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Molecular diffusion and perfusion of biological water quantified by MRI for the diagnosis of pathological human placentas

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Summary. — The study aimed to find biomarkers to characterize and differentiate healthy and pathological placentas using the nuclear magnetic resonance diffusion weighted imaging (DWI) technique. Fetal and maternal placentas tissues are characterized by a different diffusion behavior. Diffusion and perfusion can be quantified using intravoxel-incoherent-motion (IVIM) model of DWI signal acquired using a specific acquisition sequence. The dataset is divided into two groups: 33 healthy subjects and 15 pathological subjects classified as Fetal Growth Restriction (FGR) by an ultrasound investigation. The perfusion fraction f has a significant difference between fetal and maternal side which is connected to the role of the villi involved in the exchange of nutrients between fetal and maternal blood. It also discriminates healthy and FGR placentas. In conclusion, diffusion and perfusion of water quantified by DWI is a powerful non-invasive, radiation-free tool for prenatal diagnosis.

1. – Introduction

The placenta is the organ dedicated to the exchange of nutrients between maternal and fetal blood. It has a discoidal shape and it is divided into maternal and fetal side, each one with its proper diffusion and perfusion behavior. The maternal part is composed by the basal decidua where there are the spiral arteries and the maternal veins which respectively supply and drain the maternal blood basin. The fetal zone is characterized by the presence of villi covered by layers of trophoblastic cells that allow the exchange of nutrients between the mother and the fetus. The villous trees are contained in the maternal blood basin [1].

Placenta could be affected by morphological abnormalities responsible for pregnancy complications such as Fetal Growth Restriction (FGR) and preeclampsia. In particular, the FGR is characterized by an estimated fetal weight below the 10th percentile due to insufficient supply of nutrients from maternal blood [2-5]. An early diagnosis of this kind

of pathologies is necessary since they are related to the onset of neurological and heart diseases in the baby [6]. In this regard, the non-invasive and non-ionizing Magnetic Resonance Imaging (MRI) may be an important tool of diagnosis. In fact, Diffusion-Weighted Imaging (DWI) provides microstructural and physiological information of placenta tissues exploiting the water diffusion inside biological tissues. This technique has an important role on the prenatal diagnostic since it is radiation-free and it has an intrinsic resolution of some tens of micrometers depending on the diffusion of the water molecule instead of the device features [7]. The DWI signal is the Fourier transform of the motion propagator of the water molecules. In the case of water diffusing in biological tissues, the propagator is a complex function, so models as the intravoxel inchoerent motion (IVIM) were developed in order to approximate the function of the propagator [8-18].

This study aimed to evaluate the capability of the IVIM model for the discrimination between healthy and pathological placentas.

2. – Methods

The study was approved by the ethical committee of the University Hospital Policlinico Umberto I of Rome and all the patients signed a written informed consent for the execution of the experimental protocol. Data were acquired from 33 healthy singleton placentas, 12 pathological placentas classified as FGR by an ultrasound investigation and 3 accreta placentas. Data acquisitions were performed on pregnant women (Age, GA, mean+/−std = 26.8+/−5.2w) at 1.5 T scanner (Siemens Avanto, Erlangen, Germany). The acquisition protocol included a diffusion-weighted spin-echo echo-planar imaging with repetition time/echo time, TR/TE = 3900 ms/74.8 ms; bandwidth = 1184 Hz/px; matrix size = 192 × 192, FOV 220 × 220, number of slices = from 18 to 30. The in-plane resolution was $2.0 \times 2.0\,\mathrm{mm}^2$ and the slice thickness 5 mm. The diffusion encoding gradients were applied along 3 non-coplanar directions using ten different b-values (0, 10, 30, 50, 75, 100, 200, 400, 700, $1000\,\mathrm{s/mm}^2$) and averaged over the three directions x, y and z. The number of averaged signal (NS) for each b-value was NS = 4. Data analysis was performed using a Matlab (MathWorks, 2016b) home-made script and a machine learning algorithm based on bugged tree was used to obtain the parametric maps.

2˙1. *Multi-compartment model.* – The model used in this study is the IVIM model characterized by two compartments: the former is the fastest one connected to the fetal perfusion, the latter is connected to the maternal diffusion. The model is thus represented by eq. (1),

$$\frac{S}{S_0} = f e^{-bD^*} + (1-f)e^{-bD}, \tag{1}$$

where D is the diffusion coefficient related to the blood flowing in the intravillous space, D^* is the perfusion coefficients of the fetal compartment. The parameter f is the perfusion fraction.

2˙2. *Post-processing.* – The parametric maps were obtained by a machine learning algorithm based on the bugged tree. The diffusion D maps were used to visualize and select two region of interest (ROI) of the placentas on the fetal and maternal side for the umbilical, peripheral and central zone of the organs. In case of accreta placentas a ROI was located on the accretion zone.

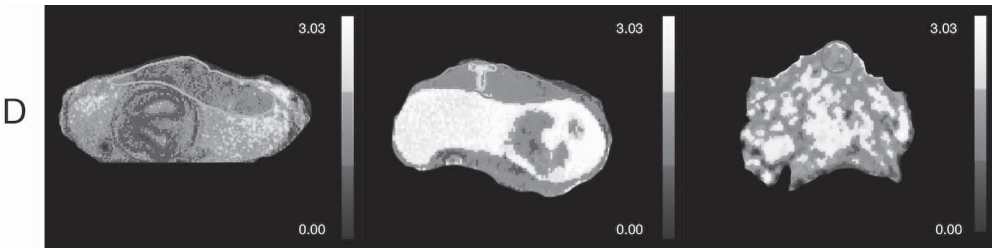

Fig. 1. – Magnetic resonance diffusion maps. The dimension of the colours bar is $10^3\,\mathrm{mm}^2/\mathrm{s}$. The first image on the left shows a normal placenta of 22 w GA, whose highest diffusivity is given by the amniotic fluid ($D \simeq 2.710^3\,\mathrm{mm}^2/\mathrm{s}$). The placenta shows different diffusivity given by the cotyledon. On the left side at the bottom there is the umbilical cord characterized by a low diffusivity and high perfusion given by the pressure of the blood. The central image is an FGR placenta of 19.7 w GA. The amniotic fluid has the highest diffusion coefficient. On the top of the placenta there is a T-shaped zone characterized by a high diffusion coefficient, probably due to the anomalous trophoblastic invasion which causes a decreasing of the thickness of the spiral arteries. The third image represents placenta accreta (GA = 28.6 w) characterized by heterogeneous and rugged tissues.

3. – Results and discussion

The parametric maps are shown in fig. 1: the first row contains the diffusion maps of an healthy placenta, a FGR case and an accreta placenta. The amniotic fluid is characterized by a high diffusivity both on the normal and FGR placentas. Moreover, in the normal placenta, the cerebral ventricles of the fetus are characterized by a high diffusion coefficient and this trend is also confirmed by the physiology of the brain whose ventricles contain molecules of water. The accreta placenta shows heterogeneous and rugged tissues.

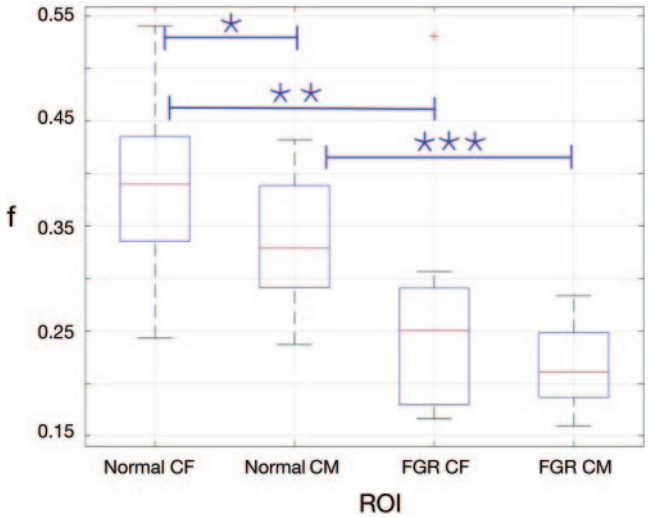

Fig. 2. – ANOVA results obtained from the comparison between central ROIs selected in maternal and fetal placentas of healthy and pathological placentas. CF: central fetal side; CM: central maternal side. (*) $p < 0.037$; (**) $p < 0.002$; (***) $p < 0.0003$.

In healthy subjects, the IVIM perfusion fraction f was found to be higher on the fetal side than on the maternal side due to the greater concentration of villi ([12, 13]). The f perfusion fraction was also found to be statistically lower in the FGR placentas than on the healthy ones reflecting the origin of the pathology that is given by a lack of exchange of nutriments between mother and fetus. The differences were evaluated performing a one-way ANOVA test whose significant results are reported in fig. 2.

The accretion zone was found to have the same perfusion fraction f of the healthy placentas.

The f parameter significantly discriminates between the normal fetal and normal maternal side of placenta: it is higher in the fetal side. Indeed, fetal placenta is characterized by a higher amount of villis. On the other hand, the diffusion parameter D estimated by IVIM model does not differentiate between healthy and pathological placentas. Importantly, f discriminates with $p < 0.0003$ between healthy and pathological placentas (fig. 2).

4. – Conclusion

The magnetic resonance IVIM model has been found to be a promising tool for the early diagnosis of placental pathologies such as the FGR condition. The perfusion fraction f related to the action of the villi is a sensitive parameter for the perfusion inside the tissues. The fetal side of the placenta is more perfused than the maternal side because of the presence of the villous trees. In fact, the perfusion fraction f was found to be higher on the fetal side than on the maternal side, reflecting the physiology of the organ.

The FGR placenta is characterized by an insufficient supply of blood to the organ due to the thickness of the spiral arteries. This thickness is given by the abnormal infiltration of the trophoblastic cells, so the blood flows with higher pressure than in a normal placenta. The perfusion fraction f was found to be lower in a FGR placenta than in a normal once. This means that the perfusion due to the exchange of nutriments is lower for a pathological placenta.

In conclusion, this work suggests that the perfusion fraction f is a powerful biomarker for placenta pathologies involving abnormalities on the circulatory system of this organ. Future researches will investigate a larger cohort of subjects in order to validate this new diagnostic approach.

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