Impaired Global and Regional Cerebral Perfusion in Newborns with Complex Congenital Heart Disease

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Objective To compare global and regional cerebral perfusion in newborns with congenital heart disease (CHD) and healthy controls using arterial spin labeling (ASL) magnetic resonance imaging (MRI) prior to open heart surgery.
Study design We performed brain MRIs in 101 newborns (58 controls, 43 CHD) using 3-dimensional fast spin echo pseudo-continuous ASL. Cerebral blood flow (CBF) ASL images were linearly coregistered to T2-weighted images for anatomic delineation and selection of regions-of-interest. Anatomic regions included frontal white matter (FWM), occipital white matter (OWM), thalami, and basal ganglia (BG).
Results Newborns with single ventricle CHD demonstrated significantly lower global (P = .044) and regional BG (P = .025) CBF compared with controls. Mean regional CBF in the thalami in cyanotic newborns with CHD was lower compared with controls (P = .004). Mean regional CBF in thalami (P = .02), BG (P = .01), and OWM (P = .03) among newborns with cyanotic CHD was lower than those with acyanotic CHD. Newborns with CHD ventilated prior to MRI had increased global (P = .016) and OWM (P = .013) CBF compared with those not ventilated.
Conclusions Newborns with uncorrected cyanotic or single ventricle CHD show disturbances in cerebral perfusion compared to healthy controls using ASL. Cardiac physiology and preoperative hemodynamic compromise play an important role in preoperative alterations in global and regional cerebral perfusion. Our data suggest that ASL may be useful for studying cerebral perfusion in newborns at high risk for cerebral ischemia, such as those with complex CHD. *(J Pediatr 2015;167:1018-24)*.

Neurodevelopmental disability is a well-established complication of congenital heart disease (CHD).[1-4] Children with CHD have lower intelligence scores and increased risk of seizures.[5-7] More recently, quantitative fetal magnetic resonance imaging (MRI) has shown that third trimester fetuses with CHD requiring neonatal open heart surgery have lower brain volumes and evidence of impaired neuroaxonal development and metabolism.[8] Furthermore, fetuses with hypoplastic left heart syndrome demonstrate delayed cortical development, marked by decreased gray matter volume and delayed cortical gyrification.[9] Collectively, these data suggest that hemodynamic disturbances with CHD play an important role in early brain development.[8]

Arterial spin labeling (ASL) MRI is an imaging sequence that measures tissue perfusion without an exogenous contrast agent. Since first described in 1992, technological and methodological advances have increased its application in recent years, with many research and clinical applications described.[10] ASL uses arterial blood water as a tracer to evaluate tissue perfusion by an inversion or saturation pulse proximal to the tissue of interest.[11] ASL has been studied primarily in the brain because of its high relative perfusion rates, spatially consolidated blood supply, decreased motion artifact, and the association between regional cerebral blood flow (CBF) and neuronal activity.[12] Pseudo-continuous ASL (pCASL), as opposed to continuous ASL, has become the preferred technique in neonates and children because of its high signal-to-noise ratio and insensitivity to motion.[13]

The use of ASL is an emerging noninvasive method for evaluating CBF in high-risk neonates.[14] Only 1 study has examined the role of ASL in newborns with CHD. Licht et al[15] described decreased preoperative CBF using ASL MRI in a small series of neonates with CHD. However, the association between baseline CBF and the type of CHD was not delineated and comparison to a control group was not made. The primary objective of our study was to compare global and

3D	3-dimensional	GA	Gestational age
ASL	Arterial spin labeling	MRI	Magnetic resonance imaging
BG	Basal ganglia	OWM	Occipital white matter
CBF	Cerebral blood flow	pCASL	Pseudo-continuous ASL
CHD	Congenital heart disease	PET	Positron emission tomography
CPR	Cerebral placental ratio	ROIs	Regions of interest
FWM	Frontal white matter	SNAP	Score of acute neonatal physiology

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regional cerebral perfusion in neonates with CHD before open heart surgery compared with healthy controls using ASL MRI. As a secondary objective, we also examined prenatal and postnatal risk factors associated with abnormal brain perfusion in CHD neonates.

Methods

As part of a prospective observational study, we recruited newborns with complex CHD prior to open-heart surgery, as well as healthy newborn controls at Children's National Medical Center in Washington, DC. Normal controls were recruited from healthy pregnant volunteers, and cases were recruited from pregnant mothers with fetal CHD confirmed by neonatal echocardiography. Exclusion criteria for both cases and controls included contraindication to newborn MRI, multiple-gestation pregnancy, congenital infection, gestational diabetes controlled by means other than diet, gestational age (GA) at birth <36 weeks, prenatally documented chromosomal abnormalities and dysmorphic features such as dysgenetic brain lesions or anomalies of other organ systems by clinical exam, ultrasound, or MRI. Only subjects with diagnostic-quality ASL images were included, defined as CBF maps that correspond to the anatomic images and were not affected by motion or magnetic susceptibility artifact, as determined by the neuroradiologist. The study was Health Insurance Portability and Accountability Act compliant and approved by the Institutional Review Board. Informed consent was obtained from each study participant's parents.

MR Image Acquisition

Newborns underwent MRI on a 3.0 T scanner (Discovery MR750; GE Healthcare, Waukesha, Wisconsin) using an 8-channel receive-only head coil array (In-Vivo Corporation, Gainesville, Florida). A 3-dimensional (3D) fast spin echo pCASL sequence with echo time/repetition time = 4305/11 ms, 512 points by 8 arms spiral acquisition, voxel size = $1.875 \times 1875 \times 3$ mm^3, postlabeling delay = 1025 msec, scan time = 3 minutes, pixel bandwidth = 62.5 kHz, labeling duration = 1450 ms was obtained in the axial plane with the imaging plane placed at the lower level of the pons. Background suppression was achieved using 1 presaturation and 5 inversion pulses. Labeling location was 2.2 cm below the imaging slab and was not optimized in individual neonates. Labeling efficiency was not calibrated for neonates.

Control images were acquired; however, only difference images (label-control) were available for viewing. CBF was calculated using difference images and proton density images based on the general kinetic model.[16] Though the existing literature is limited, our scanning measurements are similar to some of the recent studies examining pCASL in newborns.[17,18] One study using pCASL in neonates used 2-dimensional gradient recalled echo imaging, which provides lower signal to noise and more susceptibility artifacts than our methods.[19]

Other conventional MRI sequences were obtained in the axial plane including a 3D T2 fast relaxation fast spin echo echo time/repetition time = 2000/102, echo train length = 48, voxel size = $1.875 \times 1875 \times 3$ mm^3, scan time 2 minutes, using the same coverage as the ASL acquisition. Additional sequences including a 3D fast spoiled gradient echo, a 2-dimensional single-shot spin-echo echo planar imaging diffusion tensor imaging and a multi-echo susceptibility-weighted angiography were acquired and qualitatively reviewed for evidence of injury and/or structural abnormalities.

Newborns were not sedated during imaging and were positioned in the coil to minimize head tilting. Newborns were fitted with earplugs (Quiet Earplugs; Sperian Hearing Protection, San Diego, California) and neonatal ear muffs (MiniMuffs; Natus, San Carlos, California).

Oxygen saturation, heart rate, and temperature were monitored and recorded throughout the scan by a nurse using an MRI-compatible vital signs monitoring system (Veris; MEDRAD, Inc, Indianola, Pennsylvania). The pulse oximeter probe was attached to the newborn's foot outside the receive coil. The fiber-optic temperature probe was taped on the neonate's abdomen.

MR Image Interpretation and Analysis

All MRI studies were reviewed by a board-certified, fellowship-trained pediatric neuroradiologist (U.N.) who was blinded to the subjects' clinical data and case vs control status. CBF images were generated on the scanner using Functool software (GE Healthcare, Waukesha, Wisconsin) in mL/100 g/min. Mean global CBF was calculated using FSL software (www.fnrib.ox.ac.uk/fsl) on an off-line Linux workstation.

ASL images were linearly coregistered to the axial T2-weighted images for anatomic delineation and selection of regions of interest (ROIs) to evaluate further regional CBF using NiftyReg software (sourceforge.net/projects/niftyreg). ROIs were manually defined in Insight Segmentation and Registration Toolkit-SNake Automatic Partitioning (www.itksnap.org) and were calculated as an average of both brain hemispheres (**Figure**, A-B). ROIs were created by drawing 2 round 4 mm diameter spheres in the bilateral frontal white matter (FWM), occipital white matter (OWM), thalami, and basal ganglia (BG) (**Figure**, B). FWM ROIs were drawn immediately anterior to the frontal horns of the lateral ventricles on axial images at the level of the foramina of Monro. OWM ROIs were drawn either immediately posterior to or lateral to the atria of the lateral ventricles on axial images. Intrarater reliability was measured in 10 randomly selected subjects using the coefficient of variation, defined as the ratio of the SD to the mean. Reliability measures were as follows: 4.9% for the thalami, 4.8% for the FWM, 8.1% for the OWM, and 5.5% for the BG.

In addition to evaluating CBF, anatomic images were reviewed for structural abnormalities/cerebral injury, marked by areas of restricted diffusion on isotropic diffusion tensor imaging, hemorrhage marked by T1 shortening on fast