Pediatric Cardiac Surgery Annual

CONTROVERSIES IN PEDIATRIC/CONGENITAL HEART SURGERY

Perioperative Neuroprotective Strategies

David P. Nelson,[a] Dean B. Andropoulos,[b] and Charles D. Fraser, Jr[c]

Long-term neurodevelopmental impairment is common in newborns and infants undergoing corrective or palliative congenital heart surgery. The etiologies of neurodevelopmental morbidity in these children are multifactorial and include prenatal, preoperative, intraoperative, and postoperative factors. Perioperative neurologic monitoring is thought to be integral to prevention or rescue from adverse neurologic events. Recent advances in perfusion techniques for congenital heart surgery now ensure adequate cerebral O_2 delivery during *all* phases of cardiopulmonary bypass. Periventricular leukomalacia and other serious neurologic injury can be minimized by an optimized perfusion strategy of continuous high-flow, high hematocrit cardiopulmonary bypass, minimal use of deep hypothermic circulatory arrest, antegrade cerebral perfusion during aortic arch reconstruction, pH-stat blood gas strategy, and cerebral monitoring with NIRS and trans-cranial Doppler. Because there is evidence that brain injury can also occur in the prenatal, preoperative, and postoperative periods, improved strategies to prevent injury in these arenas are much needed. Extensive further clinical investigation is warranted to identify neuroprotective management strategies for the operating room and intensive care unit to preserve neurologic function and optimize long-term neurodevelopmental outcomes in children with congenital heart disease.
Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 11:49-56

KEYWORDS Congenital heart surgery, CNS injury, Neurologic injury, neuroprotection, neurodevelopmental outcomes

With improving long-term survival for children with congenital heart disease,[1] interest in minimizing morbidities to improve quality of life has become paramount, with particular attention focused on neurocognitive and developmental outcomes. Although severe central nervous system (CNS) sequelae like stroke and seizures are rare after congenital heart surgery,[2,3] more subtle neurologic abnormalities such as attention and behavioral problems, learning disabilities, and difficulties with high-level integration are common.[4,5] In reports from various centers, long-term neurodevelopmental impairment occurs in 21% to 69% of children undergoing cardiac surgery as newborns or young infants.[5-10] Recent data from long-term follow-up studies of children with complex congenital heart disease reveal a "developmental signature" similar to that of very low birth weight premature infants, including problems with fine and gross motor control, visual-motor integration, executive functioning, and attention that often result in poor school performance and loss of self esteem.[5] A study from Finland reported that patients with correction of simple congenital heart anomalies are functioning well as adults,[11] but little is known about the long-term neurodevelopmental outcomes of children with more complex heart defects.

Etiology and Potential Mechanisms of Neurologic Injury

Recent studies have shown a surprisingly high incidence of neurologic injury in children with congenital heart disease.[5-10] One of the most frequent and severe of these injuries is periventricular leukomalacia (PVL), a white matter injury

[a]Sections of Cardiology, Departments of Pediatrics, Anesthesiology, and Surgery, Texas Children's Hospital, Baylor College of Medicine, Houston, TX.
[b]Cardiovascular Anesthesiology, Departments of Pediatrics, Anesthesiology, and Surgery, Texas Children's Hospital, Baylor College of Medicine, Houston, TX.
[c]Cardiothoracic Surgery, Departments of Pediatrics, Anesthesiology, and Surgery, Texas Children's Hospital, Baylor College of Medicine, Houston, TX.
Address correspondence to David P. Nelson, MD, PhD, Associate Professor of Pediatrics, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin Ave, MC19345C, Houston, TX 77030-2399; e-mail: dpnelson@bcm.edu

1092-9126/08/$-see front matter
doi:10.1053/j.pcsu.2008.01.003

specific to the developing neonatal brain.[12] Until recently, it was generally accepted that neurodevelopmental and cognitive impairment in children with congenital heart disease were primarily due to intraoperative neurologic injury. Recent findings now indicate that the etiologies of neurodevelopmental morbidity in these children are instead multifactorial, and include pre-existing brain malformations, genetic factors, chromosomal abnormalities, abnormal cerebral blood flow patterns in-utero, preoperative cerebral hypoxia and/or hypoperfusion, cerebral ischemia secondary to cardiac surgical or cardiopulmonary bypass techniques, and postoperative factors such as low cardiac output syndrome and inadequate cerebral perfusion.[12-18] PVL and other types of CNS injury have been observed in both pre- and postoperative patients with congenital heart disease, indicating CNS injury is not simply an intra-operative phenomenon.[12,17,18] In infants with both cyanotic and acyanotic congenital heart disease, Limperopoulis et al reported that more than 50% had at least one abnormal finding on preoperative neurologic examination,[19] and that preoperative neurodevelopmental status was predictive of postoperative status.[16] Interprovincial data from a Canadian neonatal congenital heart surgery program suggest that preoperative, intraoperative. and postoperative factors all contribute equally to neurodevelopmental outcomes.[20]

Genetic Predisposition

A variety of host factors can increase the risk of neurologic impairment in children with congenital heart disease. Coexisting anatomic brain abnormalities accompany many of the chromosomal abnormalities and congenital anomaly syndromes associated with congenital heart disease.[4,21-23] Some children are at greater risk for CNS injury because of abnormalities in cerebral vasculature, extensive aortopulmonary collaterals, and genetic factors such as pro-thrombotic disorders and polymorphisms of apolipoprotein E and other inflammatory mediators.[24] Fetuses with the most severe forms of congenital heart disease are thought to be at increased risk of CNS injury, especially those with an abnormal circulation.[13,14]

Prenatal Factors

Injury to the developing brain can occur in the prenatal period because of inadequate cerebral blood flow or low blood oxygen content. Recent studies using fetal imaging techniques demonstrate decreased cerebral blood flow and abnormal cerebral vascular resistance in fetuses with congenital heart disease.[13,14]

Preoperative Factors

In a similar manner, neonates with congenital heart disease may acquire CNS injury preoperatively because of poor brain perfusion and cyanosis. Infants with ductal-dependent lesions commonly have diastolic hypotension, which may compromise brain perfusion.[12] Using magnetic resonance imaging (MRI) to quantify cerebral blood flow in neonates with congenital heart disease, Licht et al[15] observed that decreased cerebral blood flow preoperatively correlates with PVL. Embolic events caused by intra-cardiac shunting may result from inadvertent intravenous infusion of air bubbles, thrombotic events, and catheterization procedures. McQuillen et al[17] reported a high incidence of embolic brain infarcts in neonates with transposition of the Great arteries who had undergone balloon atrial septostomy, thus suggesting embolic events are common during the balloon atrial septostomy procedure. Preoperative CNS injury could also result from ongoing systemic inflammation, which is common in neonates with congenital heart defects. Systemic inflammation in these patients is thought to result from persistent translocation of endotoxin, presumably because of persistent mesenteric hypoperfusion.[25,26]

Intraoperative Factors

Although CNS injury may occur before surgical correction or palliation, children are at high risk for CNS injury perioperatively, in both the operating room and the cardiac intensive care unit. The intraoperative period of cardiac surgery is still thought to be responsible for much of the lifetime potential for brain injury, as evidenced by recent studies showing a 50% to 70% incidence of significant new PVL and other hypoxic-ischemic lesions occurring at the time of surgery, documented by postoperative MRI.[12,27,28] Cognitive deficits are present in more than half of adult cardiac surgery patients at the time of hospital discharge.[29] A recent retrospective study reported that the intelligence quotient scores of children who have undergone surgical atrial septal defect closure were lower at follow-up than those who have undergone transcatheter closure,[30] suggesting that even simple bypass procedures may impact neurologic outcome.

Operative factors that contribute to brain injury include poor perfusion, anesthetic-induced brain toxicity, cardiopulmonary bypass-mediated inflammation, ischemia-reperfusion injury, thromboembolic events, and glucose, electrolyte, or acid-based disturbances.[4,21,31-34] Among the chief causes of intraoperative brain injury are cardiopulmonary bypass techniques that result in limited or no oxygen delivery to the brain for significant time periods.[32] Although there is disagreement about the optimal way to protect the brain during congenital heart surgery, factors that can contribute to brain ischemia include prolonged deep hypothermic circulatory arrest,[35,36] alpha-stat pH management,[37-43] low hematocrit,[44] inadequate or non-uniform brain cooling,[45] and low-flow bypass techniques.[10,46]

Postoperative Factors

Although preservation of brain perfusion in the operating room is clearly critical, the early postoperative period after congenital heart surgery may be a time of equal or even greater risk for CNS injury, because of periods of poor perfusion, cyanosis, abnormal vascular reactivity, hyperthermia, endocrine abnormalities, poor glycemic control, and acid-based or electrolyte disturbances.[47,48] Postoperative variables such as cyanosis, low systolic and diastolic blood pressures, and prolonged periods of poor cerebral O_2 saturation are