Published in final edited form as:

World J Pediatr Congenit Heart Surg. 2016 September ; 7(5): 611–613. doi:10.1177/2150135116650650.

Anomalies of Ventriculo-Arterial Connections and Immature Brain Development

Nobuyuki Ishibashi, M.D. and Richard A. Jonas, M.D.

Department of Cardiac Surgery and Center for Neuroscience Research, Children's National Medical Center, Washington, DC

Keywords

Brain; Cerebral circulation; Neurocognitive deficits; Congenital heart disease; Congenital heart surgery

Over the six decades since open heart surgery became possible following the introduction of cardiopulmonary bypass (CPB), amazing advances have been made in reducing the mortality risk for patients across the entire spectrum of congenital heart disease (CHD). In the last 2 to 3 decades even the mortality of severe and complex CHD such as hypoplastic left heart syndrome has been reduced from close to 100% to less than 10%. This accomplishment is directly attributable to the net effect of therapeutic successes from the innovative work of surgeons and cardiologists and the courageous devotion of patients and families. With increased survival rates, the focus of current research in the pediatric cardiac population has clearly transitioned from short-term surgical survival to the improvement of functional outcome and quality of life. It has been increasingly recognized that many children with severe and complex CHD suffer important developmental delay, neurological impairment or behavioral problems. In neonatal and infant cardiac surgery, surgical and perioperative care and management have been dramatically advanced; however, recent multi-center analysis has demonstrated that early neurodevelopmental outcomes after cardiac surgery in newborns and infants have not significantly improved in recent years even after adjustment for center and class.¹ In the study, improved neurological outcomes have been revealed by a modest degree over time only after adjustment for patient and preoperative medical factors.¹ The personal, family, and societal costs of these gross and subtle neurological morbidities are inestimable. Therefore as the pediatric heart network of the NHLBI has stated one of the most important current challenges for children with CHD is to improve neurodevelopmental deficits.

It is becoming clear that the etiology of neurological deficits associated with CHD is cumulative and multifactorial. Early clinical trials and laboratory research including our own studies focused on brain damage occurring during surgery and CPB. Using neonatal brain imaging, however, Dr. Miller and colleagues has shifted the field, concluding that term

Correspondence: Nobuyuki Ishibashi, MD, Children's National Medical Center, 111 Michigan Avenue, N.W., Washington, DC, 20010-2970. Tel: 202-476-2388, Fax: 202-476-5572, nishibas@childrensnational.org.

Presented at World Society for Pediatric and Congenital Heart Surgery, "Kyoto Symposium", November 27, 2015, Kyoto, Japan

newborns with CHD have widespread brain abnormalities before cardiac surgery.² A simple scoring system for brain MRIs named the “Total Maturation Score” has been introduced as a measure of brain development in the neonate with CHD. The criteria include: i) myelination; ii) cortical folding; iii) germinal matrix (also called ventricular and subventricular zone); and iv) bands of migrating glial cell. Studies using the scoring method have demonstrated that before surgery term infants with HLHS and transposition of the great arteries have brains that corresponding to a delay of 1 month in structural development. Importantly newly developed brain injury after surgery is common in neonates whose brains are immature at the time of surgery. More recently sophisticated quantitative fetal imaging techniques have further brought the role of prenatal events in neurological injury into increasing focus. Normally *in utero* cerebral blood flow involves preferential streaming of the most highly oxygenated blood to the developing brain. However, when CHD exists - particularly anomalies of ventriculo-arterial connections such as d-transposition of the great arteries or hypoplastic left heart syndrome (HLHS) - these beneficial patterns of flow are altered, resulting in desaturated or reduced cerebral blood flow (Figure 1).³ Recent advances in imaging technologies have identified: 1) a progressive third trimester fall-off in the volumes of cortical gray, subcortical gray matter, and white matter; 2) significant decrease in cortical gyrification; 3) local cortical folding delays in the frontal, parietal, calcarine, temporal, and collateral regions in the fetus with HLHS.⁴ However cellular mechanisms underlying a wide variety of immature and dysmature brain development due to CHD-induced chronic hypoxia remain poorly understood. Importantly this gap in knowledge prevents developing novel treatment and management to reduce brain immaturity in the neonate and infant with severe and complex CHD, and to improve neurodevelopmental outcomes in this population.

We have studied cellular mechanisms underlying white matter injury and dysmaturity associated with CHD and CPB, focusing on oligodendrocytes which are responsible for axonal myelination and are the most prominent cell population in the white matter.³ We developed a porcine CPB model, which displays area-dependent white matter maturation.⁵ In this model white matter dysmaturity was identified following CPB-induced ischemia-reperfusion injury.⁵ The degree of injury was inversely correlated with the maturation stage, indicating maturation-dependent vulnerability of white matter.⁵ Within four identified stages of oligodendrocyte maturation including: 1) oligodendrocyte progenitor cells; 2) pre-oligodendrocytes; 3) immature oligodendrocytes; and 4) mature oligodendrocytes, our studies in both porcine and mouse models showed selective vulnerability of pre-oligodendrocytes, while oligodendrocyte progenitor cells were resistant to insults associated with cardiac surgery.^{5,6} Oligodendrocyte progenitor cells as well as neural stem/progenitors retain mitotic and differentiation potential throughout their life span, as the brain is able to replace damaged neurons and glia. Thus our study suggested that earlier cardiac repair potentially promotes enhanced brain development because the number of oligodendrocyte progenitor cells decreases with age.⁵ On the other hand, studies also demonstrated that vulnerability of oligodendrocyte progenitor cells to damage increased after pre-operative chronic hypoxia.⁶ However, results obtained from a mouse brain slice model indicate that hypothermia at 15°C protects vulnerable oligodendrocyte progenitor cells from reperfusion-reoxygenation injury.⁶ Since abnormal cerebral circulation due to CHD results in significant abnormalities in white matter and cerebral cortex by the time of birth, our results suggest

that earlier normalization of cerebral circulation by cardiac surgery using deep hypothermia with concomitant therapy aimed at promoting neuronal regeneration is the most promising cellular based approach for successful brain development in children with severe and complex CHD.^{5,6}

Within the perinatal and adult brain, the subventricular zone represents the largest source of neural stem/progenitor cells. Endogenous brain repair mechanisms - including functional recovery of white matter axons by oligodendrocyte progenitor cells migrating from the subventricular zone - have been described in rodent models. Therefore the subventricular zone is a critically important brain region to promote endogenous neuronal regeneration. Interestingly it has been well documented that in the rodent brain the subventricular zone is a vascular-rich brain region and factors derived from the vasculature regulate neural stem/progenitor cells in the subventricular zone. Therefore alterations in cerebral circulation and vasculature due to CHD and cardiac surgery are likely to modulate developmental process in neural stem/progenitor cells. In studies of developmental neuroscience, findings from the human brain often require validation and mechanistic investigation in their rodent counterparts. However there are marked structural differences between the rodent and human subventricular zone. Therefore, there is an essential need for more animal models suitable for cellular and molecular studies that are not feasible in the human subventricular zone. Our own studies have shown that the cytoarchitecture of the porcine subventricular zone is uniquely similar to the human subventricular zone, demonstrating that exploration of porcine subventricular zone is relevant to elucidating the cellular mechanisms underlying the perinatal human brain development and dysmaturation. Our research has endeavored to elucidate cellular dynamics involving generation, migration, and maturation of neural stem/progenitors and oligodendrocyte progenitor cells under normal physiological and pathological conditions using the perinatal porcine brain. The goal of these laboratory-based studies is to determine fundamental cellular mechanisms underlying the causes of brain immaturity and dysmaturity in the neonate with CHD. We believe that the findings are likely to assist decision-making regarding optimal timing and techniques of surgery in order to improve neurodevelopmental outcomes. The studies also have significant potential to identify and assess novel treatment approaches aimed at promoting neuronal regeneration in the CHD patient in the future.

Acknowledgments

Our research is supported by National Institutes of Health (NIH) Grant R01HL104173, R01HL128546, the NIH Intellectual & Developmental Disabilities Research Center Grant P30HD40677, a Grant from the Children's Heart Foundation, and Foglia and Hills families.

References

1. Gaynor JW, Stopp C, Wypij D, et al. Neurodevelopmental outcomes after cardiac surgery in infancy. *Pediatrics*. 2015; 135(5):816–25. [PubMed: 25917996]
2. Miller SP, McQuillen PS, Hamrick S, et al. Abnormal brain development in newborns with congenital heart disease. *N Engl J Med*. 2007; 357(19):1928–38. [PubMed: 17989385]
3. Morton PD, Ishibashi N, Jonas RA, Gallo V. Congenital cardiac anomalies and white matter injury. *Trends Neurosci*. 2015; 38(6):353–63. [PubMed: 25939892]

4. Clouchoux C, du Plessis AJ, Bouyssi-Kobar M, et al. Delayed cortical development in fetuses with complex congenital heart disease. *Cereb Cortex*. 2013; 23(12):2932–43. [PubMed: 22977063]
5. Ishibashi N, Scafidi J, Murata A, et al. White matter protection in congenital heart surgery. *Circulation*. 2012; 125(7):859–71. [PubMed: 22247493]
6. Agematsu K, Korotcova L, Scafidi J, Gallo V, Jonas RA, Ishibashi N. Effects of preoperative hypoxia on white matter injury associated with cardiopulmonary bypass in a rodent hypoxic and brain slice model. *Pediatr Res*. 2014; 75(5):618–25. [PubMed: 24488087]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

Fetal cerebral blood flow: In normal fetuses (A), oxygenated blood (red arrows) from the placenta is preferentially directed to the left ventricle through the foramen ovale, exits through the left and right carotid arteries before the ductus arteriosus and flows to the developing brain. In fetuses with hypoplastic left heart syndrome (HLHS) (B), oxygenated and deoxygenated (blue arrows) blood mixes (purple arrows) in the right heart. Retrograde flow of deoxygenated mixed blood from the ductus arteriosus exits through the carotid arteries at a low flow rate to the brain. Thus in HLHS developing fetal brains receive reduced flow of hypoxic blood which may be a cause of delayed brain maturation.