Editorial

In Utero Brain Development in Fetuses With Congenital Heart Disease

Another Piece of the Jigsaw Provided by Blood Oxygen Level–Dependent Magnetic Resonance Imaging

Mike Seed, MBBS

In his seminal textbook on the physiology of congenital heart disease (CHD), Dr Rudolph suggests that disruption of the normal streaming of well-oxygenated blood from the placenta to the cerebral circulation via the ductus venosus and foramen ovale resulting from the abnormal connections and obstructions of blood flow that characterize congenital heart malformations should result in hypoxemia of the blood supplied to the developing brain in utero.[1] More recently, Dr Rudolph has pointed out that this blood may also be depleted of glucose, resulting in a reduction in the delivery of these 2 primary substrates for normal brain growth and development.[2] Donofrio et al[3] and others have since produced Doppler evidence of the known adenosine-mediated fetal cerebral vasodilatory response to acute hypoxemia in fetuses with CHD, whereas magnetic resonance oximetry has been used to confirm desaturation of the blood supplied to the fetal brain in the setting of transposition, single-ventricle hearts, and tetralogy of Fallot.[4,5] In their article published in this issue of *Circulation: Cardiovascular Imaging*, Lauridsen et al[6] provide further evidence that the blood in the brains of fetuses with CHD contains less oxygen than normal controls. This time, the evidence is comprised by the diminished blood oxygen level–dependent magnetic resonance imaging signal obtained from the brains of fetuses with a range of congenital cardiac anomalies. The blood oxygen level–dependent signal, or T2*, of brain tissue is determined by several factors, including the oxygen saturation of the blood in the small arteries and veins, hemoglobin concentration, the density of blood vessels in the brain, and the magnetic properties of the surrounding cerebral parenchyma. It follows that the diminished brain blood oxygen level–dependent signal in fetuses with CHD compared with normal controls demonstrated in this study is primarily because of desaturation of the blood passing through their cerebral vasculature.

See Article by Lauridsen et al

Findings by Lauridsen et al are, therefore, significant because they provide additional evidence that the brains of fetuses with CHD are likely to be developing at a lower oxygen tension. The impact of this desaturation on cerebral oxygen delivery remains uncertain because the cerebral vasodilation induced by acute fetal hypoxemia may preserve cerebral oxygen delivery at the expense of other fetal organs. However, animal models indicate a waning of cerebral vasodilation with prolonged hypoxemia, whereas changes in cell metabolism may downregulate the brain's requirement for oxygen and other metabolic substrates.[4,7,8] In vitro adaptations to even small reductions in oxygen delivery include the switch to anaerobic metabolism, diminished mitochondrial respiration with a slowing of flux along the electron transfer chain, and changes in gene expression mediated by hypoxic inducible factor.[9] In concert with activation of the hypothalamic–pituitary–adrenal axis, the downstream effects of oxygen conformance on protein synthesis and cell cycling may account for the delayed myelination and reduced synaptogenesis typical of animal models of chronic fetal hypoxia.[10,11] Recent work in mice engineered to overexpress hypoxic inducible factor identifies a role for Wnt signaling resulting in arrest of premyelinating oligodendrocytes and hypomyelination.[12] Thus, chronic cerebral hypoxemia could account for the impaired brain growth and delayed white matter maturation and metabolism that is typical of newborns with CHD and histological abnormalities in the white matter of fetuses terminated for hypoplastic left heart syndrome in the second trimester.[13] Alternatively, genetic variation associated with CHD could impact brain growth and development such that the fetal brain's requirement for oxygen and other nutrients is diminished. Homsy et al[14] showed that children with CHD have an increased incidence of de novo mutations compared with normal controls and that when CHD is associated with malformations of other organ systems and neurodevelopmental delay, the incidence of these mutations is even higher. Furthermore, one fifth of these mutations are also present in children with neurodevelopmental delay with normal hearts. Although the role these mutations play in disorders of brain development is not yet known, there are numerous examples of genetic causes of developmental delay, including copy number variations and aneuploidy. It seems likely, therefore, that certain genetic mutations may result in disorders of both heart and brain development.

The importance of subtle in utero brain dysmaturation with regard to long-term neurodevelopmental outcome remains uncertain. Delays in myelination or limited

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(*Circ Cardiovasc Imaging*. 2017;10:e007181. DOI: 10.1161/CIRCIMAGING.117.007181.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**

DOI: 10.1161/CIRCIMAGING.117.007181

periods of diminished brain growth may not necessarily result in permanent neurological deficits, and a range of postnatal factors, including the development of hemodynamic instability with compromised cerebral blood flow, as well as inflammation and exposure to neurotoxic agents around neonatal cardiac surgery, may be more important for subsequent outcome than fetal circulatory physiology. Postoperative neurodevelopment is likely to be influenced profoundly by environmental cues, particularly the family environment and the family's level of social support. However, brain immaturity at birth seems to predispose the newborn to ongoing white matter injury—the predominant form of injury in neonates with CHD.[15] As we seek to provide neuroprotective strategies for our patients, research by Lauridsen et al have provided another important indicator of a potential link between chronic cerebral hypoxemia and fetal brain dysmaturation in CHD and a reminder that the neurodevelopmental problems that are increasingly recognized to be an important feature of CHD may have their origins in prenatal life.

Disclosures

None.

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KEY WORDS: Editorials ■ glucose ■ neuroimaging ■ pregnancy ■ white matter

Circulation
Cardiovascular Imaging

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Circ Cardiovasc Imaging. 2017;10:e007181
doi: 10.1161/CIRCIMAGING.117.007181
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080