly used to facilitate surgical repair of cardiovascular defects in children and was used in the hypothermic low-flow CPB group in our study. Some investigators have suggested that low-flow hypothermic CPB may be

preferable to hypothermic circulatory arrest because of concerns about worse neurologic recovery with the latter.¹ However, animal experiments show that as pump flow is decreased during hypothermic CPB, cerebral oxygen delivery decreases; furthermore, below a critical pump flow, cerebral oxygen delivery becomes insufficient for cerebral metabolic demand, at which point brain intracellular energetics decrease and become indistinguishable from circulatory arrest.²⁹ Thus the neurologic advantage of low-flow CPB over circulatory arrest disappears when pump flow falls below the critical value. To identify this critical pump flow in infants and children, Kern and colleagues³⁰ examined the effect of pump flow reduction on CBF, $CMRO_2$, and cerebral oxygen extraction ratio during moderate hypothermic CPB. They found that a 45% to 75% reduction in pump flow was accompanied by decreased CBF and $CMRO_2$ and increased cerebral oxygen extraction; this suggests that the critical pump flow is in the 50 to 75 ml/kg per minute range at 25° to 28° C in infants and children. Our ScO_2 data in the hypothermic low-flow CPB group using a 50% pump flow reduction is consistent with their data.

Among the limitations of our study was the homogeneity of the patient population, the type of CPB circuit used, and when NIRS was recorded. We studied young children with simple cardiovascular lesions and good hemodynamics; therefore CPB was brief and the system included a bubble oxygenator, respiratory alkalosis, and hemodilution. The effect of long CPB runs, membrane oxygenators, and other strategies of pH and hematocrit management on cortical oxygen extraction is unknown. Practical considerations prevented our recording NIRS before induction of anesthesia and beyond the immediate postoperative period. The effect of anesthesia and postoperative recovery of cortical oxygen extraction in relation to CPB remain unknown.

Despite advances in the care of children undergoing cardiac operations during the past decade, neurologic sequelae continue to occur.¹⁻³ Histopathologic and radiologic studies describe a spectrum of neurologic lesions after cardiac operations consistent with an ischemic pathogenesis.^{4,5} The incidence of neurologic sequelae differs between institutions, although it is not clear whether this is attributable to different methods of detecting neurologic injury or to perioperative management.² However, CPB management of temperature, hematocrit value, and pump flow frequently differs between institutions. Our results show that CPB meth-

ods differing in temperature, hematocrit value, or pump flow can result in different cortical oxygen supply/demand relationships during CPB, as well as after CPB. Whether this underlies some of the reported differences in neurologic outcome represents the next step in this avenue of investigation.

We thank Brian Uher for technical assistance and the nurses and perfusionists in the cardiac surgical operating rooms for their assistance with this study.

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Commentary

Current methods of monitoring during cardiopulmonary bypass (CPB) provide only indirect information regarding the adequacy of delivery of oxygen to the brain.

Information about blood pressure, pump flow rate, hematocrit, temperature, and mixed venous oxygen saturation allow limited inferences regarding support of the brain. For example, even complete occlusion of the superior vena cava cannula with cessation of cerebral blood flow might change few if any of these parameters. Near infrared spectroscopy (NIRS) is a relatively new technique that holds out the promise of providing more information regarding the adequacy of brain support during CPB. However, there are important differences in various NIRS machines currently under development.

The preceding paper by Kurth and colleagues describes a study of 40 children who underwent a brief period of CPB with variable cooling, hemodilution, and flow rates. The authors found that cerebral oxygen saturation determined by NIRS increased during moderately hypothermic full-flow CPB but remained at baseline if flow was reduced to half flow or if hematocrit value was less than 20% with full-flow moderately hypothermic CPB. After CPB there was an increase in cerebral oxygen saturation in the low-hematocrit group. The authors have concluded that warm full-flow CPB maintains the cerebral oxygen supply/demand relationship, that cooling increases oxygen supply relative to demand, and that low hematocrit and low flow during CPB alter the postbypass oxygen supply/demand relationship.

Although the authors have made an honest attempt to conduct a careful study of cerebral oxygen/supply demand during CPB, any inferences that can be drawn from this study are severely limited by the nature of the NIRS instrument used. Their instrument measures only the degree of oxygenation of hemoglobin within the brain, approximately 70% of which is venous with the remainder within capillaries and the arterial system. In any situation in which the oxyhemoglobin dissociation curve is shifted, particularly when shifted to the left by factors such as

alkalosis and hypothermia (present in all groups in their study), no direct inferences can be drawn regarding adequacy of oxygen supply to the critical end-organelles within the brain, namely neuronal mitochondria. An increase in mean cerebral oxyhemoglobin saturation during hypothermic CPB might just as well represent inadequate oxygen release to neuronal tissue in need of oxygen as representing an increase in supply relative to demand. In fact, one could argue, as the authors have indeed done in their discussion, that the postbypass increase in oxygen saturation may represent repayment of an oxygen debt incurred during the low-hematocrit CPB.

In contrast to the instrument used by Kurth and associates, there are other machines in development that use additional wavelengths of near infrared light and thereby have the potential to measure the redox potential of cytochrome aa3 within cerebral mitochondria. Because cytochrome aa3 is the terminal cytochrome of the electron transport chain, its redox status provides direct information regarding delivery of oxygen within cerebral neurons.

Cerebral injury continues to be one of the most important sources of morbidity after CPB, particularly when there are extreme manipulations such as deep hypothermic circulatory arrest. Although near infrared assessment of cerebral oxyhemoglobin oxygenation is a step in the right direction in improving our monitoring of the brain during CPB, it is by no means the complete solution. The development of NIRS instruments that allow reliable measurement of the redox status of cytochrome aa3 should be a high priority.

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