Brain Sparing in Fetal Mice: Using BOLD MRI to Study Blood Redistribution During Hypoxia

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Introduction. Fetal growth restriction (FGR), characterized by fetal hypoxia resulting from reduced placental function, affects 1 in 30 pregnancies in Canada and is associated with increased risk of perinatal mortality and impaired neurodevelopment [1]. Severe FGR is often associated with *brain sparing* whereby a greater proportion of oxygenated fetal blood is directed to the brain at the expense of other organs. Understanding the physiology of this brain sparing response may lead to better diagnostic procedures for predicting fetal risk. Doppler ultrasound is presently the standard tool for monitoring fetal well-being but it does not provide direct information on fetal oxygenation and is prone to false negatives when predicting FGR, particularly during late gestation [2]. Blood oxygen level-dependent (BOLD) MRI provides a non-invasive method for measuring the state of oxygenation of the fetus and has been demonstrated in pregnant sheep [3-5]. The purpose of this study is to use BOLD MRI contrast to characterize the redistribution of fetal blood flow that occurs in mice under hypoxic conditions.

Materials and Methods. Healthy, pregnant CD-1 mice at 17.5 days gestation were mechanically ventilated under ketamine/xylazine (150 mg/kg and 10 mg/kg respectively). MRI and ultrasound measurements were performed in four dams (1 and 2 fetuses per dam respectively for each imaging modality). Placental dysfunction was simulated by cycling the oxygen content of the gas mixture inhaled by the dam between 100% O_2 and 8% O_2. BOLD fetal MRI scans were obtained using a 7T Varian magnet. 2D $T2^*$-weighted images were acquired down the mid-sagittal plane of a given fetus using a gradient echo sequence with 200 μm in-plane resolution, TR = 50 ms, TE = 10 ms, flip angle = 17°, slice thickness =1 mm and NEX = 8. Three images were acquired for each gas condition. BOLD signal intensity (SI) was measured for the fetal brain and fetal liver. Normalized BOLD SI was calculated using $SI = (SI_{hypoxia}/SI_{control})x100\%$ [2,3]. Doppler ultrasound was used to measure blood velocity waveforms in the fetal cerebral arteries and umbilical vessels.

Results and Discussion. Figure 1 shows a representative 2D MR image of mouse fetuses and placentas. As the maternal inspired gas mixture is varied, large signal changes were observed in the fetal liver but not in the fetal brain (Figure 2). In all of the animals studied, the normalized BOLD SI under hypoxic conditions (8% O_2) decreased from 100% (control plateau) to 50 ± 6% in the liver and only 89 ± 3% in the brain. This is consistent with active regulation of cerebral oxygenation at the expense of other organs, the brain sparing effect. On the basis of Doppler ultrasound studies in humans, brain sparing is believed to help preserve the supply of oxygen to organs that are essential for survival by increasing fetal blood flow [6]. Using Doppler ultrasound measurements, cerebral blood flow was observed to rise under maternal hypoxia conditions in fetal mice, consistent with the human findings (Figure 3).

We have shown it is feasible to use BOLD MR imaging as a noninvasive tool to study autoregulation in the mouse. This provides new opportunities to use mouse models of FGR that have highly controlled and reproducible placental pathology. Mice are valuable for developing a robust model of brain sparing under a broad range of conditions, for testing novel therapies, and for obtaining a comprehensive set of outcome measures.

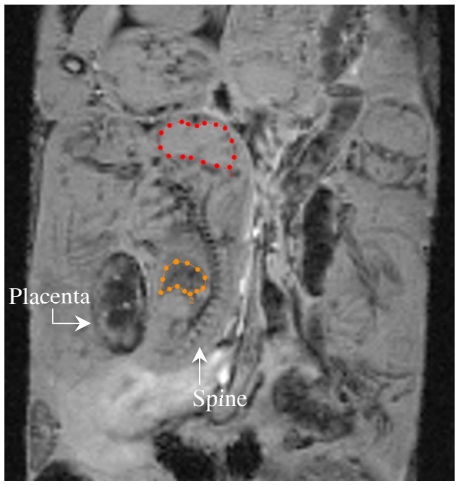

Figure 1. Representative horizontal MRI scan through a 17.5 days gestation pregnant mouse. Multiple fetuses and placentas are seen in this view. ROIs are placed in the fetal brain (red) and liver (orange).

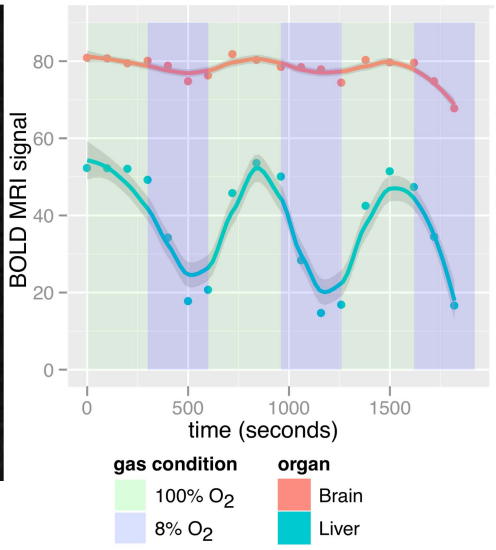

Figure 2. Absolute BOLD MRI signal for ROIs in the fetal brain and liver as the inspired oxygen mixture is varied.

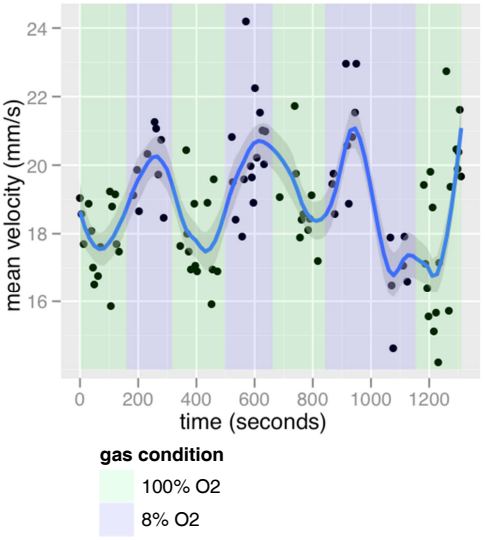

Figure 3. Mean posterior cerebral artery blood flow as the oxygen mixture is varied, measured using Doppler ultrasound.

References. [1] Pryor, British Journal of Obstetrics and Gynaecology (1996), 103:1116-1122. [2] Figueras et al. Pediatrics (2009), 124:e934-941. [3] Wedegartner et al., Radiology (2005), 237:919-926. [4] Wedegartner et al. Radiology (2006) 238:872-8880. [5] Sorensen et al. Ultrasound Obstet Gynecol (2009) 34:687-692. [6] Hecher et al. Circulation (1995) 91:129-138.