Placenta 36 (2015) 255–261

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

Automatic differentiation of placental perfusion compartments by time-to-peak analysis in mice

F. Kording [a, *], N.D. Forkert [b], J. Sedlacik [c], G. Adam [a], K. Hecher [d], P. Arck [d], C.C. Remus [a]

[a] Department of Diagnostic and Interventional Radiology, Centre for Radiology and Endoscopy, University Medical Centre Hamburg-Eppendorf, Germany
[b] Department of Radiology and Hotchkiss Brain, University of Calgary, Canada
[c] Department of Diagnostic and Interventional Neuroradiology, Centre for Radiology and Endoscopy, University Medical Centre Hamburg-Eppendorf, Germany
[d] Department of Obstetrics and Fetal Medicine, Center for Obstetrics and Paediatrics, University Medical Centre Hamburg-Eppendorf, Germany

ARTICLE INFO

Article history:
Accepted 14 December 2014

Keywords:
Magnetic resonance imaging
Placenta
Perfusion
Computer-assisted image processing

ABSTRACT

Introduction: The aim of this study was to develop an automatic differentiation of two perfusion compartments within the mouse placenta based on times of maximal contrast enhancement for a detailed and reproducible perfusion assessment.
Methods: Placentas (n = 17) from pregnant BALB/c mice (n = 10) were examined in vivo at 7T on gestation day 16.5. Coronal dual-echo 3D T1-weighted gradient-echo sequences were acquired after application of contrast agent for dynamic MRI. An adapted gamma variate function was fitted to the discrete concentration time curves to evaluate the effect of noise on perfusion and segmentation results. Time-to-peak maps based on fitted and discrete curves of each placenta were used to classify each voxel into the high- or low-blood flow compartment using k-means clustering. Perfusion analysis was performed using the steepest slope model and also applied to fitted and discrete curves. Results were compared to manually defined compartments from two independent observers using the Dice coefficient D.
Results: Manually defined placental areas of high-flow and low-flow were similar to the automatic segmentation for discrete (D = 0.76/0.75; D = 0.76/0.79) and fitted (D = 0.80/0.80; D = 0.81/0.82) concentration time curves. Mean perfusion values of discrete and fitted curves ranged in the high-flow compartment from 134 to 142 ml/min/100 ml (discrete) vs. 138–143 ml/min/100 ml (fitted) and in the low-flow compartment from 91 to 94 ml/min/100 ml (discrete) vs. 74–82 ml/min/100 ml (fitted).
Discussion: Our novel approach allows the automatic differentiation of perfusion compartments of the mouse placenta. The approach may overcome limitations of placental perfusion analyses caused by tissue heterogeneity and a potentially biased selection of regions of interest.

1. Introduction

Placental vascularization is known to play a key role in fetal development. Alterations in placental perfusion flow have been associated with gestational pathologies in mice, humans, and other mammalian species [1]. The analysis of placental function has been challenging in the past and was often limited to descriptive approaches such as histomorphology. Generally, the placenta can be considered as a counter-current exchange system between maternal and fetal compartments. It has been found that increased uterine vascular resistance or reduced uterine blood flow are predictors for fetal growth restriction and high-risk pregnancies [2]. Hence, the quantification of placental perfusion could prove valuable for assessment of fetal growth restriction or treatment responses of pregnancy complications.

Dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) is an emerging imaging technique for perfusion analysis in the mouse placenta [1,3] and even enables longitudinal studies since no histology is required. DCE MRI has, for example, been used by Salomon et al. [3] to analyse placental

* Corresponding author. Department of Diagnostic and Interventional Radiology, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany. Tel.: +49 152 22827311.
E-mail address: f.kording@uke.de (F. Kording).

http://dx.doi.org/10.1016/j.placenta.2014.12.010
0143-4004/

perfusion. The authors reported that the contrast agent kinetics of DCE MRI datasets display the gradual filling of the intervillous space and central arterial canal, which is in accordance with the vascular physiology described by Adamson et al. [4], who depicted placental circulation on the basis of vascular casts and histologic studies. DCE MRI datasets do not only enable to analyse the dynamic distribution of the contrast agent but also a quantification of the perfusion. However, DCE datasets have been mainly used to determine an average perfusion value across the entire placenta ignoring different conditions of blood flow within the placenta, e.g. arterial inflow via the central arterial canals, blood transitioning through the intervillous space of the labyrinth, and venous drainage. In pathological conditions such as intrauterine growth restriction, arterial blood flow to the fetal circulation is often altered, which can affect the exchange rate of the placenta. Thus, averaging across the entire placenta may mask significant differences or may also result in erroneous significant differences. Hence, perfusion measurements may be inaccurate and not comparable between studies.

It was recently shown that two placental compartments – a high- and a low-flow compartment – can be differentiated using DCE MRI datasets by visually analysing the gradual filling of the intervillous space [5,6]. More precisely, the two perfusion compartments were interactively defined in both studies by drawing regions-of-interest (ROIs) based on the contrast agent distribution at different time points. Although this procedure leads to more valid results regarding the subsequent calculation of average perfusion values, the differentiation in two compartments itself is subject to observer errors and biases.

The aim of this study was to develop and evaluate a method for the automated differentiation of the two placental perfusion compartments using a k-means clustering algorithm to overcome the limitations associated with manual definitions, thereby enabling a more objective placental perfusion analyses.

2. Materials and methods

2.1. Magnetic resonance imaging

MRI was performed in DBA/2J-mated BALB/c female mice (n = 10) on gestation day (gd) 16.5. One to three placentas (n = 17) were evaluated per dam using a dedicated small-animal 7T MR-scanner (Clinscan, Bruker, Germany) and a circularly polarized transmit/receive coil with an inner diameter and resonator length of 40 mm. An isoflurane/O2 inhalations mixture (1–1.5% vol/vol) was used for anaesthetization during data acquisition. The respiration rate was closely monitored and maintained at 70–85 breaths/min.

First, a turbo-spin-echo MR imaging sequence (TR: 3.1 s, TE: 64 ms, FoV: 35 × 50 mm, flip angle: 180°, matrix: 448 × 640, slices: 16, slice thickness 4 mm) in coronal orientation was used to locate the placentas and fetal mice (see Fig 1a). A coronal dual-echo three-dimensional T1-weighted gradient-echo sequence (see Fig 1b–e) was then used for DCE MRI (TR: 10 ms, TE: 1.78/4 ms, FoV: 40 mm, flip angle: 20°, matrix: 128 × 128, slice thickness 1 mm, slices: 16, time points: 50, temporal resolution: 10 s). After acquisition of four baseline 3D image volumes, 100 μl of the gadolinium chelate gadobenate dimeglumine (Multihance, Bracco, Germany) with a dose of 0.16 mmol/kg body weight diluted 1:10 in saline was injected manually via a 30-gauge tail vain catheter (Smith Medical International, Germany) followed by a 100 μl saline flush. The injection of contrast agent and saline flush took about 8 s and was performed by the same investigator with 4 years of dedicated small animal research experience in all mice.

2.2. Perfusion analysis

An experienced medical expert manually delineated each placenta by drawing ROIs in the corresponding slices (Fig. 1e). These placenta segmentations were used as masks for all further processing steps. Placentas not fully covered by the DCE MRI datasets were excluded from further analysis.

Prior to perfusion analysis, a baseline signal intensity value correction was performed for all concentration time curves. More precisely, the mean pre-contrast baseline value of the first four time points was calculated for each curve and subtracted from all values of the same curve in a second step.

After this, perfusion analysis was performed using the steepest slope model, originally introduced by Miles et al. [7] and defined by:

$$F = \frac{\max(C'(t))}{\max(AIF(t))} \tag{1}$$

where $C'(t)$ denotes the first derivation of the concentration time curve $C(t)$, which was calculated using piecewise linear regression, and $AIF(t)$ the arterial input function. The arterial input function was interactively selected in the kidney hilus since signals in larger placental arterial vessels are distorted by pulsation artefacts. Finally, tissue perfusion F was converted to the perfusion unit of ml/min/100 ml placenta tissue.

2.3. Automatic compartment differentiation

In general, high contrast agent doses are necessary to study leakage effects of contrast agent into the circulation of the fetus [8]. Using atomic emission spectrophotometry [3], it was shown that leakage effects into the fetus can be neglected in case of small contrast agent doses as used in this study. Hence, only the maternal circulation of the placenta is studied in this work.

The automatic method for differentiation of the placenta compartments described in the following is based on the observation that placental blood flow is characterized by different contrast agent enhancement patterns, which is also used for manual definition. The contrast agent enhancement of the placenta appears stereotypic on dynamic images (Fig. 1b–e). The maternal blood enters the uterus through radial arteries that branch into spiral arteries and is then carried via central arterial canals to the fetal side of the placenta (Fig. 1f). Hence, the placental base with the feeding maternal blood flow enhances first. Maternal oxygenated blood then percolates through the intervillous space of the labyrinth back to the maternal side of the placenta and is drained from the labyrinth through venous sinusoids, leading to a gradual enhancement of the entire placental region. This gradual filling of the placenta can be used to divide the placenta into two perfusion compartments. The region consisting of arriving oxygenated maternal blood percolating into the sinusoids of the labyrinth is considered as high-flow compartment. In contrast to this, the low-flow compartment consists of the more peripheral labyrinth with transiting blood and the venous sinusoids with the draining deoxygenated blood (Fig. 1f). It needs to be pointed out that this differentiation does not correspond to anatomical compartments, e.g. labyrinth, junctional zone and decidua, as the high- and low-flow regions represent perfusion compartments.

Several criteria have been proposed in the past to determine contrast agent bolus arrival times, whereas the time-to-peak (TTP) criterion is employed most frequently for this purpose [9] and is also used in this work. The TTP parameter was estimated for each concentration time curve by determining the time from the start of the DCE MRI acquisition to the peak enhancement of the concentration time curve (Fig. 1g).

After calculation of the TTP parameter for each voxel within the placenta segmentation, a k-means clustering algorithm based on the Euclidean distance [10] of the TTP values was used for the automatic classification of each voxel into the high- or low-flow compartment.

2.4. Modelling of concentration time curves by a gamma variate function

Due to the required calculation of the first derivation of the concentration time curve, the steepest slope model is sensitive to noise, especially in case of low signal-to-noise ratios that may in particular appear in the low-flow placental zone. Apart from this drawback, the concentration time curves are only represented by discrete sample points, which may also downgrade the accuracy of the perfusion estimation as well as the TTP parameter estimation that is used as the basis for the automatic compartment differentiation. The usage of concentration time curves represented by discrete sample points for TTP and perfusion estimation is referred to as the “discrete method” in the following. One possibility to overcome this drawback is a previous fitting of continuously defined hemodynamic models to each discrete concentration time curve. After curve fitting, the perfusion value (i.e. the slope) and TTP parameter can be determined based on the fitted hemodynamic function.

To evaluate a potential benefit of a previous hemodynamic model fit, the automatic differentiation of the perfusion compartments and subsequent calculation of average perfusion values was also performed after fitting of the adapted gamma variate function G (see Fig. 1g) with an additional time integral term in the shape function as described by Glyn Johnson et al. [11].

$$G = g(t) + \lambda \int_0^t g(t - t')dt' \tag{2}$$

Here, λ is a constant and g a gamma variate function often used to describe the shape of the bolus in the indicator dilution theory [12].

$$g = \begin{cases} (t - t_0)^{\alpha} \exp(-\beta(t - t_0)) & t > t_0 \\ 0 & t > t_0 \end{cases} \tag{3}$$

where t_0 is the bolus arrival time and α and β parameters that describe the shape of the bolus. The goodness of fit was evaluated by calculating the correlation coefficient r. Fitted curves with $r < 0.8$ were excluded from further analysis.