



Published in final edited form as:

Circulation. 2015 April 14; 131(15): 1307–1309. doi:10.1161/CIRCULATIONAHA.115.016024.

The Path Forward is to Look Backward in Time – Fetal Physiology: The New Frontier in Managing Infants with Congenital Heart Defects

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Keywords

heart defects; congenital; brain development; fetal physiology; Editorial; fetal heart; brain imaging; developmental biology; cerebral blood flow and metabolism

The luxury of studying the cognitive outcomes of survivors of infant heart surgery only occurs as a consequence of the success of the surgeries. The last two decades of improvement in surgical survival has allowed us to focus our attention beyond survival and cardiac outcomes, to a more holistic view of the child, their academic achievement and prospects for successful independence. Most of what we know about long-term outcomes is from the Boston Circulatory Arrest Study, which began in 1988 and followed the lives of 171 infants with transposition of the great arteries (TGA) randomized to a surgical strategy that either included hypothermic circulatory arrest or did not. The most recent report on 139 adolescent survivors (age 16.1 ± 0.5 years) from this study documented some significant psycho-educational challenges that were not so severe as they were prevalent.¹ Briefly, grade retention occurred in 17%, special education in 25% and psychotherapy or counseling in 25%. Most significantly, the study reports the negative finding that surgical strategy failed to identify increased risk for the outcome measures. To quote the report “In many respects, the similarities in the outcomes of the 2 groups have been more striking than the differences.” Both groups suffered from poor academic achievement, fine motor function, visual spatial skills, sustained attention and social cognition.

Concurrent with this study, investigations of white matter injury (WMI) have been ongoing. In 2002, Dr. Mahle and his colleagues reported that nearly 20% of infants with mixed types of severe congenital heart defects (CHD) had evidence of WMI *before* surgery despite optimal medical management from birth.^{1,2} This number, it appears, is remarkably robust; study after study has shown WMI in about 1 in 5 infants before surgery. The second number from Mahle's study that is equally robust is the prevalence of WMI after surgery, which rests at about 50%. In more homogeneous populations of infants with CHD, the prevalence of WMI varies. In populations of infants with transposition of the great arteries (TGA), Petit

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Disclosures: None.

et al³ reported a pre-operative WMI prevalence of 38% while Beca et al⁴ report an incidence of 27%. In TGA, all agree that there is no progression of the injury after surgery, likely due to its corrective nature. The same is not true in populations of hypoplastic left heart syndrome (HLHS) where WMI is seen in 15 to 20% before surgery^{5, 6} but increases to 70% after.⁷ The palliative nature of the first heart surgery corrects the direction of flow in the arch and limits the pulmonary diastolic run off but does nothing to correct the oxygen content of the blood. Nonetheless, there seems to be a significant benefit in performing the surgery early after birth.^{7, 8}

These investigations on the causes of WMI have led to the recognition that pre-operative factors and patient specific factors (heart diagnosis, age at surgery, prenatal diagnosis) rather than surgical or post-operative factors are the major risks. Questions about how alterations in fetal circulation may affect brain growth and maturation first appear with Dr. Miller's publication in 2007.⁹ Here the authors used diffusion tensor imaging (MRI) and MR spectroscopy to demonstrate significant differences in white matter microstructure and biochemistry between newborn infants with CHD compared to infants without. Soon after our group at CHOP demonstrated, using an MRI-based observational metric called the Total Maturation Scale (TMS), that brain maturation in full-term pre-surgical infants with CHD was equivalent to expected brain maturation of a 35-week premature infant.¹⁰ Others have since shown that the TMS not only predicted risk for pre- and post-operative WMI, but TMS also predicted neurodevelopmental testing (Bailey scales of infant development) at 2-years.^{11, 12}

The landmark study to seal the question about altered brain growth and development in fetuses with CHD came from Dr. Limperopoulos and her Boston group.¹³ Here Dr. Limperopoulos performed brain MRI in fetuses with and without CHD, to demonstrate that the brain volumes of infants with CHD diverge from expected normal growth at the beginning of the 3rd trimester. Using fetal MR spectroscopy, Dr. Limperopoulos also demonstrated that markers of white matter maturation (N-acetyl aspartate to choline ratios) lagged normal development and were most abnormal in the fetuses with left outflow track obstruction (HLHS). These findings not only validated the findings of Miller and Licht, but also added a time reference as to when during pregnancy the pathological changes were occurring. This wealth of data on abnormal brain growth and development suggests that while opportunities for postnatal neuroprotective interventions exist, their yield might be much less than one would hope for. Novel strategies for fetal intervention and neuroprotection are needed. Yet, what all the above studies lacked was a clear understanding of the fetal pathophysiology that led to this divergence of brain growth and maturation. Without this knowledge, progressing to fetal interventions (medical or surgical) is stalled, or at least uninformed.

In this issue of *Circulation*, Dr. Sun and colleagues¹⁴ from Toronto hospital for Sick Children publish their results on fetal MRI measurements of cerebral blood flow and cerebral oxygenation in fetuses with and without serious CHD. The significance of this report cannot be overstated and it goes well beyond the findings they observed in the 60 patients (30 with and 30 without CHD) studied. It is the technical achievement of being able to make non-invasive measurements of vascular and metabolic physiology in a moving fetus

that is the most eye-opening. The introduction of metric optimized gating (MOG) by co-author Dr. MacGowan has allowed for phase contrast measurements of blood flow and oximetry in fetal vessels.¹⁵ There are some assumptions made for the calculations used in this manuscript, but they are equitably applied to the CHD fetuses and controls. Eventually numbers like the T2₀ (T2 of fully oxygenated blood) of fetal blood will be measured and the absolute quantification of oxygen saturations will be known. For now these numbers are good, if not perfect, and suffice for comparisons with normal. We must consider that it has only been 7 years since the multislice snapshot technique for measuring fetal brain volumes was published¹⁶ and only 5 years since Dr. Limperopoulos demonstrated discrepant in brain growth in fetuses with CHD.¹³ These leaps in technology take time.

The main findings in this report by Sun and colleagues highlight the limitations of our perhaps simplistic understanding of how CHD alters fetal physiology. The most striking example of this is the finding that umbilical venous saturations in CHD fetuses were lower than in controls suggesting placental pathology may be an important contributor to the central nervous system changes observed in the newborn with CHD. These MRI findings support some preliminary findings by Goff et al¹⁷ who demonstrated gross differences in placental weights and vascularity. Also unexpected was the finding that cerebral oxygen consumption was significantly lower in fetuses with CHD, while oxygen delivery was not (though trended towards significance).

Both the abnormal cerebral oxygen consumption and placental function raise chicken/egg questions that will need to be clarified with the advancement of these MRI techniques. Currently the major limitation of these MR sequences is certain types of movement and vessel size. As such, all measurements are restricted to late gestation fetuses where motion is limited and vessels are larger. But instead of focusing on the limitations, we need to revel in the quantum leap of the advancements the authors bring. Studies in more homogeneous populations (just TGA or HLHS) will follow, as will comparison of fetal and neonatal physiology. Eventually, the refined techniques will allow longitudinal study across the entire gestation. The authors are to be congratulated for such remarkable accomplishments. Implementation of these fetal imaging techniques will improve our understanding of fetal development and will give birth to a new field of fetal medical intervention.

Acknowledgments

Funding Sources: The author is funded by NIH for research related to brain injury in neonates with severe congenital heart defects.

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