Time to peak based differentiation of functional placental compartments in the mouse model

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Introduction

Placental vascularization is known to play a key role in fetal development and alterations in blood flow have been associated with gestational pathologies in mice, humans, and other mammalian species [1]. Dynamic contrast enhanced (DCE) MRI is the most commonly applied imaging technique for perfusion quantification and is frequently used in experimental setups for functional placenta analysis [1-2]. However, the mouse placenta consists of two functional zones: The highly vascularized labyrinth zone and the junctional zone. To date, placental perfusion analysis is mostly performed by averaging the perfusion values of both compartments, which leads to the fact that physiological differences between both zones are neglected. The purpose of this study was to evaluate the feasibility of a semi-automatically differentiation of the two placenta zones in a mouse model based on time-to-peak values, which would enable a separate perfusion assessment of the two functional placenta compartments.

Materials and Methods

Three pregnant mice at gestation day 16.5 underwent MRI examination using a 7 Tesla small-animal MR-scanner (Clinscan, Bruker, Germany). A turbo-spin-echo (TSE) MR imaging sequence (TR: 3.1s, TE: 64 ms, FoV: 35 x 50 mm, flip angle: 180°, matrix: 448 x 640, slice thickness 4 mm) in coronal orientation was used to locate the placentas and fetal mice. Coronal dual-echo three-dimensional T1-weighted gradient-echo sequences were acquired after application of contrast agent (Multihance, Bracco, Germany) for dynamic MR-imaging (TR: 10 ms, TE: 1.78/4 ms, FoV: 40 mm, flip angle: 20°, matrix: 128 x 128, slice thickness 1 mm, slices: 16, 50 time points). The contrast agent was diluted 1:10 with saline and administered via a tail vain catheter. The two echo times were used for correcting $T2^*$ relaxation effects caused by high contrast agent concentrations [2]. Each placenta was delineated prior to the automatic functional zone differentiation by manually drawing a ROI. A baseline value correction was performed for all concentration time curves prior to perfusion analysis by subtracting the post-injection values from the mean baseline values. The arrival time of the contrast agent bolus was manually determined for each image sequence. Subsequently, time-to-peak (TTP) maps were calculated in a voxel-wise fashion. More precisely, the time-to-peak (TTP) was defined as the time when the concentration time curve achieves its peak, corrected with the corresponding contrast agent bolus arrival time. The calculated TTP maps were used to classify each voxel of the previously defined placenta ROIs into two zones using k-mean clustering. A third cluster was added in order to differentiate placental high and low flow zones from non-placenta regions and to neglect partial volume effects. The mean TTP values were calculated for the differentiated high and low flow compartments. Furthermore, the area under the curve (AUC) parameter map was calculated in a voxel-wise manner by calculating the curve integral within an interval of 120 seconds (AUC-120) after bolus arrival for each concentration time curve. The mean AUC-120 value was determined for the two separated zones and employed for statistical analysis using a paired t-test.

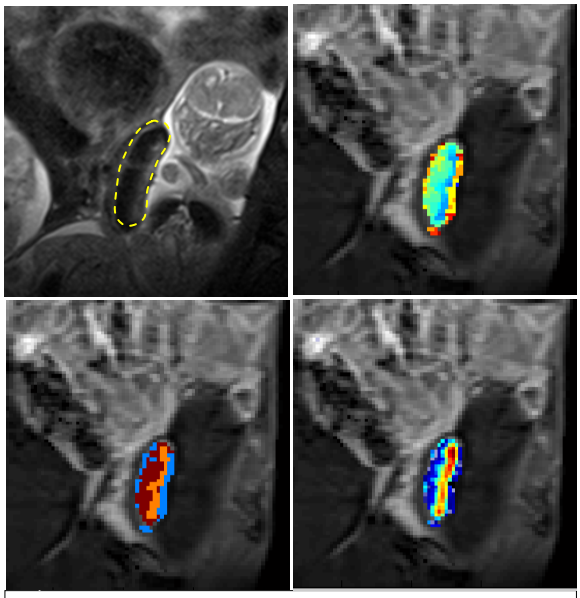

Figure 1 a) T2w image of the fetoplacental unit on gestation day 16.5; b) time to peak map; c) time-to-peak based segmentation; d) AUC map

Results

The proposed functional zone differentiation using k-means clustering based on the time-to-peak values was feasible for all three placentas. More precisely, a close match between the differentiated low flow (red) and high flow (orange) compartments (see Fig. 1c) with the anatomical structures (see Fig. 1a) could be identified by visual assessment. Blue regions represent pixel of non-placenta regions with high time to peak values. Volumetric analysis demonstrated that the low perfusion zone (25.2 ± 0.9 mm^3) was approximately 50% larger than the high perfusion zone (12 ± 2 mm^3). The high flow zone had a mean TTP of 55 ± 4 s and the low flow zone a mean TTP of 109 ± 5 s. Furthermore, statistical analysis revealed significant a difference between the mean AUC-120 values of the high flow (13.7 ±8) and low flow (2.3 ± 1.1) zones ($p = 0.01$) (Fig. 1d).

Discussion and outlook

The first results of this study suggest that the two functional zones of a placenta can be differentiated based on time-to-peak analysis and subsequent k-means clustering. The classification of high and low flow compartments of the placenta appears to agree with physiological compartments but needs further evaluations to validate this finding on a broader basis. AUC analysis demonstrated that the two zones feature significantly different perfusion values, which indicates that placenta perfusion analysis should not be averaged over the different functional zones. Therefore, a separated analysis of the functional placental compartments may be beneficial for further studies.

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