Gestational age dependent increase in placental perfusion quantified using MRI

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Background: The placenta is a highly vascularized organ and is critical to ensure normal fetal growth and development. Placental insufficiency is one of the leading causes of abnormal materno-fetal circulation which could lead to intrauterine growth restriction (IUGR) [1]. Murine model of pregnancy is an important means of studying and understanding the aetiology of this condition due to their functional similarities with the human placenta [2]. The placenta is a dynamic structure which changes with the gestational age. Hence understanding the natural course of placental perfusion characteristics in normal mice pregnancy is critical to contrast it with changes that occur in the different pathologies at different gestational ages. Anatomically, as well as in dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) studies, mice placenta could be segmented into high perfusion zone (HPZ) and low perfusion zone (LPZ) based on their contrast up-take characteristics [3, 4].This study reports quantitative evaluation of longitudinal changes in placental perfusion in murine pregnancy.

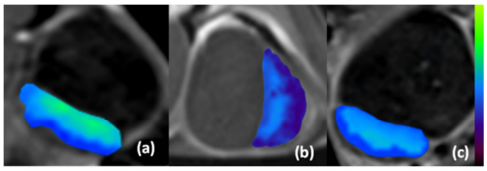

Figure 1. TSM maps showing the segmented high-perfusion (bright-blue) and low-perfusion zones (dark-blue) in a mice placenta for (a) GD 13; (b) GD 15 and (c) GD 17.

Purpose: To quantify the longitudinal variations in perfusion characteristics of the high and low blood perfusion compartments of normal murine placenta using DCE-MRI.

Material and Methods: The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of Wayne State University. Seven timed-pregnant CD-1 mice were imaged using a 7.0Tesla animal MRI system (Bruker Clinscan) under the influence of anaesthesia (2% Isoflurane) at gestation day (GD) of 13, 15 and 17 days (term gestation in mice - 18 to 21 days). 0.05 M concentration of a gadolinium based contrast agent Magnevist (Gadopentetic acid – Gd-DTPA) diluted with 0.25 ml of saline was injected through a catheter placed in the tail vein. Gradient echo flash based DCE-MRI data with the following parameters was acquired: TE=2.02ms, TR=43ms, flip angle = 30^0, resolution = 0.27×0.27×1.5 mm^3, bandwidth = 260 Hz/pixel. A total of seven slices were acquired with a temporal resolution of 5.5 seconds and the scan was run for 150 time points. Tissue similarity mapping (TSM) [5] technique was applied to the central slice of the placenta which automatically segmented it into two regions [11]. The two segmented regions were corresponding to HPZ and LPZ. Steepest slope technique [6, 7] was used on the original concentration-time (c-t) curves to quantify perfusion in each of the constituent zones, in units of ml/min/100ml. Maternal muscle tissue was used as reference for the estimation of the arterial input function [8]. A single-factor ANOVA and Tukey's post-hoc test were applied for statistical comparison at significance $p<0.05$.

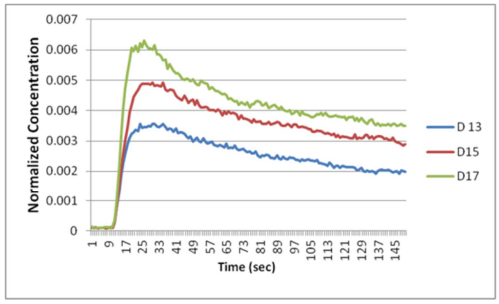

Figure 2. Normalized concentration curves for high perfusion zone (HPZ) in normal mice placenta from GD13-GD17

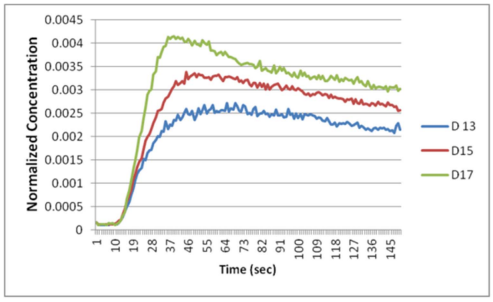

Figure 3. Normalized concentration curves for low perfusion zone (LPZ) in normal mice placenta from GD13-GD17

Results: Quantitative analysis was performed on 19 placentas on GD13, 20 placentas on GD15 and 14 placentas on GD17. Figure-1 shows the segmented regions of the placenta generated by TSM. Figures-2 and -3 show the average c-t curves of HPZ and LPZ respectively. To enable comparison across mice, the curves are normalized to the area under the respective maternal muscle c-t curves. An increase ($p=0.03$) in perfusion in HPZ was observed between GD13 and GD17. Perfusion in LPZ showed a slight increasing trend, but was not statistically significant ($p=0.35$) (Figure 4). Perfusion in HPZ was 107.9±50.7, 128.3±53.4 and 168.8±90.2 ml/min/100ml for GD13, GD15 and GD17 respectively. In LPZ, perfusion was 61±25.2, 75.7±38.2 and 76.4±44 ml/min/100ml for GD13, GD15 and GD17 respectively.

Discussions: In this longitudinal study, we have demonstrated changes in quantitative perfusion characteristics of the HPZ and LPZ in normal murine placenta at three time points along gestational axis. The results indicate increased perfusion to HPZ with increasing gestational age while perfusion to the LPZ changes only marginally. The high and low perfusion zones roughly correspond to the labyrinth and junctional zones of the placenta [4, 6]. Our results using DCE-MRI are in broad agreement with the published stereology or *in-vitro* studies which suggested that as the gestation age proceeds, the placental perfusion improves due to remodelling of maternal and fetal vasculature, decrease in vascular resistance and an increase in the overall volume of the placental compartments and their blood volume fractions [9, 10]. Our results are in contrast with a recent study (Remus et al.'s) which showed no difference in placental perfusion in a cross-sectional mice cohort [6]. This may be due to the difference in the strain of mice used in either studies (CD1 vs. BALB/c) or due to the influence of partial voluming. As opposed to the volume based approach [6], we have used average c-t curves from the central equatorial plane of the mice placenta for the analysis so that partial voluming is avoided. The average c-t curves in Figures 2&3 show distinct contrast-takeup characteristics at different gestational days indicating that this may act as potential biomarker for identifying perfusion changes in placental insufficiency or pre-eclampsia.

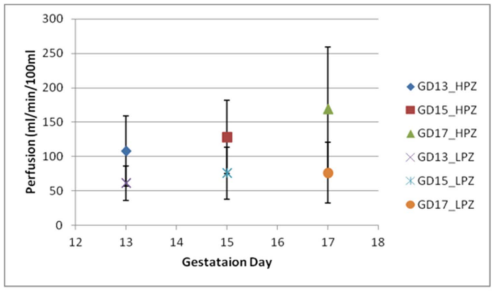

Figure 4. Perfusion plot for high perfusion zone (HPZ) and low perfusion zone (LPZ) in mice placenta from GD13-GD17.

Conclusion: Placental perfusion increases with increasing gestational age in normal murine placenta which can be evaluated quantitatively using dynamic contrast enhanced MRI studies. Specifically, significant increase in perfusion is seen in the high perfusion zone of the placenta which roughly corresponds to the labyrinth zone.

References: [1].Krishna, U. et.al,. JOGI, 2011. 61(5): p. 505-11. [2].Georgiades, P., et.al, Placenta, 2002. 23(1): p. 3-19. [3]. Alison, M., et al., Invest Radiol, 2013. 48(7): p. 535-42. [4]. Salomon, L.J., et al., Radiology, 2005. 235(1): p. 73-80. [5]. Haacke, E.M., et.al,MRI, 2013. 31(4): p. 481-9. [6]. Remus, C.C., et al.,Placenta, 2013. 34(10): p. 899-906. [7]. Miles, K.A., Br J Radiol, 1991. 64(761): p. 409-12. [8].Yankeelov, T.E., et al., MRI, 2005. 23(4): p. 519-29. [9]. Rennie, M.Y., et al., A JPHCP, 2012. 302(6): p. H1261-73. [10]. Coan, P.M., et al., J Physiol, 2010. 588(Pt 3): p. 527-38. [11]. Yadav B.K. et.al, Proc. ISMRM 2014 (abstract).