Kinetics of Cerebral Deoxygenation during Deep Hypothermic Circulatory Arrest in Neonates

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Brain injury associated with neonatal congenital heart operations performed during deep hypothermia and/or total circulatory arrest is often attributed to cerebral hypoxia. We studied the kinetic changes in cerebrovascular hemoglobin O₂ saturation (HbO₂%) and total hemoglobin concentration (Hbtotal) in 17 neonates undergoing cardiac surgery as they were cooled to 15°C, underwent total circulatory arrest, and were rewarmed. HbO₂% and Hbtotal in brain vasculature were monitored noninvasively by near-infrared spectroscopy. Neonates were cooled over 12 min and rewarmed over 15 min while being perfused using cardiopulmonary bypass (CPB). Total circulatory arrest lasted from 20 to 70 min. We found that HbO₂% in brain vasculature increased during the initial 8 min of CPB as nasopharyngeal temperature decreased, and then remained constant until circulatory arrest. After the onset of circulatory arrest, cerebrovascular HbO₂% decreased curvilinearly for 40 min; no further hemoglobin desaturation was observed from 40 to 70 min of arrest. The changes in cerebrovascular Hbtotal were quite different from those in HbO₂%; as Hbtotal decreased during the initial minute of CPB and circulatory arrest and then remained constant until recirculation. Brain intravascular HbO₂% and Hbtotal increased within 3 min after the onset of recirculation to prearrest levels, and during rewarming, HbO₂% decreased to normothermic baseline values. The results demonstrate that cerebral oxygenation decreased during CPB cooling; O₂ was consumed by the neonatal brain during the initial 40 min of deep hypothermic circulatory arrest; and cerebral oxygenation was restored on recirculation. These observations may be important in identifying the etiologies of brain injury during neonatal congenital heart surgery. (Key words: Anesthesia; cardiovascular; neonatal; pediatric. Brain: hypothermia; hypoxia; ischemia. Monitoring: hemoglobin; near-infrared spectroscopy; oximetry.)

REPAIR of cardiovascular malformations in neonates often involves the use of deep hypothermia and total circulatory arrest. Neurologic complications frequently are associated with deep hypothermic circulatory arrest. Histopathologic and radiologic evidence suggests that many of these complications arise from cerebral hypoxia/ischemia during cardiopulmonary bypass (CPB), deep hypothermia, and/or total circulatory arrest. However, the kinetics of cerebral O₂ supply during cooling and rewarming with CPB, as well as during total circulatory arrest and recirculation, remain unknown in neonates.

Noninvasive measurement of hemoglobin saturation (HbO₂%) and total hemoglobin concentration (Hbtotal) in the cerebral circulation has become feasible in recent years by near-infrared spectroscopy. Near-infrared spectroscopy differs from pulse oximetry in that it monitors hemoglobin mainly in the gas-exchanging circulation (capillaries, arterioles, and venules) and not just in arteries. Near-infrared spectroscopy has been used to monitor the kinetics of cerebral O₂ supply in premature infants, adult humans, and experimental animals during hypoxia/ischemia. In this study, we used near-infrared spectroscopy and examined the kinetics of cerebral deoxygenation in neonates during deep hypothermic circulatory arrest, and to examine the kinetics of cerebral O₂ supply during CPB cooling, recirculation, and rewarming.

Materials and Methods

We studied 17 neonates (aged 4–21 days, mean 9 days). Infants < 1 month of age in whom cardiac surgery using deep hypothermic circulatory arrest was planned were eligible for study. Infants with neurologic disease or a history of cardiovascular instability were excluded. All studies were conducted in the operating room and were approved by the Institutional Review Board at The Children’s Hospital of Philadelphia; informed parental consent was obtained.

Anesthetic and surgical care was performed according to standard clinical procedure. Infants received atropine (20 μg·kg⁻¹ orally) as a preanesthetic premедакtion. They were anesthetized with intravenous fentanyl 40 μg·kg⁻¹ and intravenous pancuronium 0.20 mg·kg⁻¹. After induction, the trachea was intubated and the lungs were mechanically ventilated. Intravenous fluids consisted of 5% dextrose in lactated Ringer’s solution (4 ml·kg⁻¹·hour⁻¹) and lactated Ringer’s solution (10 ml·kg⁻¹ as needed). Mean arterial pressure, blood gases and pH, and hematocrit were measured from an umbilical or radial artery catheter. Arterial hemoglobin O₂ saturation (SO₂) was determined by means of a pulse oximeter sensor applied on the tongue before CPB and by cooximetry during
CPB. Temperature was monitored in the nasopharynx, esophagus, and rectum. Bags of ice surrounded the infant's head during cooling on CPB and circulatory arrest.

We used a dual wavelength near-infrared spectrophotometer (NIMS Inc., Philadelphia, PA) to monitor \(\text{HbO}_2\)\% and \(\text{Hb}_{\text{total}}\) in brain vasculature, as previously described. Briefly, near-infrared spectroscopy relies on the relative transparency of the brain and overlying tissues to light in the near-infrared spectrum (700–1000 nm), where oxygenated and deoxygenated hemoglobin have distinct near-infrared absorption spectra. Our instrument monitored change in absorbance at 800 nm (\(\Delta A_{800}\)), an isosbestic point for oxygenated and deoxygenated hemoglobin, and at 760 nm, an absorption maxima for deoxygenated hemoglobin. Change in \(\text{Hb}_{\text{total}}\) in the cerebral circulation is represented by \(\Delta A_{800}\), and change in \(\text{HbO}_2\)\% is given by the change in the absorbance difference (\(\Delta A_{760-800}\)). The change in \(\text{HbO}_2\)\% and \(\text{Hb}_{\text{total}}\) in the cerebral circulation are linearly related to their respective change in absorbance values over a wide range of oxygenation states. The instrument used a small optical probe connected to the main unit by a 0.5-m wire bundle that was secured by means of a cloth strap on the head 2 cm above the supraorbital ridge. Recent studies using light pulses and computer modeling to describe light migration through the head indicate that the probe illuminates approximately a 10-ml hemispherical volume of tissue, the radial depth of which is about 6 cm. The contribution of the overlying skin, soft tissues, and skull is negligible (<10%)\(^{11,13-15}\). \(\Delta A_{760-800}\), \(\Delta A_{800}\), and arterial pressure were recorded continuously (Linear Instruments 512).

Baseline data were recorded after right atrial and arterial cannula were placed, immediately before CPB was instituted, when all infants were hemodynamically stable. Infants' blood was anticoagulated (intravenous heparin 200 units · kg\(^{-1}\)) before placement of the cannula. Arterial blood gases during CPB were maintained according the principles of \(\alpha\)-stat management\(^{17}\). The CPB circuit used a bubble oxygenator supplying \(\text{O}_2\) (11 · min\(^{-1}\)) that delivered blood with a nonpulsatile pump at a constant flow (150 ml · kg\(^{-1}·\) min\(^{-1}\)). \(\text{CO}_2\) was not used. Type-specific adult whole blood 500 ml, sodium bicarbonate 25 mEq, calcium chloride 500 mg, heparin 200 units, cephalexin 25 mg · kg\(^{-1}\), pancuronium 0.2 mg · kg\(^{-1}\), and Plasma-lyte A 50 ml were added to the circuit. Mixed venous hemoglobin \(\text{O}_2\) saturation (\(\text{SV}_{\text{O}_2}\)) was monitored continuously (Bentley Laboratories Oxyusat meter SM-0100) from the venous return tubing of the circuit. Data also were collected during cooling and rewarming on CPB and during circulatory arrest.

Body temperature was decreased by lowering the blood temperature in the circuit to 12–15°C. When nasopharyngeal temperature reached 15–17°C, the heart was perfused with 4°C cardioplegia solution until asystolic, and the CPB pump was turned off. Nasopharyngeal temperature remained within 1°C of the initial temperature during circulatory arrest. The duration of arrest varied, depending on the surgical repair. After circulatory arrest, CPB was resumed at 150 ml · kg\(^{-1}·\) min\(^{-1}\), and infants were rewarmed over 15 min by gradually increasing the blood temperature in the circuit. No additional fentanyl, pancuronium, or other anesthetic drugs were administered during rewarming. Three days postoperatively, infants were examined and the charts reviewed by one of us (JMS) for evidence of neurologic sequelae.

Data are presented as means ± SEM. The changes in \(\Delta A_{760-800}\), \(\text{SV}_{\text{O}_2}\), arterial blood gases and \(\text{pH}\), \(\text{SO}_2\), hematocrit, and mean arterial pressure over time were analyzed by one-way analysis of variance with repeated measures. For significant F values, multiple comparisons were made with the paired t test using Bonferroni’s correction. Significance was defined as \(P<0.05\).

Results

Cardiac diagnoses among the 17 infants studied included transposition of the great arteries (n = 7), hypoplastic left heart syndrome (n = 7), truncus arteriosus (n = 1), isolated ventricular septal defect (n = 1), and total anomalous pulmonary venous connection (n = 1). The only preoperative medication was prostaglandin E in 9 infants. There were no intraoperative deaths. Generalized seizures occurred 24–48 h postoperatively in 2 infants whose circulatory arrest lasted for 70 min. Otherwise, the intraoperative and postoperative courses with respect to arterial blood gases, \(\text{pH}\), and mean arterial pressure of these 2 neonates were similar to those of the other 15 neonates. No other neurologic complications were noted in any neonate.

Arterial \(\text{pH}\), \(\text{P}_{\text{O}_2}\), and \(\text{SO}_2\) were significantly less, and \(\text{P}_{\text{CO}_2}\) and hematocrit were significantly greater at baseline than during CPB; all values remained constant during CPB (table 1). Figure 1 illustrates the absorbance changes attributed to \(\text{HbO}_2\)\% and \(\text{Hb}_{\text{total}}\) in brain vasculature as well as mean arterial pressure of a representative neonate during the study. Figures 2–4 summarize the changes in cerebrovascular \(\text{HbO}_2\)\%, \(\text{SV}_{\text{O}_2}\), and nasopharyngeal temperature for all neonates. In the cerebral circulation, \(\text{HbO}_2\)\% and \(\text{Hb}_{\text{total}}\) were stable in all neonates at baseline (fig. 1). CPB lasted for 9 min in all 17 neonates and for as long as 12 min in 6 neonates before institution of circulatory arrest (fig. 2). In the 1st min of CPB, the behavior of brain intravascular \(\text{HbO}_2\)\% was variable. In 3 infants with low prebypass \(\text{SO}_2\) (48%, 48%, and 64%), \(\text{HbO}_2\)\% in brain vasculature increased tremendously when CPB was begun, whereas in the others with higher prebypass \(\text{SO}_2\) (range 82–100%), it either decreased minimally (n = 5)
or remained unchanged (n = 9). However, after 2 min of CPB, brain intravascular HbO₂% increased in all infants (P < 0.05). As nasopharyngeal temperature decreased, HbO₂% in brain vasculature and SVo₂ increased (P < 0.001). HbO₂% in brain vasculature, SVo₂, and nasopharyngeal temperature did not change further after 8 min of CPB. In contrast to cerebrovascular HbO₂%, Hb total decreased in the 1st min of CPB but remained relatively constant thereafter (fig. 1).

During circulatory arrest (fig. 3), HbO₂% in brain vasculature decreased curvilinearly for 40 min (P < 0.001). Interestingly, in the initial minute of arrest, brain intravascular HbO₂% did not change in 13 neonates, whereas in the other 4 neonates it decreased. However, by 7 min of arrest, brain intravascular HbO₂% had decreased in all infants. Brain intravascular HbO₂% did not change further after 40 min of arrest. The kinetics of Hb total in the brain during circulatory arrest were quite different from HbO₂%, as Hb total decreased during the first few minutes and then remained unchanged (fig. 1).

When CPB was reestablished, HbO₂% and Hb total in brain vasculature increased rapidly (P < 0.001) in all infants, such that by 3 min, the values were similar to those immediately before arrest (figs. 1 and 4). During recirculation, HbO₂% in the brain never exceeded the value immediately before arrest. As nasopharyngeal temperature increased, HbO₂% in brain vasculature and SVo₂ decreased (P < 0.001), and after 15 min of rewarming, both had returned to baseline levels.

### Discussion

A major source of morbidity after pediatric cardiac operations is brain injury thought to result from hypoxia/ischemia during CPB, deep hypothermia, and/or circulatory arrest. It has been difficult to test these hypotheses. Using near-infrared spectroscopy in neonates undergoing

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**Table 1. Arterial Blood Values**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Min of Cooling</th>
<th>4 Min of Recirculation and Warming</th>
<th>14 Min of Recirculation and Warming</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.44 ± 0.02</td>
<td>7.60 ± 0.02</td>
<td>7.50 ± 0.02</td>
<td>7.48 ± 0.02</td>
</tr>
<tr>
<td>Pco₂ (mmHg)</td>
<td>30.8 ± 1.8</td>
<td>27.6 ± 1.5</td>
<td>26.4 ± 1.6</td>
<td>25.2 ± 0.2</td>
</tr>
<tr>
<td>Po₂ (mmHg)</td>
<td>112 ± 36</td>
<td>587 ± 28</td>
<td>484 ± 23</td>
<td>524 ± 16</td>
</tr>
<tr>
<td>SVo₂ (%)</td>
<td>87 ± 3</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM; N = 17. Arterial blood pH, partial pressure of CO₂ (Pco₂), and O₂ (Po₂) measured at 37° C, hemoglobin O₂ saturation (SVo₂) and hematocrit measured by pulse oximetry before car-

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**Fig. 1.** Kinetics of hemoglobin O₂ saturation (ΔA865-805) and total hemoglobin concentration (ΔA660) in brain vasculature and mean arterial blood pressure (MAP) in a representative neonate before, during cardiopulmonary bypass (CPB) cooling from 36° C to 15° C, circulatory arrest, and CPB recirculation and rewarming to 36° C. Hb = deoxygenated hemoglobin; HbO₂ = oxygenated hemoglobin. Upward deflections in ΔA865-805 and ΔA660 indicate an increase in saturation and total hemoglobin concentration, respectively.

**Fig. 2.** Kinetics of brain intravascular hemoglobin O₂ saturation (ΔA865-805), mixed venous hemoglobin saturation (SVo₂), and nasopharyngeal (NP) temperature during cooling. Values are mean ± SEM.
The determinants of the cerebral O₂ supply–O₂ demand relationship include arterial hemoglobin concentration and S₀₂, cerebral blood flow (CBF) and cerebral metabolic rate of O₂ consumption (CMRO₂). The role of arterial HbO₂% was particularly evident in severely cyanotic neonates when brain intravascular HbO₂% increased sharply with the onset of CPB and perfusion with fully oxygenated blood. Hemodilution had little effect on cerebrovascular HbO₂% as denoted by the minimal change or lack of change in the other neonates during the 1st min of CPB. In animal studies, 19–21 CBF and CMRO₂ decreased during cooling, although CMRO₂ seemed to decrease out of proportion to CBF. For example, Michenfelder and Mildè 20 observed that in dogs, CMRO₂ decreased 93% from 37°C to 14°C, whereas CBF decreased only 58%. Greeley et al. 17 measured CBF and CMRO₂ as children were cooled during cardiac surgery and also found that CMRO₂ decreased considerably more than did CBF. In our study, the increase in cerebrovascular HbO₂% after several minutes of CPB cooling when arterial hemoglobin concentration and S₀₂ were constant was also indicative of a greater decrease in CMRO₂ compared with CBF.

Several studies 22–24 measured brain O₂ partial pressure using an electrode placed into the cerebral cortex as animals were cooled to deep hypothermia and found that brain P₀₂ remained constant. Considering that the oxyhemoglobin–O₂ dissociation curve shifts leftward as temperature decreases, 25 one might expect HbO₂% in the cerebrovasculature to increase as P₀₂ remained constant. Our observations of HbO₂% in brain vasculature during cooling and rewarming are consistent with this process.

There has been some question regarding O₂ availability during deep hypothermia circulatory arrest. Although we found that O₂ was available in vivo, as attested by the

![Graph](image-url)
desaturation during circulatory arrest, this desaturation does not imply that cerebral $O_2$ demand was being quenched during the entire period of arrest. According to Connell and colleagues,\textsuperscript{26} as $O_2$ tension in the tissue decreases, $O_2$ may initially remain available in sufficient quantity to drive normal oxidative metabolism, but then $O_2$ may be available only in insufficient supply (i.e., rate-limiting) so that oxidative metabolism decreases, and finally $O_2$ may become unavailable (anoxia). During complete cerebral ischemia in animals, $O_2$ supply seems to become rate-limiting when the rate of hemoglobin desaturation in brain vasculature begins to decrease, and cerebral anoxia is indicated by the absence of further hemoglobin desaturation.\textsuperscript{27,28} If these temporal relationships pertain to our study, they suggest that $O_2$ was not available in sufficient quantity to meet cerebral $O_2$ demand beginning about 15 min after the onset of arrest, as indicated by the change in the slope of the hemoglobin desaturation curve (fig. 5), and that no $O_2$ was available after 40 min of arrest.

Several factors may have improved $O_2$ availability during circulatory arrest. Increases in brain tissue $P_{CO_2}$ and decreases in brain tissue pH during deep hypothermic circulatory arrest\textsuperscript{29,23} may have steadily shifted the hemoglobin–$O_2$ dissociation curve to the right and facilitated $O_2$ unloading. Interestingly, unlike normothermic cardiac arrest,\textsuperscript{9,27} we observed that cerebrovascular $HbO_2$% did not begin to decrease until a few minutes after the onset of arrest. We speculate that because cerebrovascular $HbO_2$% may have been 100% before deep hypothermic arrest, soluble $O_2$ was consumed until $P_{CO_2}$ had decreased enough to reach the steep portion of the oxyhemoglobin dissociation curve.

The kinetics of cerebral deoxyxgenation during deep hypothermic cardiac arrest have not been reported in neonates. However, in adult humans and animals, cerebral deoxyxgenation occurs within approximately 40 s of complete ischemia at normothermia\textsuperscript{30,27} and within 20 min at deep hypothermia.\textsuperscript{22,23} Considerably faster than in our study. Many factors influence the kinetics of deoxyxgenation, including $O_2$ demand and $O_2$ solubility and diffusivity, as well as hemoglobin concentration, $HbO_2$, and partial pressure at 50% saturation; however, $O_2$ demand is the most important factor.\textsuperscript{29} Because cerebral $O_2$ demand in neonates is less than in adults,\textsuperscript{30,31} and cerebral $O_2$ demand is less at deep hypothermia than at normothermia,\textsuperscript{32} decreased $O_2$ demand in our neonates was certainly involved in the slower kinetics of deoxyxgenation. The extent to which the other factors played a role has not been examined.

The duration of CPB cooling in our study was less than that reported by others,\textsuperscript{17,55} who induced deep hypothermia over 20–60 min. Rapid cooling is postulated to result in a nonhomogeneous reduction in brain temperature. Evidence against this in our study was the finding that nasopharyngeal temperature did not change during arrest, since persistent temperature gradients would be expected to increase nasopharyngeal temperature as heat was redistributed. However, if the brain were not of uniform temperature, the warm regions would have hastened deoxyxgenation because $O_2$ demand would have been greater. Thus, the kinetics of deoxyxgenation in homogeneously cooled neonates might be slower than what we observed.

Hypothermic protection during ischemia has been generally attributed to the longer time it takes to deoxyxgenate, as anoxia and energy failure initiate a cascade of injurious reactions.\textsuperscript{28} As noted in figure 3, 14 of the neonates experienced circulatory arrest of 50–70 min during which cerebral anoxia and energy failure were likely present for the final 10–30 min, yet only 2 of the neonates manifested evidence of neurologic injury postoperatively. Apparently, the neonatal brain is able to tolerate a long period of anoxia at deep hypothermia. It is not clear from our data why 2 of the neonates developed seizures and the other 12 neonates did not.

The kinetics of $HbO_2$ in brain vasculature were distinct from $HbO_2$%. The immediate decrease in $HbO_2$ on beginning CPB surely corresponded with the acute hemodilution. During circulatory arrest, $HbO_2$ kinetics were identical to the arterial blood pressure tracing and depicted the redistribution of blood from the brain to the central circulation/pump reservoir. These findings are not unique to deep hypothermic arrest; Rosenthal et al.\textsuperscript{57} made similar observations during normothermic complete cerebral ischemia in cats.

A marked hyperoxia of hemoglobin in the brain vasculature during reperfusion has been noted after normothermic cardiac arrest,\textsuperscript{9,27} which Smith et al.\textsuperscript{9} postulated arose from postischemic hyperemia. We did not observe any instances of reperfusion hyperoxia after deep hypothermic cardiac arrest, nor did we find evidence of hyperemia as $HbO_2$ in brain vasculature always returned to prearrest levels. However, "reperfusion" was complicated by the fact that rewarming occurred simultaneously so that hyperoxia and other reperfusion phenomena may have been masked. We believe that the gradual decrease in cerebrovascular $HbO_2$% during recirculation/rewarming was attributed to rewarming rather than "reperfusion" because the changes in $HbO_2$% were opposite to those during cooling.

Progress in reducing the incidence of brain injury after congenital cardiac surgery has been hampered by the inability to monitor cerebral oxygenation. While near-infrared spectroscopy is a qualitative technique the ultimate clinical utility of which depends on further developments, these preliminary observations during CPB cooling, deep hypothermic circulatory arrest, and recirculation may be...
important in unraveling the events leading to brain injury during congenital heart surgery.

References


