Cerebral Oxygenation during Pediatric Cardiac Surgery Using Deep Hypothermic Circulatory Arrest

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Background: Deep hypothermic circulatory arrest is a widely used technique in pediatric cardiac surgery that carries a risk of neurologic injury. Previous work in neonates identified distinct changes in cerebral oxygenation during surgery. This study sought to determine whether the intraoperative changes in cerebral oxygenation vary between neonates, infants, and children and whether the oxygenation changes are associated with postoperative cerebral dysfunction.

Methods: The study included eight neonates, ten infants, and eight children without preexisting neurologic disease. Cerebrovascular hemoglobin oxygen saturation (Sc_{O_2}), an index of brain oxygenation, was monitored intraoperatively by near-infrared spectroscopy. Body temperature was reduced to 15°C during cardiopulmonary bypass (CPB) before commencing circulatory arrest. Postoperative neurologic status was judged as normal or abnormal (seizures, stroke, coma).

Results: Relative to preoperative levels, the age groups experienced similar changes in Sc_{O_2} during surgery: Sc_{O_2} increased 30 ± 4% during deep hypothermic CPB, it decreased 62 ± 5% by the end of arrest, and it increased 20 ± 5% during CPB recirculation (all $P < 0.001$); after rewarming and removal of CPB, Sc_{O_2} returned to preoperative levels. During arrest, the half-life of Sc_{O_2} was 9 ± 1 min in neonates, 6 ± 1 min in infants, and 4 ± 1 min in children ($P < 0.001$). Postoperative neurologic status was abnormal in three (12%) patients. The Sc_{O_2} increase during deep hypothermic CPB was less in these patients than in the remaining study population (3 ± 2% *versus* 33 ± 4%, $P < 0.001$). There were no other significant Sc_{O_2} differences between outcome groups.

Conclusions: Brain oxygenation changed at distinct points during surgery in all ages, reflecting fundamental cerebral

responses to hypothermic CPB, ischemia, and reperfusion. However, the changes in Sc_{O_2} half-life with age reflect developmental differences in the rate of cerebral oxygen utilization during arrest, consistent with experimental work in animals. Certain intraoperative cerebral oxygenation patterns may be associated with postoperative cerebral dysfunction and require further study. (Key words: Anesthesia: pediatric; cardiac. Brain: hypoxia; injury; ischemia; metabolism. Hypothermia. Monitoring: hemoglobin; near-infrared spectroscopy; oxygenation.)

DEEP hypothermic circulatory arrest is a widely used technique in the repair of cardiovascular malformations in neonates, infants, and children. Although the technique permits repair of otherwise inoperable lesions and may facilitate repair of others, there is a risk of neurologic injury. Clinical studies have identified risk factors for cerebral dysfunction after deep hypothermic arrest, including duration of arrest,[1–3] duration of cooling and arterial carbon dioxide tension (Pa_{CO_2}) during cardiopulmonary bypass (CPB) before arrest,[2–5] and arterial pH, electroencephalographic activity, and somatosensory evoked potentials during recirculation after arrest.[2,6] However, the causal relation between these risk factors and neurologic outcome remains unclear. Experimental studies[7–11] suggest that another risk factor for cerebral dysfunction after deep hypothermic arrest is age of the patient, in that neurologic risk is less in neonates than in children. It has been known for many years that neurologic tolerance to ischemia is greatest in the newborn and decreases with development.[7,8] Subsequent work has shown that developmental changes in the rate of cerebral oxygen utilization, maintenance of cellular energetics, and brain ionic regulation play a substantial role in the neonate's neurologic tolerance to ischemia.[9,11–13] However, the existence of developmental changes in the rate of cerebral oxygen utilization in pediatric patients during deep hypothermic arrest is unknown.

In a previous study[14] of neonates undergoing heart surgery using hypothermic arrest, we observed distinct changes in cerebral oxygenation with cooling during

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CPB, during circulatory arrest, and upon reinstituting CPB. Near-infrared spectroscopy (NIRS) was used to monitor cerebrovascular hemoglobin oxygen saturation (Sc_{O_2}) as the index of oxygenation. NIRS is a relatively new, optical method to monitor hemoglobin located in the gas-exchanging circulation (capillaries, arterioles, venules). Because NIRS is portable, noninvasive, and sensitive to changes in tissue oxygenation, it has clinical promise to investigate the rate of cerebral oxygen utilization during deep hypothermic arrest as well as to examine putative mechanism(s) of neurologic dysfunction associated with cerebral oxygen transport during cardiac surgery. The primary aim of the current study was to determine whether changes in Sc_{O_2} during cardiac surgery using deep hypothermic arrest vary with the age of the patient (neonates *vs.* infants *vs.* children). A secondary aim was to examine the association of intraoperative changes in Sc_{O_2} with postoperative cerebral dysfunction in these patients.

Materials and Methods

Neonates (aged <1 month), infants (aged 1–12 months), and children (aged 1–4 yr) in whom cardiac surgery using deep hypothermic circulatory arrest was planned were eligible for study. Patients with preexisting neurologic disease or a history of cardiovascular instability were excluded. All studies were approved by the Institutional Review Board at The Children's Hospital of Philadelphia, and informed verbal assent was obtained from a parent.

Anesthetic and surgical procedures were performed according to our institutional clinical practice. Preanesthetic medications included atropine (20 μg/kg orally), pentobarbital (4 mg/kg orally), and meperidine (3 mg/kg orally) for children, and atropine only for infants and neonates. All children were anesthetized with isoflurane (0.5% inspired), fentanyl (15 μg/kg intravenously), and pancuronium (0.2 mg/kg intravenously). After induction, the trachea was intubated and the lungs were mechanically ventilated. Heparin (200 U/kg) was administered intravenously before CPB. Management of CPB was according to alphastat principles. The CPB circuit used a bubble oxygenator and a nonpulsatile pump flowing at 150 ml · kg^{-1} · min^{-1}. The pump prime (approximately 700 ml) contained 25 mEq sodium bicarbonate, 500 mg calcium chloride, 200 U/kg heparin, 40 μg/kg fentanyl, 0.2 mg/kg pancuronium, 30 mg/kg methylprednisolone, 1 mg/kg furosemide, and 0.5 g/kg mannitol.

Whole blood and Plasma-lyte A (Travenol Laboratories) were added to yield a hematocrit of 22–25%. No other anesthetics or vasoactive drugs were administered during CPB.

Deep hypothermia was induced by core cooling during CPB. Arterial perfusate temperature in the CPB circuit was 12°C. Total circulatory arrest commenced when nasopharyngeal, esophageal, and rectal temperatures were between 15°C and 20°C. Hypothermia was maintained during arrest by use of ice bags surrounding the head, a cold ambient temperature (15°C), and a circulating water blanket (15°C) underneath the patient. The duration of CPB and circulatory arrest varied among the patients, depending on the rate of body temperature decrease and the complexity of the surgical procedure. After circulatory arrest, CPB was resumed at 150 ml · kg^{-1} · min^{-1}. Normothermia was achieved in 15–20 min by gradually increasing the arterial perfusate temperature in the CPB circuit. CPB was discontinued when hemodynamics were acceptable. In the intensive care unit, mechanical ventilation was discontinued, and the trachea was extubated when patients were awake, lung function and hemodynamics were satisfactory, and bleeding from chest tubes was minimal. Extubation was planned on postoperative day 1 for infants and children and on postoperative day 1 or 2 for neonates. These patients did not receive opioids, muscle relaxants, or other sedative drugs in the intensive care unit postoperatively.

NIRS Methodology

NIRS is a noninvasive, optical technique based on the relative transparency of biologic tissues to near-infrared light (700–1,000 nm), where oxygenated and deoxygenated hemoglobin have distinct absorption spectra. By measuring change in optical density at wavelengths in which the extinctions of oxygenated and deoxygenated hemoglobin differ, it is possible to monitor Sc_{O_2}.[15–17] NIRS differs from pulse oximetry in several respects. Pulse oximetry looks for a pulse-gated change in optical density and thereby determines arterial hemoglobin oxygen saturation (Sa_{O_2}). In contrast, NIRS looks at total optical density in the tissue and thereby monitors hemoglobin oxygen saturation in a cross-section of the circulation (capillaries, arterioles, and venules). Pulse oximetry monitors absolute Sa_{O_2}, although its accuracy is limited to a narrow range (80–100%). In contrast, NIRS monitors change in Sc_{O_2} relative to an unknown baseline, and it can accurately measure the change in Sc_{O_2} throughout the entire saturation

range (0–100%).[15-17] The change in NIRS-derived Sc_{O_2} reflects a change in the oxygen supply/demand relation in the brain, as it is influenced by cerebral blood flow (CBF), Sa_{O_2}, and rate of cerebral oxygen consumption (CMR_{O_2}).[15,18,19] In contrast, pulse oximetry-derived Sa_{O_2} reflects only one component of cerebral oxygen supply.

The near-infrared spectrophotometer used in this study (NIM, Philadelphia, PA) consisted of a custom-designed optical probe that housed the light source and two photodiode detectors filtered for 760 and 800 nm, respectively. Change in the optical density difference (ΔOD) between 760 and 800 nm was converted to ΔSc_{O_2} by an algorithm in the form of $\Delta Sc_{O_2} = m\Delta OD + b$, where m and b are experimentally derived constants.[15-17,20] The probe was connected to a main unit housing the electronic hardware, which sent data to a strip chart recorder (Linear Instruments, Reno, NV). The optical probe was placed on the right, frontal aspect of the forehead below the hairline. Previous work[15,21,22] has indicated that, in this position, the probe monitors Sc_{O_2} located in the frontal cerebrum and that the scalp and skull overlying the brain do not contribute to the optical signal.

Study Protocol

Baseline Sc_{O_2} was obtained after anesthetic induction, when patients were normothermic and hemodynamically stable. Changes in Sc_{O_2} were recorded continuously thereafter until the surgical procedure was completed. For purposes of analysis, we noted the changes in Sc_{O_2} relative to baseline at the following points during the procedure: (1) on deep hypothermic CPB immediately before the onset of circulatory arrest (cCPB), (2) the end of circulatory arrest (arrest), (3) on recirculation 3 min after resuming CPB (rCPB), (4) on normothermic CPB 15 min after resuming CPB (wCPB), and (5) 15 min after discontinuing CPB (end). In addition, the half-life of Sc_{O_2} ($t_{1/2}$) during circulatory arrest was calculated in each patient as follows. Previous studies[14,23] have reported a curvilinear decrease in Sc_{O_2} during circulatory arrest, which can be described by an exponential function,

$$\Delta Sc_{O_2} = ae^{-kt}, \tag{1}$$

where t is time after the onset of arrest, and k and a are constants. This function may be expressed in terms of the half-life of ΔSc_{O_2} ($t_{1/2}$), given by the equation;

$$t_{1/2} = 0.693/k. \tag{2}$$

The change in Sc_{O_2} *versus* time curve during circu-

latory arrest in each patient was fit to equation 1 by least-squares regression, and k was determined. The half-life of Sc_{O_2} during arrest was calculated according to equation 2.

Demographic and physiologic data that might influence Sc_{O_2}, $t_{1/2}$, or neurologic outcome were recorded. These data included duration of CPB and circulatory arrest; nasopharyngeal temperature, hematocrit, mean arterial pressure, arterial blood gases and pH, and Sa_{O_2} at points 1 through 5, above; and episodes of cardiac arrest in the intensive care unit. Neurologic status was assessed for 3 days postoperatively by one of us (J.M.S.), who was blinded to the NIRS data. Neurologic outcome was judged as either normal or abnormal based on physical examination; abnormal was defined as presence of seizures, stroke, or coma (prolonged loss of consciousness, lasting >24 h postoperatively).

Statistical Analysis

Data are presented as mean ± SEM. Analysis of variance was used to compare data between groups (neonates *vs.* infants *vs.* children, abnormal *vs.* normal neurologic postoperative status, or Sc_{O_2} at baseline *vs.* each of the 5 points). For significant F values, multiple means were compared by Tukey's test. Least-squares regression was used to analyze the relation between Sc_{O_2} half-life and age of the patient. Significance was defined as $P < 0.05$.

Results

Eight neonates (aged 11 ± 3 days), ten infants (aged 5 ± 1 months), and eight children (aged 23 ± 3 months) were studied. Table 1 displays the cardiovascular diagnoses and duration of CPB and circulatory arrest in each age group. CPB and circulatory arrest durations were similar between age groups. Circulatory arrest ranged from 17 to 60 min. Surgical operations included complete repair of the malformation, or for single ventricle lesions, palliation with either the Norwood, hemi-Fontan, or Fontan procedures. There were no deaths or episodes of cardiac arrest in the intensive care unit during the study. Table 2 presents the physiologic data at baseline, cCPB, wCPB, arrest, and end of the study in the age groups. Comparing physiologic data between age groups, there were no significant differences except for mean arterial pressure at baseline and end, which were lower in neonates than in infants and children.

Figure 1 illustrates the changes in Sc_{O_2} during the

Table 1. Cardiovascular Diagnoses and Duration of CPB and Circulatory Arrest by Age Group

	Neonates (n = 8)	Infants (n = 10)	Children (n = 8)
Diagnosis (n)			
VSD	1	4	
AVC	1	3	
SVL	4	2	5
TOF	1		1
APV			2
TGA	1		
ACA		1	
Time (min)			
Prearrest CPB	10 ± 1	11 ± 2	12 ± 1
Arrest	44 ± 5	36 ± 5	34 ± 4
Postarrest CPB	24 ± 2	21 ± 2	23 ± 2

Values are mean ± SEM or number of patients.

VSD = ventricular septal defect; AVC = atrioventricular canal; SVL = single ventricle lesion; TOF = tetrology of Fallot; APV = anomalous pulmonary veins; TGA = transposition of great arteries; ACA = anomalous coronary artery; CPB = cardiopulmonary bypass.

study in a representative patient as well as the times (cCPB, arrest, rCPB, wCPB, and end) from which ΔSc_{O_2} was recorded. Figure 2 summarizes the changes in Sc_{O_2} from baseline to each of the times for the age groups. Evident in figure 2, significant changes in Sc_{O_2} occurred relative to baseline in each age group at cCPB ($P < 0.001$), arrest ($P < 0.001$), and rCPB ($P < 0.001$). The changes in Sc_{O_2} at all times were similar in neonates, infants, and children. For the age groups, ΔSc_{O_2} averaged +30 ± 4% at cCPB, −62 ± 5% at arrest, and +20 ± 4% at rCPB. After rewarming during CPB (wCPB) and after CPB (end), Sc_{O_2} was not significantly different from baseline.

Figure 3 presents the half-life of Sc_{O_2} during circulatory arrest as a function of the patient's age. Sc_{O_2} half-life was inversely related to age, ranging from 12 min in a neonate to slightly less than 3 min in a child aged 17 months. As indicated by the log function, the changes in Sc_{O_2} half-life were greatest during the first year of life. When grouped according to age, Sc_{O_2} half-lives were 9 ± 1 min for neonates, 6 ± 1 min for infants, and 4 ± 1 min for children ($P < 0.001$).

Postoperative neurologic status was abnormal in 3 of 26 patients (12%), 1 patient in each age group: after closure of a ventricular septal defect, a neonate had seizures on postoperative day 1; after repair of an anomalous coronary artery, an infant had coma (consciousness did not return until postoperative day 2); and after a Fontan procedure, a child had coma (con-

sciousness did not return until postoperative day 3). The other 23 patients had normal neurologic status postoperatively: they were awake and responded appropriately to tactile, verbal, and visual stimulation within 24 h postoperatively, and they did not manifest seizure activity or evidence of stroke. Age of the patients with abnormal neurologic status (9 ± 7 months) was similar to those with normal status (9 ± 2 months).

Comparing the abnormal and normal neurologic status groups, two significant differences emerged. First, in cerebral oxygenation (fig. 4), ΔSc_{O_2} at cCPB was less in the abnormal neurologic status group compared with the normal group (3 ± 2% vs. 33 ± 4%, $P < 0.001$).

Table 2. Physiologic Data during the Study by Age Group

	Neonates (n = 8)	Infants (n = 10)	Children (n = 8)
Sa_{O_2} (%)			
Baseline	94 ± 3	97 ± 2	92 ± 2
cCPB	100	100	100
wCPB	100	100	100
End	94 ± 3	97 ± 3	93 ± 5
Pa_{CO_2} (mmHg)			
Baseline	29 ± 3	30 ± 2	29 ± 1
cCPB	25 ± 2	26 ± 1	26 ± 2
wCPB	28 ± 2	28 ± 2	26 ± 1
End	28 ± 2	31 ± 2	29 ± 2
pH			
Baseline	7.49 ± 0.04	7.45 ± 0.02	7.44 ± 0.02
cCPB	7.46 ± 0.04	7.45 ± 0.03	7.48 ± 0.02
wCPB	7.46 ± 0.04	7.45 ± 0.03	7.49 ± 0.02
End	7.51 ± 0.03	7.49 ± 0.02	7.51 ± 0.03
Hct (%)			
Baseline	33 ± 2	33 ± 2	36 ± 2
cCPB	24 ± 1	25 ± 1	24 ± 1
wCPB	24 ± 1	25 ± 1	24 ± 1
End	32 ± 2	32 ± 2	34 ± 1
MAP (mmHg)			
Baseline	51 ± 5*	68 ± 3	73 ± 4
cCPB	47 ± 2	58 ± 4	51 ± 5
Arrest	0	0	0
wCPB	61 ± 5	65 ± 5	67 ± 4
End	64 ± 3*	74 ± 2	82 ± 4
NP temperature (°C)			
Baseline	35 ± 1	36 ± 1	35 ± 1
cCPB	15 ± 1	16 ± 1	16 ± 1
Arrest	17 ± 1	17 ± 1	18 ± 1
wCPB	36 ± 1	36 ± 1	36 ± 1
End	36 ± 1	36 ± 1	36 ± 1

Values are mean ± SEM.

Sa_{O_2} = arterial hemoglobin O_2 saturation; Pa_{CO_2} = arterial carbon dioxide tension; Hct = hematocrit; MAP = mean arterial pressure; NP = nasopharyngeal.
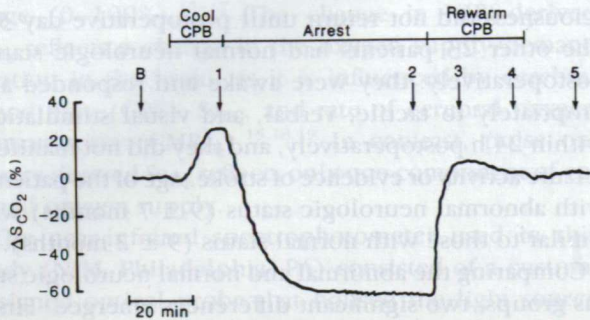
* $P < 0.05$ versus infants and children.

Fig. 1. Near-infrared spectroscopy (NIRS) record of the changes in cerebrovascular hemoglobin oxygen saturation (ΔSc_{O_2}) illustrating the points at which ΔSc_{O_2} was captured and the deoxygenation curve during circulatory arrest. The patient was aged 9 months undergoing a hemi-Fontan operation. B = baseline at normothermia; 1 = on deep hypothermic cardiopulmonary bypass (cCPB); 2 = at the end of circulatory arrest (arrest); 3 = on recirculation 3 min after resuming CPB (rCPB); 4 = normothermic CPB (wCPB); 5 = after CPB (end). By definition, ΔSc_{O_2} = 0 at baseline.
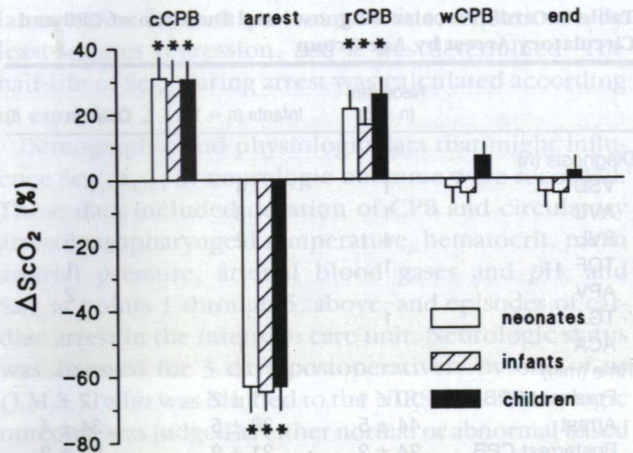
Second, in the CPB and physiologic data (table 3), the duration of prearrest CPB was significantly shorter in the abnormal neurologic status group compared with the normal group ($P < 0.05$). No other significant differences existed in CPB, physiologic, or ΔSc_{O_2} data between neurologic status groups. Sc_{O_2} half-life also was not significantly different between groups (abnormal vs. normal, 5.6 ± 1.2 min vs. 6.2 ± 0.5 min, $P = 0.30$).

Discussion

Neonates, infants, and children experienced distinct changes in Sc_{O_2} during cardiac surgery. The magnitude of the Sc_{O_2} changes during hypothermic CPB, the end of arrest, and during recirculation were identical between age groups, reflecting fundamental cerebral responses to hypothermic CPB, ischemia, and reperfusion. The rate of Sc_{O_2} change during arrest, however, was inversely related to age, reflecting a lower rate of cerebral oxygen utilization during hypothermic ischemia in neonates than in children, consistent with experimental work in developing animals during normothermic ischemia.[9,11–13] As a secondary aim, the changes in Sc_{O_2} were examined with respect to acute neurologic outcome in the entire study population. Interestingly, of all the Sc_{O_2} changes during surgery, the one associated with postoperative cerebral dysfunction was ΔSc_{O_2} during hypothermic CPB before arrest. This supports other work[4,5,24,25] suggesting the period of

Fig. 2. Changes in cerebrovascular hemoglobin oxygen saturation (ΔSc_{O_2}, from baseline) at each condition during cardiac surgery in neonates (n = 8), infants (n = 10), and children (n = 8). B = baseline at normothermia; 1 = on deep hypothermic cardiopulmonary bypass (cCPB); 2 = at the end of circulatory arrest (arrest); 3 = on recirculation 3 min after resuming CPB (rCPB); 4 = normothermic CPB (wCPB); 5 = after CPB (end). By definition, ΔSc_{O_2} = 0 at baseline. Values are mean ± SEM. *Significantly different from 0.

hypothermic CPB before arrest is important to neurologic outcome. Larger studies are needed to establish relations between Sc_{O_2} and neurologic outcome before NIRS can guide intraoperative management.

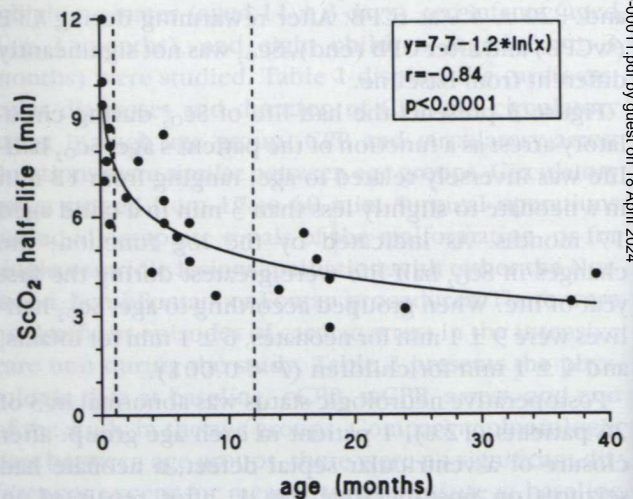NIRS is an emerging technology with applicability to anesthesiology and intensive care medicine.[18,19] The

Fig. 3. Relation of patient age to cerebrovascular hemoglobin oxygen saturation (Sc_{O_2}) half-life during deep hypothermic circulatory arrest (n = 26). Dashed lines demarcate the age groups (neonates, infants, children).
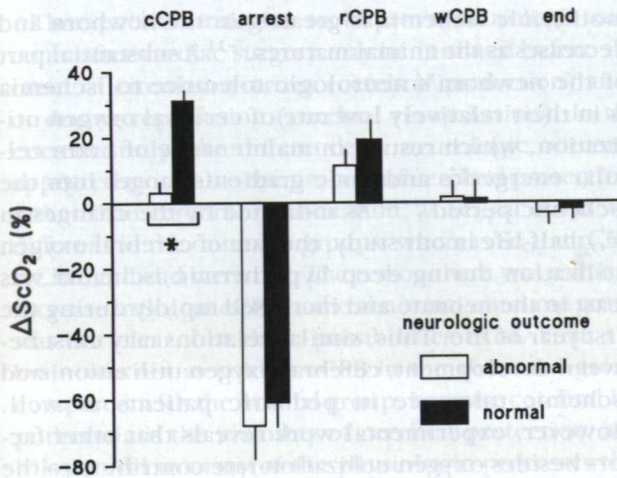
Fig. 4. Changes in cerebrovascular hemoglobin oxygen saturation (ΔSc_{O_2}, from baseline) at each condition during cardiac surgery in patients who had abnormal postoperative neurologic status (n = 3) *versus* normal postoperative neurologic status (n = 23). B = baseline at normothermia; 1 = on deep hypothermic cardiopulmonary bypass (cCPB); 2 = at the end of circulatory arrest (arrest); 3 = on recirculation 3 min after resuming CPB (rCPB); 4 = normothermic CPB (wCPB); 5 = after CPB (end). By definition, ΔSc_{O_2} = 0 at baseline. Values are mean ± SEM. *Significantly different between groups.

spatial domain of NIRS monitoring merits some comment. The optical probe illuminates a volume of tissue beneath it. Because this volume depends on the geometry of the light emitter and detector with respect to the head,[15,21,22] probe position and design determines the region of brain that is monitored. Studies[15,22] employing pulse lasers, computer modeling, and image construction indicate that our probe illuminates approximately 10 ml of tissue beneath it. Thus, the probe on the forehead appears to monitor oxygenation changes located in the right frontal cerebrum.

NIRS is sensitive to oxygenated and deoxygenated hemoglobin in capillaries, arterioles, and venules within the illuminated volume of brain. Algorithms have been developed to determine either absolute hemoglobin oxygen saturation or change in hemoglobin oxygen saturation from an unknown baseline.[15–17,22] At present, uncertainty exists in the absolute Sc_{O_2} algorithms because of the complex nature of light scattering in tissue and the fact that no other method exists to verify the saturation measurements in this region of the circulation. Although normal Sc_{O_2} data in this cross-section of the circulation are not yet available, they can be estimated. During normoxic conditions, Sc_{O_2} should be well less than 100% because of deoxygenated

hemoglobin in the capillaries and venules but greater than cerebral venous saturation (which is approximately 50%) because of arterial blood in the illuminated field. During abnormal conditions, Sc_{O_2} should remain within the bounds of physiology (0–100%) and less than Sa_{O_2}. In our study, it is possible to calculate absolute Sc_{O_2} from the changes by assuming Sc_{O_2} was 0 at the end of arrest, a reasonable assumption based on oxyhemoglobin dissociation curves and measurements of brain tissue partial pressure of oxygen (P_{O_2}) in animals after comparable durations of global isch-

Table 3. Physiologic Data and CPB and Circulatory Arrest Durations by Neurologic Outcome

	Abnormal (n = 3)	Normal (n = 23)
Sa$_{O_2}$ (%)		
Baseline	96 ± 4	96 ± 2
cCPB	100	100
wCPB	100	100
End	98 ± 2	91 ± 4
Pa$_{CO_2}$ (mmHg)		
Baseline	28 ± 4	30 ± 6
cCPB	26 ± 2	26 ± 1
wCPB	25 ± 1	28 ± 2
End	30 ± 1	30 ± 6
pH		
Baseline	7.48 ± 0.05	7.45 ± 0.02
cCPB	7.56 ± 0.02	7.54 ± 0.02
wCPB	7.51 ± 0.03	7.45 ± 0.0
End	7.48 ± 0.01	7.51 ± 0.02
Hct (%)		
Baseline	33 ± 3	35 ± 5
cCPB	24 ± 1	25 ± 1
wCPB	24 ± 1	25 ± 1
End	33 ± 2	33 ± 1
MAP (mmHg)		
Baseline	65 ± 8	64 ± 3
cCPB	44 ± 8	53 ± 2
wCPB	55 ± 10	66 ± 3
End	67 ± 4	80 ± 3
NP temperature (°C)		
Baseline	36 ± 1	35 ± 1
cCPB	16 ± 1	16 ± 1
Arrest	18 ± 1	18 ± 1
wCPB	36 ± 1	36 ± 1
End	36 ± 1	36 ± 1
Time (min)		
Prearrest CPB	8 ± 1*	11 ± 1
Arrest	25 ± 5	39 ± 3
Postarrest CPB	22 ± 2	23 ± 1

Values are mean ± SEM.

Abbreviations are as in table 2.

* $P < 0.05$ between groups.

emia.[26–28] Accordingly, we calculate the average baseline Sc_{O_2} for the age groups as $63 \pm 6\%$ ($63 \pm 8\%$ in neonates, $64 \pm 7\%$ in infants, and $61 \pm 8\%$ in children, $P = 0.78$). Similar absolute Sc_{O_2} values have been reported in normoxic adult subjects.[22,29] We also calculate, for the three age groups combined, absolute Sc_{O_2} as $93 \pm 4\%$ at cCPB, $85 \pm 4\%$ at rCPB, $65 \pm 3\%$ at wCPB, and $60 \pm 3\%$ after CPB (end).

Half-life is a useful pharmacokinetics term for calculating the life of a compound in tissue, for example, a drug in plasma. At 5 half-lives, 97% of the compound will have disappeared from the tissue. The NIRS hemoglobin deoxygenation curve during circulatory arrest reflects oxygen utilization by the brain during ischemia. Pharmacokinetics modeling of this curve can be used to estimate the life of oxygen in the brain during arrest. We observed that Sc_{O_2} half-lives during deep hypothermic arrest averaged 9 min in neonates, 6 min in infants, and 4 min in children. Taking 5 half-lives, 97% of oxygen will be gone ("cerebral anoxia") after 45 min of arrest in neonates, 30 min in infants, and 20 min in children. A host of injurious biochemical reactions occur in the brain as tissue P_{O_2} decreases during ischemia.[30] Although the critical P_{O_2} that initiates these reactions is unknown, the change in Sc_{O_2} half-life with age indicates that they would begin later during arrest in neonates than in children, and consequently, the "safe" duration of arrest may be longer in neonates than in children.

The half-life of hemoglobin deoxygenation during complete ischemia is determined mainly by tissue oxygen demand.[31] The factors influencing cerebral oxygen demand include brain temperature, brain concentration of anesthetic drugs, and inherent energy costs of brain cells to maintain membrane ionic gradients and perform other vital functions. In the current study, brain temperature and drug levels were unlikely to account for our finding of Sc_{O_2} half-life differences, because the anesthetic management and nasopharyngeal temperatures were similar for all age groups. Therefore, the age-related change in Sc_{O_2} half-life appears to result from inherent differences in cerebral oxygen demand at deep hypothermia between neonates, infants, and children. To support this conclusion, Greeley *et al.*[25] have measured CMR_{O_2} at deep hypothermia in infants and children and observed CMR_{O_2} in infants to be about 60% of that children, in agreement with the relative Sc_{O_2} half-life differences of the two age groups.

Experimental work in developing rats, dogs, and swine have found that neurologic tolerance to normothermic ischemia is greatest in the newborn and decreases as the animal matures.[7–11] A substantial part of the newborn's neurologic tolerance to ischemia is in their relatively low rate of cerebral oxygen utilization, which results in maintenance of brain cellular energetics and ionic gradients longer into the ischemic period.[9–13] As indicated by the changes in Sc_{O_2} half-life in our study, the rate of cerebral oxygen utilization during deep hypothermic ischemia was least in the neonate and increased rapidly during the first year of life. Thus, similar relations may exist between development, cerebral oxygen utilization, and ischemic tolerance in pediatric patients as well. However, experimental work reveals that other factors besides oxygen utilization rate contribute to the newborn's remarkable neurologic tolerance to ischemia. These include decreased brain excitatory amino acid concentrations and receptor numbers,[10] increased lactate blood-brain-barrier transporter activity,[30] and decreased brain ion channel numbers,[9,13] which may decrease excitotoxic, lipolytic, and free-radical mechanisms of brain injury during ischemia and reperfusion.

We observed Sc_{O_2} to increase during deep hypothermic CPB, in agreement with other investigators finding that jugular venous oxygen saturation increases 20–30% during hypothermic CPB.[24,32] Jugular venous oxygen saturation and Sc_{O_2} reflect the cerebral oxygen supply/demand relation, which is given by CBF and blood oxygen content relative to CMR_{O_2}, which are influenced by temperature, Pa_{CO_2}, hematocrit, Sa_{O_2}, and arterial pressure. These factors are regulated to an extent by the method of CPB, which varies somewhat between institutions.[24,33] Although hypothermia and CPB have complex effects on tissue oxygen transport, one or more of the following physiologic processes appear to increase the cerebral oxygen supply/demand ratio during hypothermic CPB, depending on the CPB method: (1) arterial pressure may remain constant during CPB cooling while the cerebrovasculature becomes pressure passive, increasing the CBF/CMR_{O_2} ratio[25,34]; (2) Pa_{CO_2} may increase during cooling, increasing the CBF/CMR_{O_2} ratio[5]; (3) hemoglobin oxygen saturation may increase in capillaries and venules during cooling because hemoglobin oxygen affinity increases while brain tissue P_{O_2} remains constant, increasing blood oxygen content.[27,28,35] In our study, Sc_{O_2} may have increased during hypothermic CPB as a result of processes 1 and 3, but not 2, as Pa_{CO_2} did not change from baseline to cCPB.

Therapeutic strategies to improve neurologic outcome after cardiac surgery may be initiated before the onset of circulatory arrest (cerebral protection) and/or during reperfusion (cerebral resuscitation). In the current study, the difference in neurologic outcome appeared to involve the process of cerebral protection, rather than cerebral resuscitation, as Sc_{O_2} at cCPB was different in the outcome groups, whereas Sc_{O_2} at rCPB, wCPB, and end were not. The reason there was minimal increase in Sc_{O_2} at cCPB in the abnormal outcome group was not clear, but three possibilities exist. First, the brain was not as cold at cCPB in the abnormal group compared with the normal group, because cerebral hypothermia is the mainstay of cerebral protection, and it is central to many of the physiologic processes that increase Sc_{O_2} during hypothermic CPB. To support this argument, cooling time was less in the abnormal group, so perhaps not enough time was allowed for the brain to get cold. To oppose this argument, nasopharyngeal temperature, a monitor of brain temperature, and half-life of Sc_{O_2}, a marker of cerebral oxygen demand, were not significantly different between groups. The second possibility is the brain was equally cold in both groups, but other factors during hypothermic CPB in the abnormal outcome group prevented cerebral oxygen supply from increasing relative to demand. These unidentified factors may be important to the process of cerebral protection. A third possibility is baseline Sc_{O_2} was higher in the abnormal outcome group compared with the normal outcome group. Our calculations, however, reveal that baseline Sc_{O_2}s were similar between groups ($69 \pm 10\%$ in the abnormal group versus $61 \pm 5\%$ in the normal group, $P = 0.50$).

The incidence of neurologic deficits after deep hypothermic circulatory arrest remains uncertain. Earlier studies[1,33] report the incidence of acute deficits (e.g., seizures, stroke, or coma) as between 1% and 25%, while the incidence of cognitive deficits awaits long-term follow-up studies. We observed a 12% incidence of acute neurologic deficits, in agreement with these figures, although our method of detecting deficits was not very sensitive and may have underestimated the incidence.[33] There are a spectrum of brain lesions in children after heart surgery, including necrosis, atrophy, and hemorrhage,[36,37] usually located in the cortical gray and white matter and basal ganglia. Our patients manifesting deficits had seizures and coma, suggestive of cortical gray matter lesions, consistent with the field of NIRS monitoring. However, we cannot exclude the possibility that the field monitored and location of the lesions may have been different. Further, our findings are limited by small sample size and lack of long-term neurologic follow-up. Despite these limitations, our observations are consistent with the growing body of evidence[4,5,24,25] indicating that the duration and method of CPB cooling before circulatory arrest is important to the process of cerebral protection.

Recent advances in the experimental aspects of cerebral protection and resuscitation offer the possibility of reducing the incidence of neurologic deficits after pediatric heart surgery. Few tools exist to monitor the brain and assess the quality of cerebral protection and resuscitation at the time of surgery. Although NIRS remains in the development stage as a monitor, these observations suggest a potential role for it during pediatric cardiac surgery.

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