Human placental and fetal response to maternal hyperoxygenation in IUGR pregnancy as measured by BOLD MRI

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Purpose: Adequate oxygen transport across the placenta from mother to fetus is critical for fetal growth and development. Clinically there is no way to directly measure placental transport *in vivo*, and assessment of placental insufficiency primarily relies on indirect measures of umbilical artery flow by Doppler ultrasound [1]. BOLD MRI with maternal hyperoxygenation has been demonstrated to detect oxygenation level changes in the placenta and fetal organs in healthy human subjects [3,4]. In addition, it has successfully differentiated rat intrauterine growth restriction (IUGR) models from normal [2], indicating a potential role in detecting and monitoring human IUGR. In this pilot study, we demonstrate for the first time a method based on BOLD signal change to differentiate placental regions. Furthermore, we characterize BOLD signal change in an IUGR fetus in response to maternal hyperoxygenation.

Methods: This IRB approved study is enrolling subjects in both Boston and Madrid. One 24 week gestational age (GA) fetus was scanned on a General Electric Signa HDxt 3.0T scanner using the 8-channel body coil for excitation to test feasibility. After optimization of the oxygen delivery, an 32 weeks GA IUGR fetus with estimated weight at 8th percentile and diminished diastolic flow on umbilical artery Doppler was scanned on a 3T Skyra scanner (Siemens Healthcare, Erlangen, Germany) using a combined 18-channel body and 12-channel spine receive arrays. The latter case is discussed in this paper. BOLD imaging of the whole uterus was collected using single-shot gradient echo EPI sequence with matrix 110 x 110, 70 slices; in plane resolution 3 x 3 mm^2, slice thickness 3mm, interleaved; TR = 5820 ms, TE = 32 ms, FA = 90°, BW = 2.3kHz/px, number of time frames = 308. Total acquisition time was 30 min. Three different 10 min phases of maternal oxygenation were investigated:1. normoxic, 2. hyperoxic, 3. normoxic. Oxygen supply was alternated from room air (21% O_2), to oxygen (15L/min), and back to room air via non-rebreathing facial mask during BOLD acquisition. Transformation matrices between time frames were generated in Elastix [5] by B-spline transformation using mutual information with user adjusted parameter file. Manual segmentation of placenta and fetal organs on reference frame was performed using ITK-SNAP. ROIs were subsequently tracked to all time frames.

Results: Signal intensities of 10 min normoxia vs. 10 min hyperoxia were compared. Global placental region experienced significant signal increase, as well as the fetal liver, kidney, lung, heart and brain ($p<0.001$), Table 1. Notably placental signal increase in this IUGR fetus is higher than that in healthy subjects reported by [3]. During the last 2 min of the scan, fetal kidney, lung, liver and the placenta continued to show significantly elevated O_2 level ($p<0.001$).

Table 1. BOLD signal changes in placenta and fetal organs

	Mean increase %	Last 2 min residual
Placenta	28.4% (p<0.001)	6.7% ± 1.6 (p<0.001)
Liver right lobe	15.1% (p<0.001)	10.3% ± 2.4 (p<0.001)
Liver left lobe	24.3% (p<0.001)	12.8% ± 3.1 (p<0.001)
Brain	4.0% (p<0.001)	0.86% ± 2.1 (p = 0.104)
Brain vessels*	9.8% (p<0.001)	4.3% ± 2.0 (p = 0.073)
Kidney	9.6% (p<0.001)	9.5% ± 7.0 (p<0.001)
Heart	10.5% (p<0.001)	-2.4% ± 12 (p = 0.46)
Lung	13.2% (p<0.001)	6.1% ± 2.9 (p<0.001)

* Number of pixel is too small for reliable ROI tracking, therefore ROIs were manually selected.

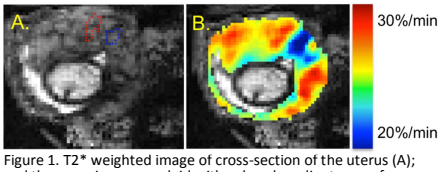

Figure 1. T2* weighted image of cross-section of the uterus (A); and the same image overlaid with colored gradient map of placenta (B); colorbar shows the gradient in %/min of the BOLD signal change; ROIs that represent high (red) and low (blue) gradient were chosen, and displayed on A.

A placental gradient map was generated from linear fitting of time points within the 1st minute of hyperoxia. A 5x5x5 smoothing filter was applied to minimize motion artifacts. In the placenta, the gradient map revealed distinct regions of response to oxygen challenge, which were not apparent on the T2* images. Regions in the placenta ~3 cm^3 in size were selected in 3D according to these gradient maps. Plots of their time curves are shown in Figure 2A. For the fetus, a clear contrast between two liver lobes was observed, in all episodes. The left lobe, which is supplied exclusively by umbilical vein [6] exhibits a faster uptake of oxygen than the right lobe (Figure 2B). It took the right lobe 2.7 min longer than the left lobe to reach 20% signal increase. In the fetal brain, we observed ~ 4% signal increase for the entire brain region, which is not reported in healthy subjects [4]; and an average of 9.8% signal increase in large vessels (sagittal sinus and internal cerebral vein), which is similar to many other organs.

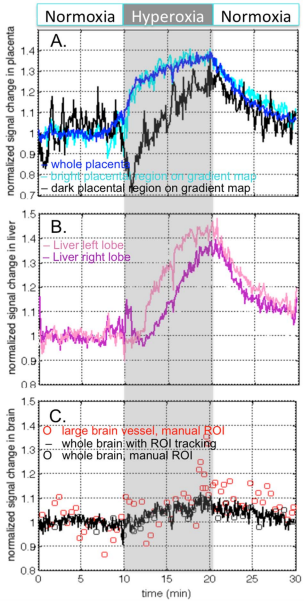

Figure 2. Normalized BOLD signal intensity changes calculated in the placenta (A), fetal liver (B), and fetal brain (C).

Discussion: The fetal blood ranges from 80% oxygenated in umbilical vein to 60% oxygenated in umbilical artery during normoxia [7], therefore offering a large dynamic range for BOLD signal increase during maternal hyperoxia. However, caution should be taken when interpreting the data since the magnitude of signal increase is confounded by physiological factors such as vascular density of tissue, blood flow, hemoglobin concentration, etc.[8]. Given the subject has diminished diastolic flow in the umbilical arteries, the high BOLD signal increase in the placenta compared to healthy subjects might be due to a low oxygenation baseline. Notably, the gradient map generated within the first minute of hyperoxia indicates different functional regions in the placenta. We hypothesize that the areas with fastest oxygenation increase represent the maternal component, whereas areas showing significant delay in O_2 uptake likely represent fetal components. Longitudinal data are needed to understand whether the distribution of these regions is transient or static. The different response of liver lobes during hyperoxia is in general agreement with their perfusion pattern. It has been shown by Doppler measurements that preferential blood supply to the fetal left liver lobe is associated with low pregnancy weight gain [9]; The delay time of BOLD signal increase that we observed between the left and right lobes might become a useful metric in fetal monitoring. Considering the % signal increase in brain vessels vs. the whole brain, it is likely that their difference owes largely to the low vascular density in the brain parenchyma. The small % increase in brain parenchymal with hyperoxia brings into question the ability to detect smaller regional resting state fluctuations at this gestational age.

Conclusion: We have demonstrated for the first time placental and fetal response to maternal hyperoxygenation in an IUGR pregnancy. Placental regions exhibit heterogeneous responses to hyperoxygenation. Fetal liver lobes also give two distinct time series during maternal hyperoxia. Instead of observing a "brain-sparing effect", we have observed comparable signal change in the fetal brain vessels as other fetal organs. More clinical cases and pathological reports of the placenta are going to be collected to determine the clinical and pathological significance of these findings. **Acknowledgements:** We would like to thank Dr. Carmen Carreira. **Support**: Comunidad de Madrid, the Madrid-MIT M+Vision Consortium, NIH R01 EB017337. **References:** **1**. Resnik R., "Fetal growth restriction: evaluation and management" UpToDate Sept 2014; **2**. Aimot-macron S., et al., Eur Radiol 2013;23:1335-1342; **3**. Sørensen, A., et al. Ultrasound Obstet Gynecol 2013;42:310-314; **4**. Sørensen, Anne, et al., Prenatal Diagnosis 2013;33:141-145; **5**. Klein, Stefan, et al. Medical Imaging, IEEE Transactions 2010;29:196-205; **6.** Haugen G., et al., Ultrasound Obstet Gynecol 2004;24:599-605; **7.** Rhoads, R. and Bell, D.R., Fetal and Placental Circulations, Medical Physiology: Principles of Clinical Medicine, 4th ed; **8.** Lu H., et al., Magn Reson Med 2008;60:364-72; **9.** Kessler J., et al., Pediatr Res (2008) 63:315-320;