Quantitative phase imaging in mouse pregnancy

Uday Krishnamurthy[1], Yimin Shen[2], Gabor Szalai[3], Jaladhar Neelavalli[2], Bing Wang[3], Tinnakorn Chaiworapongsa[3,4], Edgar Hernandez-Andrade[3,4], Nandor Gabor Than[3,4], Ewart Mark Haacke[2], and Roberto Romero[3]

[1]*Department of Biomedical Engineering, Wayne State University, Detroit, Michigan, United States,* [2]*Department of Radiology, Wayne State University, Detroit, Michigan, United States,* [3]*Perinatology Research Branch, NICHD, NIH, DHHS, Wayne State University, Detroit, Michigan, United States,* [4]*Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan, United States*

Introduction: Development of animal models is the key to expanding our understanding of human obstetrical syndromes and provides a great potential for design of novel diagnostic and therapeutic approaches. Mouse models are often used to model pregnancy due to the similarities in the developmental anatomy of the mouse and human fetus [1]. It is of interest to non-invasively measure/monitor blood flow and oxygenation within the umbilical vessels, placenta and other major vessels within the fetus to evaluate conditions like preeclampsia or hemolysis, elevated liver enzymes, Low Platelets (HELLP) syndrome. In this abstract we present our initial experiences in quantitative phase imaging in *pregnant mice* using susceptibility weighted imaging (SWI). It is known that venous phase in SWI phase is proportional to its deoxyhemoglobin content and could provide a means to assess blood oxygenation. Umbilical arteries (UA) of the mice fetuses which carry venous blood to the placenta, however, are very small, on the order of ~ 0.5mm in diameter at gestational age (GA) of 16.5 days [2]. Thus conventional methods of phase or susceptibility measurement using region of interest (ROI) analysis may not be amenable due to the small size of these vessels [4]. Hence, from the phase data, we evaluated the hypothesis that it may be possible to quantitatively ascertain relative blood oxygenation status by measuring the phase within the corresponding placentas or the fetal lungs which also contain deoxygenated venous blood.

Methods: Three normal pregnant CD-1 mice at gestational age (GA) of 17 days (gestational term is 21 days) were imaged on a 7.0T, 20 cm bore superconducting magnet (ClinScan, Bruker, Karlsruhe, Germany) interfaced with a Siemens console. Approval for the study from the local Institutional Animal Care and Use Committee (IACUC) was obtained. Conventional multi spin echo and 2D-SWI images were obtained. Sequence parameters for SWI were TE=7.84ms; TR=850ms; acquisition matrix:512x512; resolution=0.08x0.08x0.8 mm^3; bandwidth=150Hz/pixel. The total duration of the scan was 14.5 min and 45 slices were acquired covering multiple fetuses and their associated placenta. Imaging parameters for the multi-echo, T2 weighted scan were TE=15, 30, 45, 60, 75, 90ms; TR=2540ms; acquisition matrix=160x320; resolution=0.13x0.13x0.7 mm^3. Images were acquired in axial orientation relative to the magnet coordinate system. **Data Analysis:** The SWI-phase images were processed using a 32x32 homodyne filter [3]. Among the SWI data, the fetuses in which the UA, the placenta and the fetal lung were all visible were manually selected (n=12) for further analysis. Mean and standard deviation of the phase values from the three regions were obtained using a manually drawn free hand ROI. Care was taken to avoid boundary regions which had partial volume artifact. UAs from which measures were obtained were perpendicular to the direction of the main magnetic field. Correlation between the phase values measured within the umbilical vessels, the placenta and the fetal lungs were evaluated. Standard Pearson's correlation test was performed to estimate the significance of correlation via a 2-tailed test.

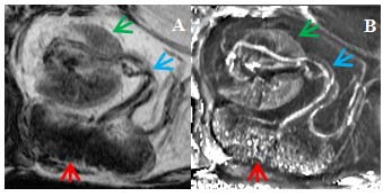

Figure 1. The projection over 4 slices to show the Placenta (red arrow), Umbilical artery (blue arrow) and lungs (green arrow) in the SWI magnitude (A) and phase (B) images within one fetus .

Results: Fig.1 shows the representative magnitude and phase images from SWI data showing the umbilical vessel, the placenta and the fetal lung. Individual correlations between the phase values in the UA and the lungs; the UA and the placenta are shown in Fig.2. Statistical analysis of the phase in the UA and the lung indicated an R^2 value for the linear regression model as 0.793, Pearson's correlation coefficient was 0.891 (p=0.0001); between the UA and placenta the R^2 value was 0.457, and the Pearson's correlation was 0.676 (p=0.015).

Discussion: Measuring phase or magnetic susceptibility of blood using BOLD to ascertain blood oxygenation utilization has been shown to be useful clinically in adults [4]. However, considering the small diameter of the UA, it becomes highly challenging to perform any quantitative measurements on it even with an in-plane resolution as high as 80µM. Ascertaining quantitative susceptibility values from sub-voxel structures or objects occupying less than 4 voxels in diameter could lead to considerable errors in the quantitative estimates [5]. Acquiring high resolution data, on the order of 50µM may provide sufficient voxels for accurate estimation. However, such high resolution acquisitions warrant long scan times which are often counterproductive in fetal imaging due to fetal motion. Hence for current imaging resolutions, surrogate measures of quantitative phase maps would be beneficial. Fetal lung, which has deoxygenated blood in its pulmonary circulation are water filled as opposed to the lungs in adults. This facilitates their dramatic appearance in the SWI phase images as shown in fig 1. Phase seen in the lung is mostly expected to be from the deoxygenated blood (and water). The correlation between phase in the UA, which is from venous blood, and that in the lung, shown in this work, clearly supports this assertion. The correlation between the phase measured in placenta and the UA is also found to be significant, but a bit weaker. This could be due to the complex blood flow pattern within the placenta and in the inter-villous space (presence of both maternal and fetal deoxygenated blood). Although SWI sequence is flow compensated in the phase-encoding direction, acceleration in blood flow could contribute to additional confounding phase. Venous blood flow in the placenta on the fetal side of circulation is, on the other hand more streamlined. This deoxygenated blood within the placenta is thus able to contribute to the phase correlation seen in this work. In addition to the points mentioned above, the correlations between UA phase and placental or phase in the fetal lung could also be influenced by (a) loss of phase information due to phase filtering (b) orientation of the fetal lung or placental relative to the main magnetic field direction, B_o, and (c) the asymmetric voxel aspect ratio [6]. Detailed analysis to ascertain the influence of each of these aspects, especially (a) and (b), is required. Although, blood hematocrit values are necessary for absolute blood oxygenation measurement using MR phase, the phase measurements from these larger anatomical structures could themselves be used for relative blood oxygenation between fetuses of the same gestational ages and for comparing fetal and the maternal blood oxygenation.

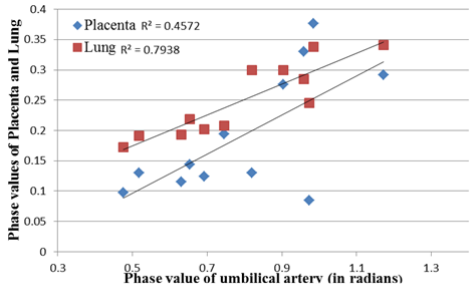

Figure 2. Correlation plot of the Phase vales of the umbilical artery (x-axis) *Vs.* the phase estimations in Lung (■) and Placenta (●).

Conclusion: We have applied SWI in imaging the fetal venous vasculature. In view of the small size of the umbilical vessels and limited imaging resolution, to facilitate a surrogate measure of blood oxygenation, we suggest an alternate approach by measuring phase in larger venous structures in mouse fetus. We have shown that there is significant correlation between venous phase in the umbilical artery and the phase measured directly from the corresponding lungs and placenta, indicating that phase measurements from the fetal lung or placenta may be used for assessing relative fetal blood oxygenation in mouse pregnancy.

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