CEREBRAL OXYGENATION AND HEMODYNAMIC CHANGES DURING INFANT CARDIAC SURGERY: MEASUREMENTS BY NEAR INFRARED SPECTROSCOPY

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ABSTRACT
Despite dramatic advances in the survival rate amongst infants undergoing cardiac surgery for congenital heart disease, the incidence of brain injury suffered by survivors remains unacceptably high. This is largely due to our limited understanding of the complex changes in cerebral oxygen utilization and supply occurring during the intraoperative period as a result of hypothermia, neuroactive drugs, and profound circulatory changes. Current techniques for monitoring the adequacy of cerebral oxygen supply and utilization during hypothermic cardiac surgery are inadequate to address this complex problem and consequently to identify the infant at risk for such brain injury. Furthermore, this inability to detect imminent hypoxic-ischemic brain injury is likely to become all the more conspicuous as new neuroprotective strategies, capable of salvaging “insulted” neuronal tissue from cell death, enter the clinical arena. Near infrared spectroscopy is a relatively new, noninvasive, and portable technique capable of interrogating the oxygenation and hemodynamics of tissue in vivo. These characteristics of the technique have generated enormous interest amongst clinicians in the ability of near infrared spectroscopy to elucidate the mechanisms of intraoperative brain injury and ultimately to identify infants at risk for such injury. This paper reviews the experience with this technique to date during infant cardiac surgery.

Keywords cerebral oxygenation; hemodynamic changes; intraoperative cerebral monitoring; near infrared spectroscopy; cardiac surgery.

1 INTRODUCTION
Brain injury remains one of the most important complications of cardiac surgery1,2 but the underlying mechanisms remain incompletely understood. For several reasons, a recent, increased interest in delineating these mechanisms has become evident among both clinicians and researchers as the clinical magnitude of this problem has become more clearly defined. Despite the dramatic increases in survival, neurologic dysfunction continues to affect up to 25% of the 14,000 infants under the age of 1 year who undergo cardiac surgery in the United States each year. Moreover, the consequences of this postoperative neurologic morbidity may include long-term, even lifelong, disturbances in motor and cognitive function.1,2

Advances in cardiac surgical techniques have led to a marked increase in the numbers of young infants subjected to cardiac surgery, with the result of improved survival rates, though at the cost of neurologic morbidity. Indeed, in earlier years, neonatal cardiac repair was impeded by the small size of the infant heart and the surgical field, which was further constricted by blood and suction catheters obscuring the often complex and delicate lesions. The development of techniques that allowed attenuation or even arrest of the systemic circulation constituted a major advance in the development of neonatal cardiac repair. Such techniques only became possible with the development of neuroprotective strategies, such as deep hypothermia (DH) and drugs that suppress cerebral oxidative demands. Although these surgical advances have markedly decreased the mortality of many previously lethal forms of congenital heart disease (CHD), this accomplishment has occurred at the expense of a substantial postoperative neurologic morbidity.1,2,4 The marked attenuation or complete arrest of the circulation required during intracardiac repair constitutes a unique controlled “clinical experiment” for the study of cerebral hypoxic-ischemic/reperfusion (HI/R) mechanisms of injury. Furthermore, these planned periods of intraoperative hypoperfusion provide an opportunity for future clinical trials of neuroprotective strategies.
The perioperative events affecting infants undergoing open heart surgery may be regarded broadly as occurring during three intraoperative phases: (1) a preparative phase, (2) a reparative phase, and (3) a recovery phase, as well as (4) an early postoperative period of intensive care. During the intraoperative phases of deep hypothermic cardiac surgery, surgical-anesthetic techniques induce profound changes in both cerebral oxygen supply and its utilization. Guidelines concerning the safe limits of these techniques have been based largely on experimental, theoretical, and anecdotal data. Monitoring of the cerebral effects of these manipulations and the identification of early indicators of hypoxia-ischemia in the human infant remain poorly defined. Recently, however, a number of neurodiagnostic techniques have been adapted to the complex logistic and technical challenges of the operating theater. The essential goals of cerebral monitoring during hypothermic cardiac surgery are to measure the efficacy of cerebral metabolic suppression and the adequacy of cerebral oxygen delivery during periods of low-flow cardiopulmonary bypass (LFB) and during reperfusion/rewarming, and to detect any impending imbalance in availability and utilization of cerebral oxygen. The relative strengths and limitations of these intraoperative monitoring techniques are reviewed briefly here.

### 1.1 TECHNIQUES FOR INTRAOPERATIVE CEREBRAL MONITORING

#### 1.1.1 Previous Approaches

The theoretical “ideal” device for cerebral monitoring during cardiac surgery should be portable to the operating room, where it should not intrude upon the surgical-anesthetic activities. It should be capable of continuous measurements of rapid and random physiological processes, and be both non-invasive and nonirradiating. Since profound changes in cerebral oxygen supply and utilization occur during hypothermic cardiac surgery, the ideal technique should measure changes in cerebral perfusion and oxygenation simultaneously.

Electroencephalography (EEG) monitors neuronal synaptic activity in the outer layers of the cerebral cortex (Table 1). The utility of EEG during deep hypothermic cardiac surgery relates to the fact that synaptic activity is highly oxygen dependent, being responsible for two-thirds of cerebral oxygen consumption. Thus the efficacy of hypothermic suppression of such synaptic activity can be monitored by EEG. However, at approximately 18°C the EEG becomes isoelectric, thereby providing no further metabolic information. In addition, metabolic activity in deeper cerebral regions is largely inaccessible to surface EEG.

Transcranial Doppler (TCD) has been used to monitor cerebral perfusion during cardiac surgery (Table 1). The TCD technique measures continuous cerebral blood flow velocity (CBFV), and thus its ability to reflect volumetric cerebral blood flow (CBF) is based on the controversial assumption that the diameter of the insonated vessel remains constant. Therefore, the TCD technique provides a qualitative rather than a quantitative measure of volumetric CBF. Furthermore, at low flow rates, the determination of CBFV may become unreliable.

Important data concerning CBF and, secondarily, cerebral metabolic rate of oxygen (CMRO₂) and cerebral metabolic rate of glucose (CMRglu) data during infant cardiac surgery have been provided by xenon-133 clearance studies (Table 1). However, this technique provides intermittent values.

<table>
<thead>
<tr>
<th>Monitoring techniques</th>
<th>Strengths and limitations</th>
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</thead>
<tbody>
<tr>
<td>1. Electroencephalography</td>
<td>Reflects oxygen-dependent cortical synaptic activity but Does not reflect metabolism of deeper cerebral structures Becomes isoelectric during deep hypothermia</td>
</tr>
<tr>
<td>2. Transcranial Doppler</td>
<td>Measures cerebral blood flow velocity but Does not measure volumetric cerebral blood flow May be unreliable during low flow rates</td>
</tr>
<tr>
<td>3. Xenon-133 clearance CBF</td>
<td>Measures quantitative cerebral blood flow Can be used to measure cerebral oxygen and glucose metabolism but Limited in repetition of measurements Radioactive tracer used</td>
</tr>
<tr>
<td>4. Jugular bulb saturations (JvSO₂)</td>
<td>Measures global cerebral venous oxyhemoglobin saturation but Cannot distinguish between perfusion and metabolic mechanisms of JvSO₂ changes Hypothermia and acid-base changes may affect JvSO₂ directly</td>
</tr>
</tbody>
</table>
and the requirement for stable CBF during the period of measurement precludes the detection of rapid changes. In addition, the xenon-133 clearance technique is associated with some degree of radiation exposure.

Continuous or intermittent jugular venous oxygen saturation (JvSO₂) measurements from the jugular bulb have been used to assess cerebral oxygenation during cardiac surgery (Table 1). Global cerebral venous saturation is dependent upon CBF, cerebral oxygen delivery, and cerebral oxygen extraction. Measurement of JvSO₂ reflects the net effect of these several processes but does not distinguish among them. Furthermore, since other intraoperative factors, such as hypothermia and acid-base status, may have significant effects on hemoglobin oxygen saturation independent of metabolic oxygen extraction, this technique is vulnerable to misinterpretation.

Perhaps the most significant limitation of the above techniques is their inability to measure simultaneously changes in cerebral oxygen utilization and cerebral oxygen delivery. Techniques such as positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) are expensive, cumbersome, and unlikely to become portable to the operating room. Near infrared spectroscopy (NIRS) (Table 2) by contrast, is capable of measuring in vivo, simultaneously and continuously, changes in intravascular oxygenation (i.e., oxyhemoglobin concentration, HbO₂), as well as intracellular oxygenation (i.e., concentration of oxidized cytochrome aa₃, CytO₂). This unique capability of NIRS allows continuous monitoring not only of intravascular oxygenation but, more important, of cerebral cellular oxygen availability. Furthermore, changes in cerebral oxygenated hemoglobin (HbO₂) as well as reduced hemoglobin (Hb) may be summed to provide changes in total cerebral hemoglobin concentration (THb). The potential of this technique during cardiac surgery has been demonstrated recently and a growing body of data is accumulating. Since the mechanisms of brain injury sustained by adults and children during cardiac surgery are likely to differ in several important respects, we confine the following discussion to the experience with NIRS in childhood cardiac surgery.

The near infrared spectroscopy technique is based upon the fact that light in the near-infrared range can pass with relative ease through skin, soft tissue, and bone and into the brain, where it is absorbed in a concentration-dependent manner by certain “chromophores,” specifically hemoglobin and cytochrome aa₃. Second, this absorption is dependent on the presence or absence of oxygen. Changes in absorption can be used to derive changes in the cerebral concentrations of these chromophores by a modification of the Beer-Lambert law. Thus, NIRS provides the capability to measure continuous quantitative changes in chromophore concentration in the brain, in vivo and in real time.

Although the interpretation and validation of the hemoglobin signals are generally well established, the interpretation of the CytO₂ signal remains controversial and validation is lacking. We have used the NIRS-500 device (Hamamatsu Photonics, Japan) which quantitates changes in cytochrome aa₃ oxidation by measuring the difference spectrum between oxidized and reduced cytochrome aa₃, rather than by attempting to measure the absolute concentrations of either compound. In a rodent model of graded hypoxia, a highly significant relationship has been demonstrated between cerebral high-energy phosphates and CytO₂ measured with this NIRS device, suggesting that CytO₂ may be an important status indicator of cerebral cellular energy.

The NIRS technique has been adapted by modifications of the Fick principle and the indicator dilution technique to allow discrete quantitative measurements of such cerebral hemodynamic variables as CBF and cerebral blood volume (CBV). The tracers utilized have included a “bolus” of oxyhemoglobin (“oxygen method”) and indocyanine green (ICG). The oxygen method is based on the

Table 2 Near infrared spectroscopy: strengths and limitations.

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>1. Continuous in vivo measurements of</td>
<td>1. Absolute quantitation currently lacking</td>
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<tr>
<td>2. Change in absolute concentration in</td>
<td>2. Assumption of constant photon path length</td>
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<tr>
<td>3. Intravascular and intracellular oxygenation and</td>
<td>3. Vulnerable to light and movement artifacts</td>
</tr>
<tr>
<td>4. Cerebral blood volume (by total cerebral hemoglobin change)</td>
<td>4. Regional changes not currently distinguished</td>
</tr>
<tr>
<td>5. Capable of discrete quantitative hemodynamic measurements</td>
<td>5. Arterial versus venous changes not distinguished</td>
</tr>
<tr>
<td>6. Portable and relatively unobtrusive</td>
<td>6. Validity of cytochrome aa₃ signal questioned</td>
</tr>
<tr>
<td>7. Captures spontaneous, random events</td>
<td>7. Dissolved oxygen not measured</td>
</tr>
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Table 3 Systemic and cerebral changes during the preparative phase.

<table>
<thead>
<tr>
<th>Systemic changes</th>
<th>Potential cerebral effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nonpulsatile flow</td>
<td>Impaired perfusion to distal capillary beds</td>
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<tr>
<td></td>
<td>Disturbed cerebral autoregulation</td>
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<tr>
<td>2. Hypothermia</td>
<td>Suppressed cellular oxidative metabolism</td>
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<tr>
<td></td>
<td>Increased hemoglobin-oxygen affinity</td>
</tr>
<tr>
<td></td>
<td>Impaired pressure-flow autoregulation</td>
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<tr>
<td>3. Hemodilution</td>
<td>Decreased oxygen carrying capacity and delivery</td>
</tr>
<tr>
<td>4. Acid-base changes</td>
<td>Vasodilatory/vasoconstrictive effects</td>
</tr>
<tr>
<td></td>
<td>Direct cellular effects</td>
</tr>
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</table>

induction of a sudden, modest increase in oxyhemoglobin in the circulation, causing a change in the oxygen content of inspired air; the input function is monitored by pulse oximetry and the cerebral function is measured by NIRS. The ICG technique, which currently awaits clinical validation, is based on the fact that this dye absorbs light in the near infrared (NIR) range, and that changes in its concentration can be measured by a peripheral indwelling densitometer and NIRS, thereby allowing quantitation of CBF. In addition, by inducing a measured change in a variable (e.g., circulating carbon dioxide tension, pCO₂), and measuring the corresponding change in total cerebral hemoglobin concentration (and hence CBV) as measured by NIRS, the cerebral vascular response to CO₂ (i.e., cerebral CO₂ vasoreactivity, CVRCO₂) has been quantitated.

The application of NIRS to the infant undergoing cardiac surgery, and the results of studies to date are discussed next in the context of the sequential phases of cardiac surgery and the early postoperative period of intensive care. Each section includes a brief review of the induced systemic and cerebral physiologic changes, followed by the cerebral hemodynamic and oxygenation data generated by NIRS.

2 CEREBRAL NIRS FINDINGS DURING INFANT CARDIAC SURGERY

2.1 PREPARATIVE PHASE

2.1.1 Systemic Physiologic Changes

During this phase, vital organ systems are metabolically “prepared” in anticipation of the often marked decreases in perfusion and oxygen delivery occurring during the subsequent intracardiac phase of the operation (Table 3). This metabolic suppression is achieved largely through DH, with adjunctive pharmacologic suppression. The physiologic changes occurring during this period of metabolic and hemodynamic “preparation” are often pronounced.

First, with the initiation of cardiopulmonary bypass (CPB), the normal pulsatile cardiac-driven perfusion is replaced by a nonpulsatile circulation. Second, the core temperature of the body is decreased to below 20 °C over a 15 to 20 min period. This DH is achieved primarily by cooling the perfused bypass blood. Third, hemodilution is used during hypothermic CPB to obviate the adverse rheological effects of hypothermia on circulating blood (i.e., increased cellular rigidity and viscosity). Finally, DH is associated with marked changes in systemic acid-base balance. Strategies for the management of these acid-base changes include widely different levels of circulating pCO₂, with divergent effects upon CBF and oxyhemoglobin dissociation.

2.1.2 Cerebral Physiologic Changes

Although the impact of a nonpulsatile circulation on cerebral perfusion remains controversial, it has been proposed that pulsatility is important for the maintenance of critical opening pressures in the distal capillary beds, as well as for the vasomotor tone required to maintain cerebral metabolic and pressure flow autoregulation. Thus, the loss of pulsatility could lead to failure to perfuse certain distal capillary beds or impaired autoregulation, or both.

Deep hypothermia is utilized to decrease cerebral oxygen utilization through a potent suppression of oxidative metabolic processes involved in both the activation of synapses as well as the maintenance of cellular integrity. In addition to its intended effects on cellular metabolism and oxygen utilization, deep hypothermic CPB may be associated with unintended, potentially adverse effects on the cerebral vasculature and circulating blood. These effects may lead to a paradoxical impairment of cerebral oxygen delivery. Specifically, oxygen delivery may be impaired by the use of hemodilution, as well as by an increase in oxygen-hemoglobin affinity, a direct effect of hypothermia, which may be augmented by more hypocarbic acid-base perfusion strategies. The combined result of these effects would be decreased oxygen delivery to tissue. Furthermore, hypothermia may impair normal myogenic vasorelaxation (“cerebrovasoparesis”) an effect that may underlie disturbances in cerebral autoregulation (discussed later). Finally, embolic and inflammatory phenomena associated with cardiopulmonary bypass may alter the cerebral microcirculation.

2.1.3 Cerebral NIRS Measurements

Continuous quantitative measurements by NIRS have demonstrated striking changes in cerebral hemodynamics and oxygenation during this preparative phase. At the onset of cardiopul-
Pulmonary bypass, a sharp decrease in total cerebral hemoglobin (THb) occurs [Figure 1(A)].\textsuperscript{11,16,21} This effect is most likely due primarily to systemic hemodilution, as well as to a decrease in perfusion pressure.\textsuperscript{17} The circulating hematocrit stabilizes within 3 to 5 min (unpublished data) after the onset of CPB and remains essentially constant throughout the remainder of CPB. Therefore the essentially constant THb during the rest of the cooling phase, as measured by NIRS, indicates a stable CBV.

Despite the initial sharp decrease in THb, there is an early and abrupt increase in HbO\textsubscript{2}.\textsuperscript{16,21} [Figure 1(A)]. This effect is maximal over the first 10 mins,\textsuperscript{16,21} but appears to continue throughout the cooling phase.\textsuperscript{27} Since the CBV (and hence presumably CBF) remains constant, this increase in HbO\textsubscript{2} indicates a decrease in cerebral oxygen extraction, the latter due to the decreased oxygen utilization and increased oxyhemoglobin affinity associated with hypothermia. Furthermore, the potential for microcirculatory disturbances (discussed earlier) may result in a distributive perfusion defect and decreased tissue oxygen extraction. Kurth, Steven, and Nicholson\textsuperscript{22} have suggested that failure of the elevation in cerebral oxyhemoglobin saturation during cooling may be associated with early postoperative neurologic dysfunction.

Measurements of change in cytochrome aa\textsubscript{3} oxidation during this period of apparent “luxury” intravascular oxygenation demonstrate a paradoxical decline in mitochondrial oxygenation, as indicated by a decrease in oxidized cytochrome aa\textsubscript{3} concentration [Figure 1(B)].\textsuperscript{17,21} These findings suggest an uncoupling of intravascular and intracellular oxygenation and an impairment of cellular oxygen delivery. The effect of hypothermia on oxyhemoglobin...
bin affinity may become a critical determinant of oxygen delivery during DH, particularly during periods of low-flow perfusion. Contrary to these findings, Greeley et al. described a decrease in both THb and HbO2 during this initial cooling phase, while the Cyto2 decrease from baseline remained insignificant. The reason for these discrepant results is unknown.

An important question generated by the unexpected finding of an “uncoupling” between intravascular and intracellular oxygenation is whether this phenomenon is artifactual in origin. In order to address this question we consider the potential effect of other simultaneous changes.

First, the possibility that these changes reflect path length changes and “cross talk” between the hemoglobin and Cyto2 signals appears unlikely for several reasons. The systemic hematocrit stabilizes within 3–5 min of the onset of hemodilution (unpublished data), while the cerebral THb and HbO2 changes show no significant correlation with those in Cyto2. Therefore, the assertion that the Cyto2 signal might not be adequately differentiated in vivo from the THb signal seems an unlikely explanation for these findings. A potential direct effect of hypothermia on the kinetics of the mitochondrial electron transport chain needs to be considered. While this possibility is difficult to exclude, it appears unlikely since in our studies the changes in Cyto2 were not significantly correlated with temperature, and Cyto2 continued to decrease well beyond the point of minimum tympanic temperature. Furthermore, it appears that hypothermia in the range used clinically has an insignificant effect upon the absorbance of NIR photons. For these reasons we propose that the observed decline in Cyto2 reflects an impairment in oxygen availability at the cerebral mitochondrial level, possibly due to an imbalance between hypothermic cerebral metabolic suppression and increased oxyhemoglobin affinity.

Animal studies using combined NIRS and magnetic resonance spectroscopy (MRS) have highlighted further the complexities of mitochondrial oxygenation during DH. In a rodent model of graded hypoxia at normothermia, a significant correlation between high-energy phosphates and Cyto2 was demonstrated. On the other hand, while animal models of hypothermic CPB have confirmed the decrease in Cyto2 during induction of hypothermia, MRS shows an increase in high-energy phosphates during this period of cooling. This divergence between cerebral high-energy phosphate levels and oxidized cytochrome aa3 during hypothermic CPB remains unexplained and requires further investigation.

### 2.2 Reparative Phase

#### 2.2.1 Systemic Physiologic Changes

During the intracardiac repair of congenital heart lesions in young infants, marked decreases (LFB), or even complete arrest (DHCA) of the systemic circulation is required to achieve access to minute and complex heart defects (Table 4). These techniques of LFB and DHCA are often combined sequentially during the same operation. The use of a predominant DHCA strategy expedites the surgical repair, but increases the risk of complete ischemia. A strategy of predominant LFB, on the other hand, prolongs the surgical procedure, but maintains a low, continuous level of perfusion. In so doing, LFB increases the exposure to the adverse inflammatory and embolic effects of CPB. Furthermore, should oxygen delivery become marginal during this continuous but decreased perfusion, the persistent supply of glucose will promote the development of lactacidosis.

<table>
<thead>
<tr>
<th>Systemic changes</th>
<th>Potential cerebral effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low-flow cardiopulmonary bypass</td>
<td>Incomplete cerebral ischemia</td>
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<tr>
<td></td>
<td>Persistent glucose supply with anaerobic metabolism (lactate formation)</td>
</tr>
<tr>
<td></td>
<td>Prolongs exposure to bypass-related embolic and inflammatory phenomena</td>
</tr>
<tr>
<td>2. Deep hypothermic circulatory arrest</td>
<td>Complete cerebral ischemia due to persistent cerebral oxygen metabolism</td>
</tr>
</tbody>
</table>

#### 2.2.2 Cerebral Physiologic Changes

Both the LFB and DHCA techniques are based on the assumption that hypothermic depression of CMRO2 effectively prevents the development of hypoxia-ischemia during the periods of decreased cerebral oxygen delivery. However, even at temperatures as low as 16 to 18 °C, cerebral oxygen utilization persists at about 10% of normothermic levels, presumably due to synthetic and other processes that maintain cellular integrity. This continuing oxygen utilization imposes a finite and, in the individual infant, unpredictable “safe duration” on these periods of decreased or arrested perfusion.

In addition to its intended suppression of cerebral oxygen metabolism, DH may limit cerebral oxygen delivery in several ways. First, as noted earlier, the normal intrinsic mechanisms of cerebral pressure-flow autoregulation may become impaired at DH. In addition, oxyhemoglobin affinity increases markedly at deep levels of hypothermia. During periods of reduced perfusion, both of these mechanisms may impose critical limitations on cerebral oxygen delivery. In fact, under these conditions, dissolved
intravascular oxygen, a parameter not measured by NIRS, may become the primary source of tissue oxygen delivery.55

The effects of predominant DHCA versus LFB strategies on neurologic outcome in infants undergoing hypothermic cardiac surgery were recently evaluated in a large, randomized clinical trial.4 In this study the use of a predominant DHCA strategy was found to be associated with a higher incidence of perioperative neurologic dysfunction, as well as a worse neurodevelopmental outcome at age 1 year.3

2.2.3 Cerebral NIRS Measurements

At the onset of LFB [Figure 1(A)] we noted a modest decrease in THb. Since systemic hemoglobin concentration remains unchanged, such a decrease in THb represents a decrease in CBV. Unlike their relationship at the onset of CPB (i.e., at higher temperatures) [Figure 1(A)], there is now a parallel, highly correlated relationship between changes in THb and HbO2. This parallel change most likely indicates that cerebral hemoglobin is completely oxygenated at this level of hypothermia. During this period of low flow, CytO2 continues to decline along a trajectory similar to that set during the initial cooling phase [Figure 1(B)].

During DHCA, several studies21,22 have demonstrated a progressive deoxygenation [Figure 1(A) and Figure 2] of the oxyhemoglobin trapped within the brain (i.e., HbO2 decreases and reduced Hb increases). This change most likely reflects the cerebral oxygen extraction required to support the low basal level of CMRO2 persisting during DHCA (discussed earlier). This dissociation of oxygen and hemoglobin follows a curvilinear decline, reaching a nadir, in our studies, after a median time of about 25 min. Other investigators22 have found this exponential decrease in oxyhemoglobin saturation during DHCA to show an apparent maturation dependency (Figure 3) with the longest half-life (9 min) occurring in neonates and the shortest half-life (4 min) in older children. This finding suggests a lower CMRO2 in neonates, a finding supported by previous studies.60,61

In our studies,21 a marked decrease in CytO2 preceded DHCA, and with the onset of DHCA there was only a modest further decrease [Figure 1(B)], suggesting that the enzyme might be close to completely reduced by this stage of the operation. In the studies by Greeley et al.,11 in which the cooling period had been associated with an insignificant

![Fig. 2](https://example.com/fig2.png)

**Fig. 2** Progressive curvilinear decrease in cerebrovascular hemoglobin oxygen saturation during deep hypothermic circulatory arrest. [From C. D. Kurth, J. M. Steven, S. C. Nicolson et al., Anesthesiology **77**, 656–661 (1992). Reprinted with permission.]

![Fig. 3](https://example.com/fig3.png)

**Fig. 3** Relationship between patient’s age and cerebrovascular hemoglobin oxygen saturation (ScO2) half-life during deep hypothermic circulatory arrest. Dashed lines demarcate the age groups (neonates, infants, children). [From C. D. Kurth, J. M. Steven, and S. C. Nicolson, Anesthesiology **82**, 74–82 (1995). Reprinted with permission.]

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Systemic and cerebral changes during the recovery phase.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic changes</strong></td>
<td><strong>Potential cerebral effects</strong></td>
</tr>
<tr>
<td>1. Reperfusion-reoxygenation</td>
<td>Increased cerebral vascular resistance</td>
</tr>
<tr>
<td></td>
<td>Disturbed cerebral reflow</td>
</tr>
<tr>
<td></td>
<td>Disturbed vasoregulation</td>
</tr>
<tr>
<td></td>
<td>Generation of oxygen free radicals</td>
</tr>
<tr>
<td>2. Rewarming</td>
<td>Reactivation of cellular oxidative metabolism</td>
</tr>
<tr>
<td></td>
<td>Decrease in hemoglobin-oxygen affinity</td>
</tr>
<tr>
<td>3. Pulsatile flow</td>
<td>Reperfusion of distal capillary beds</td>
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</table>
CytO$_2$ reduction, a major decrease occurred during DHCA.

2.3 RECOVERY PHASE

2.3.1 Systemic Physiologic Changes
The completion of intracardiac repair is followed initially by a period of reperfusion, rewarming, and reactivation of oxygen metabolism, and subsequently by the removal of CPB support and the return to a pulsatile cardiac-driven circulation (Table 5). Periods of DHCA and LFB may be followed by transient dysfunction in a number of organ systems. During this initial period of resuscitation, myocardial dysfunction may impair cardiac output, and increased pulmonary vascular resistance may elevate pressure in the right heart and hence in the central veins.

2.3.2 Cerebral Physiologic Changes
During this period of cerebral reperfusion, rewarming, and recovery of cellular oxidative metabolism, the relationship between increasing oxygen utilization and oxygen supply through the reperfused vasculature may be complex and difficult to predict. Several studies have indicated that DHCA is followed by a disturbed cerebral reperfusion.$^{10,62,63}$ Specifically, cerebral vascular resistance is elevated and diastolic CBF particularly may be decreased.$^{62}$ In addition, cerebral oxygen metabolism and mitochondrial function may be impaired following DHCA.$^{11}$ Consequently, without the ability to monitor the balance between oxygen supply and utilization, there is a risk of inadequate cerebral oxygen delivery in the face of the increasing cellular metabolism, and therefore potential further ischemia. Conversely, the use of highly oxygenated bypass blood during reperfusion in the face of a persistently suppressed cellular metabolism may promote the generation of reactive oxygen species and subsequent free radical injury. Currently there are no established techniques for monitoring the adequacy of cerebral oxygenation during this period.

Following withdrawal of CPB support, the potential for a simultaneous decrease in systemic arterial pressure and an increase in central, and hence cerebral, venous pressure constitutes a high risk period for impaired cerebral perfusion pressure. Furthermore, should cerebral ischemia occur in this phase, it does so after the neuroprotective effect of hypothermia has been withdrawn.

Cardiopulmonary bypass is often followed by an intense inflammatory syndrome,$^{50-52}$ a phenomenon that results from prolonged exposure of bypass blood to a large artificial surface, and which may be further stimulated by hypoxia-ischemia. While this inflammatory response is known to have marked effects on the systemic vasculature, its effect on the cerebral vessels is not well defined. In addition to these vascular effects, hypoxic-ischemic injury during DHCA or LFB may also trigger cellular cascades, including delayed energy failure,$^{64}$ release of toxic levels of excitatory amino acids,$^{65}$ and free radical generation.$^{66-68}$ Such cellular events may continue to evolve for hours or days following reperfusion, with potentially detrimental effects on cellular metabolism.

2.3.3 Cerebral NIRS Measurements
At the onset of reperfusion, cerebral intravascular oxygenation ($\mathrm{HbO}_2$) recovers to prearrest levels,$^{22}$ or, in our studies,$^{21}$ to levels significantly higher, [Figure 1(A)], suggesting a luxurious postarrest hyperemia. At the onset of hypothermic reperfusion, the initial changes in THb and $\mathrm{HbO}_2$ are highly correlated,$^{21}$ with minimal changes in deoxyhemoglobin, suggesting that cerebral hemoglobin is highly oxygenated at this stage.

Several studies$^{10,62,63}$ have described an apparent impairment of cerebral perfusion following DHCA. However, NIRS studies show that cerebral total hemoglobin concentration, and hence CBV, appears to recover,$^{16,22}$ and in our studies,$^{21}$ to exceed pre-LFB bypass and pre-DHCA levels. These findings are more consistent with a hyperemic reperfusion.

Despite this luxurious intravascular reoxygenation, CytO$_2$ remains depressed during these initial periods of reperfusion, and when normothermia is reached, only half the infants have recovered their baseline levels of CytO$_2$. Greeley et al.$^{11}$ had previously examined CMRO$_2$ and NIRS simultaneously in such infants and found that following DHCA there was a significant depression of both CytO$_2$ as well as CMRO$_2$, suggesting a disturbance in cerebral oxygen delivery or utilization during this period. Furthermore, we noted an apparent maturational dependency of the recovery of CytO$_2$, with younger infants recovering more rapidly and completely than older infants [Figure 4(B)] despite almost identical changes in intravascular oxygenation ($\mathrm{HbO}_2$) in the two age groups [Figure 4(A)].$^{21}$ This finding appears to support previous observations of a markedly lower CMRO$_2$$^{50}$ and a greater ‘hypoxic tolerance’$^{64}$ in the immature brain.

As recovery to normothermia is approached, deoxyhemoglobin begins to increase, and the relationship between THb and $\mathrm{HbO}_2$ becomes less correlated, suggesting a reactivation of CMRO$_2$ with increased cerebral oxygen extraction. At the same time CytO$_2$ starts to increase, suggesting an increase in mitochondrial oxidative metabolism.

After withdrawal of CPB, and the return to a pulsatile circulation, there is a further increase in THb and decrease in $\mathrm{HbO}_2$. The precise mechanism underlying these changes in increase is unclear. However, since the NIRS technique measures changes in the arterial, capillary, and venous compartments, it is possible that the increase in THb represents a sudden increase in cerebral venous volume resulting from impaired venous drainage to a relatively high-pressure right atrium (see earlier discussion).
2.4 DISCRETE ABSOLUTE NIRS MEASUREMENTS DURING THE INTRAOPERATIVE PERIOD

Measurements of discrete, quantitative hemodynamic variables during infant cardiac surgery are limited, in part because of the logistic complexities of the operating suite. Recently both the “oxygen method” and indocyanine green technique have been used to measure CBF during CPB. The sudden, rapid increase in oxyhemoglobin required for the “oxygen method” is achieved by adjustments at the CPB oxygenator, first to induce a decrease in SaO₂ into the 95% range for a brief period, and then to introduce a rapid “bolus” of oxyhemoglobin into the bypass circuit and the brain. The input function is measured by an indwelling optical oximeter in the afferent (arterial) limb of the CPB circuit, and the cerebral HbO₂ change is measured by NIRS. Using this technique, Fallon et al. measured CBF ranging from 15.9 to 53.5 cc 100 g⁻¹ min⁻¹ in four children during moderately hypothermic (25°C) CPB. By a similar technique, the authors measured CBV values of 4.3 to 8.0 cc 100 g⁻¹ in a single patient. Furthermore, by changing the CO₂ level at the CPB pump, the authors observed a significantly decreased CVR CO₂ during deep hypothermia.

Theoretical constraints to the “oxygen method” relate to the oxyhemoglobin affinity changes at deep hypothermia. With hypothermia there is a marked decrease in the P₅₀, i.e., the partial pressure of oxygen (pO₂) required to achieve a 50% oxyhemoglobin saturation. Consequently at deep hypothermia, a more pronounced decrease in pO₂ is required to induce the necessary “bolus” of HbO₂. The safety of such a maneuver in situations of potential impairment of cerebral oxygen delivery, particularly during LFB (discussed earlier), is unproven.
This potential limitation of the “oxygen method” may be circumvented by the use of indocyanine green, an inert, highly protein-bound tracer that absorbs NIR light. By this technique, very small doses of ICG are injected into the afferent limb of the CPB circuit, allowing up to 50 measurements of CBF before exceeding the maximum permitted dose. Repeated measurements can be made at 2-min intervals. The feasibility of this approach to CBF measurement has been demonstrated intraoperatively in a group of infants and children undergoing CPB. Both of these techniques for making discrete measurements of hemodynamic variables during hypothermic CPB await validation.

2.5 EARLY POSTOPERATIVE PERIOD

2.5.1 Systemic Physiologic Changes

In the early postoperative period, there is a persistent risk of cardiorespiratory instability in these infants. In particular, myocardial dysfunction, arrhythmias, ventilatory disturbances and the frequent need for multiple medications have complex circulatory effects (Table 6).

2.5.2 Cerebral Physiologic Changes

Potentially injurious cellular and vascular mechanisms initiated during the intraoperative phases may continue to evolve in the early postoperative period. Data suggest that cellular mechanisms of HI/R injury sustained during hypothermia have a more prolonged evolution than similar injury incurred at normothermia. Furthermore, the vascular effects of the systemic inflammatory response may disturb cerebral perfusion. In addition, it is well established that cerebral vasoregulatory mechanisms may be disturbed following periods of cerebral HI/R, exposing the brain to risk of further injury in this period of intensive care.

In animals and children (studied by transcranial Doppler), disturbances in cerebral perfusion are evident for 6 to 8 h following DHCA. Furthermore, studies suggest disturbed autoregulation of metabolism flow and a persistent anaerobic cerebral metabolism following DHCA. Despite the critical importance of autoregulation of cerebral pressure-flow in the postoperative period, this function has not been studied in children following hypothermic cardiac surgery. Following moderately hypothermic adult cardiac surgery, autoregulation of pressure flow and cerebral CVRCO₂ are preserved in the early postoperative period.

2.5.3 Cerebral NIRS Changes

The use of NIRS to study cerebral hemodynamics and metabolism following hypothermic cardiac surgery is limited. The current NIRS devices are extremely sensitive to movement artifacts and require a constant interoptode distance for continuous measurements of changing concentration. These restrictions have made it very difficult to extend studies from the operating room to the intensive care unit (ICU). We have used NIRS to evaluate CVRCO₂ (see earlier discussion) in 37 infants during the early ICU period of recovery. We performed 198 CVRCO₂ studies during the first 48 postoperative hours and found a highly correlated (R = 0.59, p < .001) relationship between changes in CBV and pCO₂. However, despite this indication of a response of the cerebral resistance vessels to CO₂, we found the magnitude of this response (CVRCO₂), (i.e., 0.045 ml/100 g/kPa change in pCO₂) to be strikingly lower than the CVRCO₂ measured by the same technique in normal term infants. This finding suggests a disruption of cerebral vasoregulation in this early postoperative period.

3 CURRENT LIMITATIONS OF THE NIRS TECHNIQUE DURING HYPOTHERMIC INFANT CARDIAC SURGERY

Near infrared spectroscopy represents a major potential neurodiagnostic development for the in vivo study and monitoring of cerebral hemodynamic and oxygenation changes in complex clinical situations, such as hypothermic infant cardiac surgery. However, a number of important limitations persist and continue to fuel controversy in this area (Table 2).

First, the current inability of readily available devices to measure directly changes in the path length of photons in tissue limits absolute quantitation of chromophores. This may be of particular importance in infant cardiac surgery, where profound and dynamic physiologic changes during the course of the operation have at least the theoretical potential of affecting the scatter of photons, and hence their path length. Techniques for bedside measurement of path length are being vigorously pursued by several different approaches, including...
phase modulation,\textsuperscript{85} time-of-flight,\textsuperscript{23,86} and water absorption\textsuperscript{87} techniques.

Second, the current NIRS devices interrogate a volume of tissue spanning a 6 to 8 cm radius under the optodes. From the changes measured in this volume of tissue, inferences are made about global cerebral changes. However, well-established cellular and vascular factors\textsuperscript{88} predispose the brain to a markedly heterogeneous regional vulnerability to global HI/R insults. For example, the hippocampus is significantly more vulnerable to HI/R injury than the frontal region, a common area for NIRS measurements. In addition, the embolic phenomena generated during cardiac surgery, particularly in adults, may cause vaso-occlusion and focal/multifocal injury. Current NIRS techniques are unable to distinguish these regional changes in oxygenation, although the development of such techniques is being pursued. Future techniques with this capability will greatly expand the potential of NIRS, particularly in the complex clinical arena of hypothermic cardiac surgery.

Near infrared spectroscopy acquires intravascular data from the entire cerebral vasculature (i.e., arteries, capillaries, and veins), but is unable to distinguish among contributions from these different compartments. The venous compartment constitutes about 70\% of the cerebral blood volume. In most clinical situations, cerebral venous volume is likely to remain fairly constant. However, in infants undergoing cardiac surgery, pronounced changes in central venous pressure and hence cerebral venous volume may occur, particularly after withdrawal of CPB.

Near infrared spectroscopy evaluates cerebral intravascular oxygenation by measuring the concentration of HbO\textsubscript{2}. Under conditions of normal temperature and perfusion, intravascular oxygen content is composed mainly of such hemoglobin-bound oxygen. However, during periods of hypothermia and decreased perfusion, dissolved oxygen, which is not measured by NIRS, may assume a more important role in delivery of oxygen to cerebral tissue.\textsuperscript{35}

Skepticism regarding the validity of the cytochrome aa\textsubscript{3} signal as a measure of intracellular oxygen availability has led to the use, in certain centers, of devices that measure intravascular oxygenation alone, without attempting to measure cellular oxygenation directly.\textsuperscript{16,22} Specifically, these devices measure the change in optical density difference between two wavelengths, selected for their ability to distinguish the extinction of oxyhemoglobin and deoxyhemoglobin. Cerebrovascular hemoglobin oxygen saturation is derived from these measurements. As discussed earlier, the complex changes of deep hypothermic cardiac surgery affect both cerebral oxygen supply and its utilization. In addition, there are intraoperative physiological changes during deep hypothermic cardiac surgery that directly affect the affinity between oxygen and hemoglobin, such as hypothermia itself and acid-base changes. Therefore, changes in intravascular oxygenation may result from changes in oxyhemoglobin affinity, altered oxygen delivery to the tissues, and/or induced changes in cellular metabolism. These mechanisms have widely differing clinical implications that cannot be distinguished without a simultaneous measurement of intracellular oxygen availability.

Discrete CBF measurements using the “oxygen technique” have major theoretical advantages over other techniques, such as xenon-133 clearance. Most important, this “oxygen technique” avoids exposure to non-biological chemicals and radiation. Furthermore, such measurements may be made rapidly and, with the appropriate software programs, may provide repeated bedside data. However, in our experience, this technique has proved difficult for a number of reasons. As mentioned above, the decreased P\textsubscript{50} associated with hypothermia raises safety concerns about the intraoperative use of this technique, particularly during low-flow periods in deep hypothermia. Furthermore, after correction of the heart defects these infants may have normal circulating SaO\textsubscript{2} levels in room air. Hence, “hypoxic mixtures” of nitrogen-oxygen may be required to achieve the necessary SaO\textsubscript{2} changes. In addition, in the postoperative period, impaired cutaneous perfusion may decrease the reliability of pulse oximetry. In our experience, the need for “beat-to-beat” pulse oximetry measurements increases the signal-to-background “noise” level and reduces the reliability and utility of this technique. Thus, in our hands, these difficulties tend to outweigh the benefits of the “oxygen method.”

4 CONCLUSIONS

Brain injury remains one of the most common and devastating complications of infant heart surgery.\textsuperscript{1,2} With the dramatic advances in the survival of these infants,\textsuperscript{89} the prevention of this neurologic injury with its long-term sequelae has become the next frontier in the management of infants with congenital heart disease. However, the delineation of mechanisms underlying such neurologic injury remains a formidable challenge, in part because there are no techniques capable of measuring simultaneous changes in cerebral oxygenation and hemodynamics. The multitude of complex and dynamic alterations in both the supply and utilization of cerebral oxygen that occur during hypothermic infant cardiac surgery make it one of the most demanding clinical scenarios for the evaluation of new neurodiagnostic techniques. The advent of NIRS has the potential for markedly expanding our understanding of these mechanisms, and for guiding future efforts to prevent this form of neurologic injury.
However, there are certain limitations of the technique that require resolution before its full, vast potential can be realized.

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