Brain immaturity is associated with brain injury before and after neonatal cardiac surgery with high-flow bypass and cerebral oxygenation monitoring

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Background: New intraparenchymal brain injury on magnetic resonance imaging is observed in 36% to 73% of neonates after cardiac surgery with cardiopulmonary bypass. Brain immaturity in this population is common. We performed brain magnetic resonance imaging before and after neonatal cardiac surgery, using a high-flow cardiopulmonary bypass protocol, hypothesizing that brain injury on magnetic resonance imaging would be associated with brain immaturity.

Methods: Cardiopulmonary bypass protocol included 150 mL · kg^{-1} · min^{-1} flows, pH stat management, hematocrit > 30%, and high-flow antegrade cerebral perfusion. Regional brain oxygen saturation was monitored, with a treatment protocol for regional brain oxygen saturation < 50%. Brain magnetic resonance imaging, consisting of T1-, T2-, and diffusion-weighted imaging, and magnetic resonance spectroscopy were performed preoperatively, 7 days postoperatively, and at age 3 to 6 months.

Results: Twenty-four of 67 patients (36%) had new postoperative white matter injury, infarction, or hemorrhage, and 16% had new white matter injury. Associations with preoperative brain injury included low brain maturity score ($P = .002$). Postoperative white matter injury was associated with single-ventricle diagnosis ($P = .02$), preoperative white matter injury ($P < .001$), and low brain maturity score ($P = .05$). Low brain maturity score was also associated with more severe postoperative brain injury ($P = .01$). Forty-five patients had a third scan, with a 27% incidence of new minor lesions, but 58% of previous lesions had partially or completely resolved.

Conclusions: We observed a significant incidence of both pre- and postoperative magnetic resonance imaging abnormality and an association with brain immaturity. Many lesions resolved in the first 6 months after surgery. Timing of delivery and surgery with bypass could affect the risk of brain injury. (J Thorac Cardiovasc Surg 2010;139:543-56)

Despite current survival rates of greater than 90%,[1] up to 50% of children age 5 years or older who had cardiac surgery as newborns or young infants have long-term neurodevelopmental impairment.[2] These children have problems that are similar to those seen in premature infants, including attention deficit hyperactivity disorder and other cognitive and fine motor deficits.[2] Creighton and colleagues[3] documented that 26.4% of a cohort of 53 neonates without chromosomal abnormalities who had repair of hypoplastic left heart syndrome, transposition of the great vessels, or total anomalous pulmonary venous return had a full-scale IQ score of <85 at 5 years of age. Majnemer and associates[4] documented gross motor delays in 49% and fine motor delays in 39% of a cohort of 94 patients tested at age 5 years, who had undergone complex congenital cardiac surgery as infants. Magnetic resonance imaging (MRI) has documented a preoperative incidence of white matter injury (WMI) or other ischemic lesions of 20% to 40%.[5,6] Associations with poor neurodevelopmental outcomes include chromosomal abnormalities, particularly 22.q11.2 microdeletion (common in tetralogy of Fallot, interrupted aortic arch, and truncus arteriosus), resulting in significantly lower mental and physical development.[7]

Perioperative causes of neurologic injury include cerebral hypoxia/ischemia due to cyanosis, surgical or cardiopulmonary bypass (CPB) techniques including prolonged deep hypothermic circulatory arrest (DHCA),[8] cerebral emboli,

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Abbreviations and Acronyms

2V = two ventricle
ACP = antegrade cerebral perfusion
CHD = congenital heart disease
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
KIU = kallikrein inhibiting units
MRI = magnetic resonance imaging
rSO_2 = regional cerebral oxygen saturation
SpO_2 = pulse oximetry saturation
SV = single ventricle
TE = echo time
TMS = Total Maturity Score
TR = relaxation time
WMI = white matter injury

low cardiac output, and intercurrent events such as cardiac arrests.[9] Attempts to reduce acute brain injury have included newer perfusion techniques, such as antegrade cerebral perfusion (ACP), which allow continuous delivery of oxygenated blood to the brain during CPB in neonates.[10] Monitoring of cerebral oxygenation using near infrared spectroscopy and cerebral blood flow velocity using transcranial Doppler ultrasound[11] have also been used as individualized strategies for continuous oxygen delivery to the brain. pH stat blood gas management[12] and hematocrit of 25% or greater[13] allow for more even brain cooling and provide greater oxygen delivery to the brain, resulting in improved neurologic outcomes. Despite these new intraoperative techniques, MRI studies have revealed a 36% to 73% incidence of new or worsening white matter or other ischemic brain lesions after neonatal cardiac surgery.[5,6,14]

Recently, neonates with complex congenital heart disease (CHD) have been discovered to have structural brain immaturity due to delays in myelination, cortical development, and maturation of germinal matrix and glial cell migration.[15] Magnetic resonance spectroscopy also documents delayed microcellular maturation in neonates with CHD.[16] This brain immaturity may predispose these infants to greater risk of brain injury, particularly WMI, which is frequently seen in premature infants with proven immature brain development.[17-19]

This study was undertaken to determine the incidence and severity of new MRI brain injury with high-flow CPB (maintaining full 150 mL · kg^{-1} · min^{-1} and high-flow ACP) and monitoring cerebral oxygenation with near infrared spectroscopy. We also sought to determine the patient and procedural factors that had significant associations with brain injury, particularly brain maturation. Our hypothesis was that patients with structural brain immaturity would be more likely to have pre- and postoperative brain injury.

METHODS

This study was approved by the Baylor College of Medicine Institutional Review Board, and patients were enrolled after signed informed consent was obtained from parents. It was a prospective, observational study with a single patient cohort receiving uniform CPB and perioperative treatment protocols.

Patient Population

Neonates (<30 days of age) having cardiac surgery with hypothermic (<30°C) CPB for 60 minutes or greater were eligible. Both single-ventricle (SV) and two-ventricle (2V) repairs were included. Exclusion criteria were gestational age less than 35 weeks at birth, weight less than 2.0 kg, recognizable dysmorphic syndrome, or preoperative cardiac arrest for greater than 3 minutes.

Preoperative Management

Prostaglandin E1 infusion was used in patent ductus arteriosus–dependent systemic perfusion lesions or for patients with dextrotransposition of the great arteries with significant cyanosis manifested by prolonged peripheral oxygen saturation (SpO_2) < 75%. Patients with dextrotransposition of the great arteries with intact ventricular septum had balloon atrial septostomy.

Anesthesia, Surgery, and Perfusion Protocol

Anesthetic technique consisted of fentanyl (100–400 μg/kg total dose), midazolam (0.25–3 mg/kg total dose), and isoflurane (up to 1% end-tidal concentration before and after CPB, and up to 3% inspired concentration in the CPB sweep gas). Vecuronium or pancuronium was used for neuromuscular blockade.

CPB technique consisted of arterial cannulation and bicaval or single-atrial venous cannulation. CPB flow rates of 150 mL · kg^{-1} · min^{-1} were used at all times, except for periods of DHCA, or ACP. Target mean arterial pressure was 30 to 35 mm Hg, facilitated if necessary with α-receptor blockade with phenoxybenzamine (0.25–0.5 mg/kg) or phentolamine (0.1–0.3 mg/kg). Cooling on CPB was accomplished over 20 minutes or more. pH stat blood gas management was used throughout the CPB period. One dose of methylprednisolone (20 mg/kg) was given in the CPB prime. Aprotinin was utilized for the first 55 cases: 60,000 kallikrein inhibiting units (KIU)/kg loading dose followed by infusion of 7000 KIU · kg^{-1} · h^{-1}. A CPB circuit prime of 60,000 KIU/kg of aprotinin was given. After safety concerns about aprotinin in adult cardiac surgery were known, the last 13 cases had ϵ-aminocaproic acid instead of aprotinin, at doses of 75 mg/kg intravenous load to the patient and 75 mg · kg^{-1} · h^{-1} infusion throughout surgery, with a 75-mg/kg CPB prime dose. Hematocrit was maintained at 30% to 35% during cooling and hypothermic periods and increased to 40% to 45% during rewarming. Conventional ultrafiltration was utilized throughout the CPB period; post-CPB modified ultrafiltration was not used.

ACP was utilized for aortic arch reconstruction.[10] A 3.5-mm polytetrafluoroethylene graft was sutured to the right innominate artery as arterial inflow. CPB flow during ACP was adjusted to maintain cerebral blood flow velocity, measured with transcranial Doppler ultrasound, to within 10% of full CPB baseline, and right brain rSO_2 > 90%, as described previously.[10]

Physiologic monitor data (SpO_2, intra-arterial pressure, heart rate, temperature, intracardiac pressures) as well as cerebral oximeter data were collected in 1-minute intervals and stored electronically for the pre-, intra- and 72-hour postoperative periods. (Bedmaster, Excel Medical Electronics, Inc, Jupiter, Fla; and Somanetics, Inc, Troy, Mich).

Cerebral Oxygenation Monitoring and Treatment Protocol

Regional cerebral oxygen saturation (rSO_2) was monitored with a sensor on the right forehead (Somanetics 5100A; Somanetics, Inc). If the rSO_2 was