Evaluating placental growth in normal murine pregnancy using tissue-similarity-mapping and dynamic contrast enhanced magnetic resonance imaging

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Background: The interchange of oxygen and nutrients between the mother and the fetus is performed by the placenta**.** The alteration of these processes is known as placental insufficiency, is one of the leading causes of Fetal Growth Restriction (FGR) [1]. Experimental murine models as the pregnant mouse allow the study and understanding of this condition due to their anatomical and functional similarities between the human and murine placenta [2]. Placenta is a dynamic structure which changes with the gestational age. Hence, our understanding of the natural course of placental growth and perfusion in normal murine pregnancy is critical to contrast it with changes that might occur during pregnancy complication. In dynamic contrast enhancement magnetic resonance imaging (DCE MRI) studies, murine placenta could be segmented into high perfusion and low perfusion zones based on their contrast up-take characteristics [3, 4]. While most of the previous methods employed some manual input in the segmentation of these zones, in this study we used a novel DCE MRI signal analysis tool called Tissue Similarity Mapping (TSM) for automatic segmentation of these structures.

Purpose: To quantify the longitudinal variations in the size of high perfusion and low perfusion zones of the normal murine placenta along different gestational ages using an automatic segmentation method based on TSM.

Material and Methods: Five timed-pregnant CD-1 mice were imaged using a 7Tesla animal MRI system (Bruker Biospin) under anaesthesia on gestational day (GD) 13, GD 15 and GD 17 (term gestation in mice is 18 to 21 days). 0.05 mM concentration of a gadolinium based contrast agent Magnevist, diluted with 0.25 ml of saline was injected through a catheter placed in the tail vein. Following anatomical localization, a gradient echo flash based DCE-MRI was employed with the following parameters: TE=2.02ms, TR=43ms, flip angle = 30, resolution = $0.27 \times 0.27 \times 1.5$ 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. Quantitative analysis was performed on 10 placentas on GD 13 and GD 15 and 11 placentas on GD 17. TSM [5] measures the likeness of the signal response from a reference region by calculating a mean squared error across all time points in the time-resolved data acquired. Using this novel analysis method for DCE MRI signal, the central slice covering the placenta was automatically segmented into the regions based on a reference region chosen using a threshold placental time-to-peak map. The two segmented regions were roughly corresponding to the high perfusion zone and low perfusion zone. Relative volume of these compartments were obtained and statistically compared with a single factor ANOVA test for changes in the fractional volume between different gestational days. A $p<0.05$ was considered statistically significant.

Gestation Age	High Perfusion Mean Volume Fraction (%)	Low Perfusion Mean Volume Fraction (%)
Day 13	70.29 ± 5.74	29.71 ± 5.74
Day 15	67.76 ± 8.12	32.24 ± 8.12
Day 17	84.1 ± 6.2	15.9 ± 6.2

Table 1. High perfusion zone and low perfusion zone volume fraction across gestation days 13, 15 and 17.

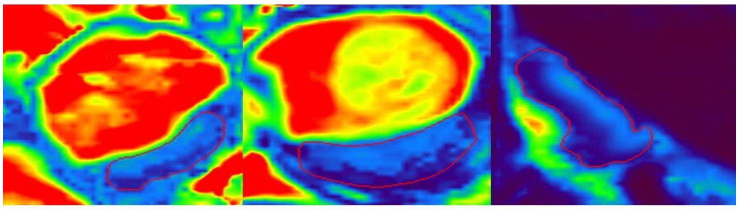

Figure 1. Tissue similarity maps showing high perfusion and low perfusion zones in GD 13, 15 and 17 (left to right) in murine placenta.

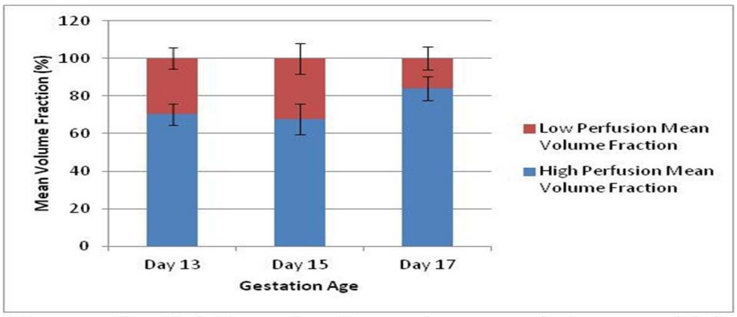

Figure 2. Relative fraction changes between high perfusion zone and low perfusion zone across the gestation axis.

Results: Figure 1. shows the segmented regions of the placenta generated by TSM. Table 1 and Figure 2 show the relative ratio in the volumes (as measured from the central slice) between high perfusion zone and low perfusion zone. The high perfusion zone fraction on GD 13 was 70.29 ± 5.74%, on GD 15 was 67.76 ± 8.12% and on GD 17 was 84.1 ± 6.2%. On the other hand, the fraction of the low perfusion zone on GD 13 was 29.71 ± 5.74%, on GD 15 was 32.34 ± 8.12% and on GD 17 was 15.9 ± 6.2 %. The fraction size of the high perfusion zone changed by almost 14% between GD 13 and GD 17. However, no significant changes were observed between GD 13 and GD 15. The fractional ratios of these individual regions across the three different gestational ages are plotted in Figure 2. The relative volume ratio of the high perfusion zone increases from 70% to 84%. One way ANOVA test across the three gestational days showed significant change in the volume fractions between GD 13 and GD 17 ($p<0.001$).

Discussion: In this longitudinal study, using DCE MRI and a novel automated segmentation method, we have been able to quantify the relative sizes of the high perfusion and low perfusion zones in the mouse placenta at three time points along the gestational age axis. The results are in reasonable agreement with those from previous histological studies [6] which signifies that high and low perfusion zones may represent the labyrinth and junctional zone of the placenta, respectively. Specifically, an increase of 14% in size of the high perfusion zone from GD 13 to GD 17 seen in this study is similar to the change in the size of the labyrinth region observed on histological sections by Coan et. al., [6]. Tissue similarity map provides a measure of similarity of tissues relative to a reference tissue region. By using a threshold placental time-to-peak maps for automatically choosing the reference region, TSM provided an objective way of segmenting the placental regions based on DCE MRI data which may be of use in automatic evaluation of changes in placental compartments in different pathological conditions.

Conclusion: Tissue similarity mapping analysis method was successfully used to show differences in relative sizes of the high perfusion and low perfusion zones of the murine placenta between GD 13 and GD 17 using DCE MRI data.

Reference: [1] Krishna, U. et al., J Obstet Gynaecol India, 2011. [2] Georgiades, P., et al., Placenta, 2002. [3] Alison, M., et al., Invest Radiol, 2013. [4] Salomon, L.J., et al., Radiology, 2005. [5] Haacke, E.M., et al., Magn Reson Imaging, 2013. [6] Coan, P.M., et al., Biol Reprod, 2004.