A novel non-invasive MRI tool for quantification of placental oxygen transport in vivo

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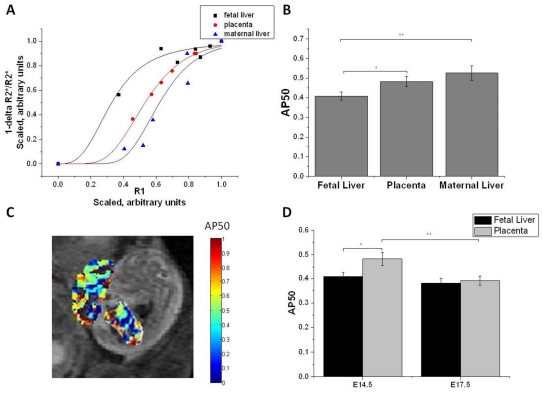
Introduction Oxygen transport, one of several key functions performed by the placenta, depends primarily on placental oxygen pressure gradient and the oxygen affinity of fetal and maternal blood. To compensate for its low oxygen tension environment, fetal hemoglobin has a greater oxygen affinity than adult hemoglobin. Obtaining oxygen-hemoglobin dissociation curves, describing the relationship between the saturation of hemoglobin and the partial pressure of oxygen, and extracting P50 values, characteristic of oxygen affinity, may provide useful information, both in animal models and in clinical settings. We describe a novel, non-invasive MRI method for deriving MRI-based oxygen-hemoglobin dissociation curves, implementing oxygen-weighted T_1 and BOLD-T_2* contrast mechanisms under different respiration challenges in pregnant mice at different gestational stages.

Methods Pregnant ICR mice were analyzed using a gradual respiration challenge from hyperoxia to hypoxia, sampling all oxygen levels from 100% to 10% oxygen, on E14.5 (n=8 mice; 58 fetuses) and E17.5 (n=10 mice; 89 fetuses). T_2*- and T_1-weighted 3D GE images were acquired sequentially at each oxygen phase. T_1-maps were generated from a series of variable flip-angle experiments performed at the initial air phase and were extrapolated at each oxygen phase from the baseline. T_2* mapping was achieved by the dual-echo method. To construct MRI-based oxygen-hemoglobin dissociation curves, $[1-\Delta R_2^*/R_2^*]$ values were plotted as a function of R_1 values for each oxygen phase. The oxygen hemoglobin dissociation curve is described by the well-known Hill function, represented graphically as a sigmoid-shaped curve. Apparent P50 (AP50) values, calculated as the x value at which y equals 0.5, were then derived by fitting the curves. Regions of interest (ROIs) were drawn for the entire placenta and fetal liver, as well as maternal liver. An automated algorithm for serial alignment was applied to align the different ROIs over time to allow accurate follow up [1].

Results R_1 and $[1-\Delta R_2^*/R_2^*]$ values derived in the placenta, fetal liver and maternal liver at each oxygen phase demonstrate the expected sigmoid-shaped curve, with a clear difference between adult and fetal tissues, manifested by a shift to the left in the curves (Figure 1A). Mean AP50 values display significantly lower AP50 values in fetal liver than in the placenta and maternal liver (Figure 1B). AP50 maps inside the placenta and fetal liver show significant heterogeneity (Fig. 1C). Fetal liver shows no significant change in mean AP50 values between the two gestational stages (Fig. 1D; 0.4±0.02 vs. 0.38±0.018; P>0.05 for E14.5 and E17.5, respectively). The placenta, however, displays a reduction by 18±4% in mean AP50 value from E14.5 to E17.5 (Fig. 1D; 0.48±0.02 vs. 0.39±0.02; P<0.05 for E14.5 and E17.5, respectively).



Conclusion We present here a non-invasive approach to probe and quantify oxygen transfer across the placenta and in the fetus. We were able to obtain, for the first time, MRI-based oxygen hemoglobin dissociation curves, without the need for direct sampling of fetal or maternal blood vessels, and to derive AP50 values for the placenta and fetus, as well as AP50 maps showing the heterogeneity within these tissues. As identifying high-risk fetuses is one of the major challenges in modern day obstetrics, this method may be used for evaluation of the fetal health.

References 1. Akselrod-Ballin, A., R. Avni, and M. Neeman, Sequence Alignment of In-Utero Fetal Tissue MRI in Mice. Biomedical Imaging (ISBI), 2014 IEEE 11th International Symposium, 2014: p. 786-789.

Figure 1 (A) Representative examples of MRI-based oxygen hemoglobin dissociation curves in placenta, fetal liver and maternal liver obtained on E14.5 pregnant mouse, demonstrating the shift to the left in AP50 values between adult and fetal organs; (B) Mean AP50 values; (C) Representative AP50 maps inside the placenta and fetal liver; (D) Mean AP50 values in the placenta and fetal liver as a function of gestation stage.