

# Newer Strategies for Neurological Protection in Pediatric Cardiac Surgery

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## Introduction

Reports from the last decade indicate that 21-69% of neonates and infants undergoing cardiac surgery with cardiopulmonary bypass suffer long term adverse neurodevelopmental effects.<sup>1-3</sup> The causes are multifactorial, and many investigators have placed the preponderance of the pathophysiological “blame” for brain injury with the patient, due to abnormal brain development resulting from the cardiac lesion itself.<sup>1,4,5</sup> It is this author’s contention that the perioperative period, especially cardiopulmonary bypass techniques, is associated with a large proportion of these brain injuries. This session will present new and novel strategies for brain protection during pediatric cardiac surgery.

## Optimized Cardiopulmonary Bypass Technique

An increasing number of cardiac surgery programs are adopting CPB techniques that ensure delivery of adequate oxygenated blood flow to the brain during all phases of CPB. This means changing a number of well-established techniques which reduce CPB flow, to allow reduced intracardiac blood return, to improve the surgeon’s visibility. Reduced flow techniques have all been associated with neurological injury from hypoxic-ischemic neuronal and white matter death, both in well established animal models, and in human studies. Avoiding or limiting the following techniques has great potential to improve neurodevelopmental outcome.

*Deep Hypothermic Circulatory Arrest (DHCA):* The landmark Boston Circulatory Arrest Study demonstrated that increasing duration of DHCA was associated with worse neurodevelopmental outcome at 8 years. A cut point of 41 minutes DHCA (95% confidence interval) before significant increase in problems was observed, but it was noted that many patients with DHCA times as short as 30 minutes or even less had an increased incidence of poor performance on some indicators.<sup>2</sup> Therefore, many programs are avoiding DHCA altogether, or limiting its use to unusual circumstances. Limiting consecutive periods to 20 minutes or less, and reperfusing the brain every 20 minutes are also strategies that are used.

*Low-Flow Cardiopulmonary Bypass (LFCPB):* Many surgeons reduce CPB flow at hypothermic temperatures. Although hypothermia confers brain and other organ protection, if flow is too low, brain injury can still occur from hypoxic-ischemic injury. At flows below 50 ml/kg/min (1/3 of normal full flow of 150 ml/kg/min for neonates and small infants), brain oxygenation decays dramatically at temperatures above 25° C, and thus LFCPB may lull the team into a false sense of security that they are providing some flow, when in reality it may be just as bad as DHCA.

Therefore, the common practice of reducing flow to 25-50 ml/kg/min is dangerous and should be avoided. If LFCPB is to be used, neurological monitoring of brain oxygenation should be used to help determine a safe level for the individual patient.<sup>6</sup>

*Antegrade Cerebral Perfusion (ACP):* In the past decade, several techniques have been described to perfuse the brain during aortic arch reconstruction, during a time that DHCA would otherwise be used. The most common of these involves suturing a synthetic graft to the innominate artery, and snaring the brachiocephalic vessels and descending thoracic aorta during the Norwood operation or other aortic reconstructions. When guided by brain oxygenation and blood flow monitoring, this technique can ensure normal levels of brain blood flow and oxygenation.<sup>7</sup> Despite this theoretical advantage, an MRI study before and after Norwood operation using ACP still revealed a 73% incidence of new or worsened ischemic brain lesions on postoperative MRI.<sup>8</sup> A retrospective comparison between ACP and DHCA for the Norwood operation reveals no difference in neurodevelopmental outcome at 1 year.<sup>9</sup> The reason for this lack of improvement may be ACP flows that are too low, i.e. 20-40 ml/kg/min. A significant proportion of patients have no detectable cerebral blood flow in the contralateral cerebral hemisphere at ACP rates of 10-30 ml/kg/min. We have demonstrated, using transcranial Doppler and NIRS monitoring, that a median of 64 ml/kg/min (range 24-94 ml/kg/min) is required to ensure adequate contralateral flow.<sup>7</sup> Therefore, many patients may be receiving inadequate flow with ACP.

These techniques often require significant change in surgical practice, and may lengthen the duration of the surgery. This is thought to be the reason that DHCA is still widely practiced in 2007.

*pH Stat Blood Gas Management.* pH stat management corrects the blood gas values for temperature, resulting in the brain experiencing higher PaCO<sub>2</sub>, higher cerebral blood flow, and brain oxygenation. Extensive animal data, and the one large comparison between pH stat and alpha stat in neonates reveal better neurological outcomes with pH stat.<sup>10,11</sup> The simplest and most effective practice is to use pH stat throughout bypass. Again, because adjusting CPB sweep gas flow, or adding CO<sub>2</sub> is more complex, difficult, and requires change of long-established techniques, many programs have been slow to change. It is time to critically examine the practice of alpha stat management as one that may significantly contribute to brain injury on CPB.

*Higher Hematocrit:* In another important study from Boston Children's Hospital, infants with hematocrit 30% on CPB vs. 20% had significantly better neurodevelopmental outcomes 1 year after cardiac surgery.<sup>12</sup> Further work studying whether even higher hct of 35% is even better. Again, this strategy delivers more oxygen to the brain during CPB. Previous concerns about sludging of erythrocytes at higher hematocrits and deep hypothermic temperatures have been disproven.

### Neurological Monitoring

Near infrared spectroscopy (NIRS) uses near infrared light to estimate the oxyhemoglobin saturation in a sample volume of the frontal lobe of the brain.<sup>13</sup> There are now 2 U.S. FDA approved devices, the Somanetics INVOS system (2 wavelengths, a trend monitor, reports regional cerebral oxygen saturation-rSO<sub>2</sub>, extensive clinical study in pediatrics), and the CAS Medical absolute tissue oximeter (4 wavelengths, potentially more accurate, recently released, little pediatric data). There is increasing evidence that prolonged low rSO<sub>2</sub> (<45% for >180 minutes in the perioperative period for Norwood stage I) is associated with brain injury on postoperative MRI.<sup>8</sup> There are a number of case reports and series demonstrating NIRS' ability to immediately detect low cerebral oxygen levels associated with CPB cannulation problems in infants, averting neurological disaster.<sup>14</sup>

### Inhaled Anesthetic Agents

Inhaled anesthetics, including isoflurane and desflurane, confer significant neuroprotection in animal models of cardiopulmonary bypass,<sup>15,16</sup> and in vitro tissue culture models of hypoxemia.<sup>17</sup> The mechanism is a slowing of neuronal metabolism, which confers protection during periods of hypoxia/ischemia, and limits the extent of cerebral infarction during CPB-mediated insults. These agents also slow apoptosis and block  $iCa^{++}$  neuronal injury and death. Anesthetic vaporizers can easily be placed in the CPB sweep gas flow, and their use has 3 desired effects: neuroprotection, anesthesia on CPB, and vasodilation, the latter often desired to maximize CPB flows at low pressures. Desflurane may be more desirable because of its low solubility, and the often low sweep gas flows of 2-400 ml/min for small infants. Therefore, it would appear desirable to use these agents liberally on CPB, even seeking to achieve a target blood level while cooling, especially if DHCA or other such techniques are to be used.

### Hypoxic Preconditioning

Hypoxic preconditioning exposes neurons to moderately low oxygen tensions without overtly damaging the brain. Moderate levels of hypoxia for periods before a major hypoxic-ischemic event have been shown to significantly protect neurons from death, and limit the size of cerebral infarction, improve neurobehavioral outcomes in a number of animal models.<sup>18</sup> Adults who experience transient ischemic attacks before a stroke have better outcomes than those who do not. Low oxygen tensions induce production of hypoxia-inducible factor-1 (HIF-1) in neurons, and also elevate EPO levels and upregulate EPO receptor numbers.<sup>19</sup> Although we would not advocate intentionally lowering brain oxygenation preoperatively before neonatal cardiac surgery, we have demonstrated that a number of preoperative neonates, particularly those with D-TGA, have significantly low regional cerebral oxygen saturation ( $rSO_2$ ), in the 40-50% range.<sup>20</sup> This may be low enough to not cause overt neuronal injury, but increase HIF-1 and EPO and protect the brain. Conversely single ventricle patients, and patients undergoing aortic arch reconstruction have significantly higher  $rSO_2$  in the preoperative period and perhaps do not undergo hypoxic preconditioning for that reason. The latter group is known to suffer a higher incidence of brain injury on postoperative MRI, and this lack of hypoxic preconditioning protection may be one contributing factor.

### Erythropoietin

It is clear from our own work and that of many others that despite optimal techniques for CPB, anesthesia, and perioperative management, that many infants still suffer significant periods of brain hypoxia in the perioperative period, and still have brain abnormalities on postoperative MRI, despite all efforts to improve oxygen delivery to the brain.<sup>21,22</sup> Therefore, newer brain protective strategies need to be studied. Erythropoietin (EPO) has the potential to significantly lessen neuronal and white matter injury and death when used before, during, and even several hours after a cerebral hypoxic event.

An important body of basic science work over the last 5 years has proven that high dose EPO protects the brain from hypoxic ischemic injury by 3 major mechanisms.<sup>23-26</sup> EPO switches off apoptosis, the genetically programmed sequence of cell death. EPO also limits excitotoxic cell death, that mediated by N-methyl-D-aspartate and its receptors, which occurs in response to a number of neuronal insults including hypoxemia. And, EPO also blocks the inflammatory cascade,

which also contributes to brain injury. Finally, EPO may be a cerebral vasodilator, which may be an important mechanism to counteract the cerebral vasoconstriction and increased cerebral vascular resistance seen after deep hypothermia in infants.

### Texas Children' Hospital Studies

Careful studies, using MRI for brain imaging, and NIRS monitoring and treatment protocols, as well as long term neurodevelopmental followup are needed to critically evaluate new modalities.<sup>27,28</sup> We have completed a 21 patient pilot study of neonates undergoing cardiac surgery with bypass. They received NIRS monitoring for 12-24 hours preoperatively, intraoperatively, and 72 hours postoperatively with a treatment protocol for rSO<sub>2</sub> <50%. Patients also received a baseline EEG and 72 hours postoperative EEG monitoring. In addition, they underwent brain MRI immediately before surgery, and 7 days after surgery. All also have a 3<sup>rd</sup> MRI at 4-6 months, and then will have developmental assessment using the Bayley Scales of Infant Development III at 1, 3, and 5 years. Early results have been submitted for publication.

In addition, we have now begun a prospective, randomized, placebo controlled trial of EPO for neuroprotection, using the same protocol noted above for the pilot study, with the addition of 3 doses EPO 1000 units/kg IV (3-5 times normal clinical dose) or placebo, for 3 doses—12 hours preoperatively, after CPB, and a third dose 24 hours after the second. Pharmacokinetics of high dose EPO are being studied as well. 80 patients are being studied in a phase I/II trial for safety and effectiveness, with a possible 240 patient trial planned if successful, with stratification into 3 groups: arterial switch for D-TGA, Norwood stage I for HLHS and variants, and aortic arch reconstruction with VSD closure and other 2 ventricle defects. It will be important to critically evaluate the success of this treatment, but it has potential to improve outcomes of this high risk population.

### Conclusions

Survival after neonatal and infant cardiac surgery has improved dramatically, but quality of life, including neurodevelopmental outcomes, still needs study and improvement. It is important to protect the brain using established strategies, and test new strategies with carefully designed follow-up studies. Potential exists for significant improvement in this area.

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