

Altered Interhemispheric Brain Connectivity in Neonates with Congenital Heart Disease Following Cardiopulmonary Bypass Surgery.

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Introduction: Neonates with congenital heart disease (CHD) are known to be at risk for impaired neurodevelopmental outcome [1-3]. In up to 50% of all children undergoing open-heart surgery for CHD during the neonatal period white matter (WM) injury can be detected by cerebral MRI including periventricular leukomalacia, cerebral infarctions, haemorrhages and decreased grey matter volume [4-6]. Diffusion tensor MRI (DTI) quantitatively assesses the microstructural development of white matter, including fiber bundle integrity, white matter myelination, and presumptive connectivity of axons. Abnormal development of the white matter bundles in infant corpus callosum (CC) has been related to prematurity [7, 8] and lower IQ [9]. The aim of this study was to investigate the impact of cardiopulmonary bypass surgery on the interhemispheric connectivity (e.g. major white matter bundles) at the microstructural level in the neonate brain.

Material and Methods: Nine neonates (mean gestational age 39.2 ± 1.1 weeks, mean birth weight = 3230 ± 381 g) with severe cyanotic CHD (8 patients with d-type transposition of the great arteries, 1 patient with hypoplastic left heart syndrome) undergoing cardiopulmonary bypass (CPB) surgery (arterial switch operation and Norwood I operation respectively) during their first weeks of life were recruited. They were scanned in natural sleep on 3T clinical MRI scanner while an anesthesiologist was monitoring them in the scan room. Ear plugs, and neonatal ear muffs were used to minimize exposure to high acoustic noise. DTI parameters are: parallel imaging (factor of 2), 35 diffusion gradient directions, $b = 700$ s/mm² and 1 T2W volume, 22cm FOV, matrix 128x128 (homodyne reconstruction in 256x256), 2.5mm slice thickness covering the whole brain. The first MRI was acquired at a mean age of 6 ± 3 days. The mean time between the 2 MRI was 15.8 ± 3.7 days. Five patients had pre and post-surgical full clinical MRI, 2 had only full pre-surgical examination, 1 only post-surgical full MRI and 1 failed to achieve DTI. The average time between surgery and 2nd MRI was 13 days \pm 5. The genu and splenium of the CC were delineated on fractional anisotropy (FA) color maps to measure parallel (λ_1) and perpendicular (λ_{23}) diffusions, apparent diffusion coefficient (ADC) and FA using DTIStudio software (John Hopkins University, www.mristudio.org). Two observers processed the data (one of them achieved a test-retest) to avoid any error related to subjective manual segmentation.

Results: Conventional clinical MRI showed no lesion in the CC, which appeared normal in shape and intensity. Some patients had small lesions and hyperintensity in T2W in other WM areas and subdural hemorrhage. The inter- and intra-observer variabilities were not statistically significant thus we averaged the 3 measurements (2 observers). Between group analysis (pre vs post surgery) was performed using univariate general linear model test correlation. Age at the time of MRI was entered as covariate. Statistical analysis revealed that following CPB there was a significant increase of perpendicular diffusion (λ_{23} , $p = 0.005$), a significant increase of mean diffusion (ADC, $p = 0.010$) and a significant decrease of anisotropy (FA, $p = 0.027$) on the splenium (Figure 1). There was no significant difference on any of the DTI metrics on the genu.

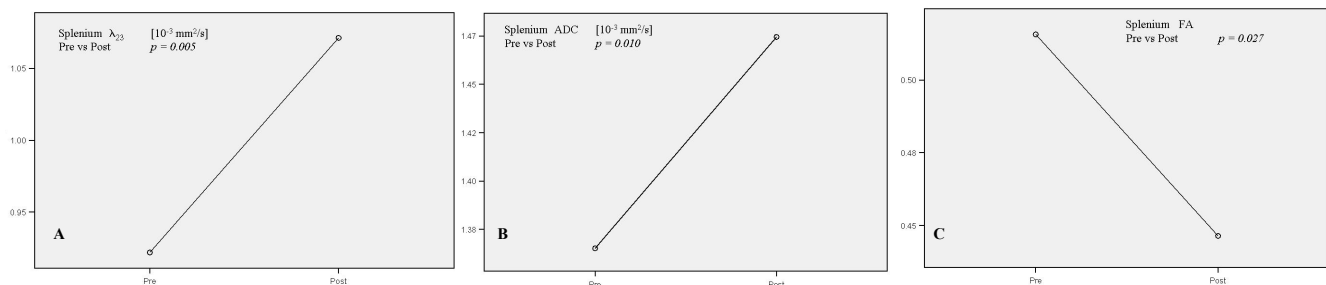


Figure 1: Plot of estimated marginal mean values showing the significant increase of perpendicular diffusion λ_{23} (A), increase of apparent diffusion coefficient ADC (B) and decrease of FA (C) measured on the splenium following cardiopulmonary bypass surgical procedure.

Conclusion: Developmental brain studies of neonates, infants and adolescents have demonstrated a dramatic increase of FA along with a decrease of ADC with age [10]. Previous investigations demonstrated a posterior-to-anterior maturation of white matter [11]. Our findings point out that earlier myelinated structures are first to be altered. This study demonstrated that in neonates with CHD the integrity of white matter and the intactness of the fiber bundles in the splenium is altered following cardiopulmonary bypass suggesting that these patients are vulnerable to abnormal neurodevelopment.

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