Antenatal liver and spleen iron quantification in a sheep model

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Introduction

The gestational condition of neonantal hemochromatosis (NH) is characterized by liver failure associated with intra- and extrahepatic iron accumulation and a poor outcome. Enabling antenatal initiation of immunomodulating therapy, intrauterine diagnosis of fetal hepatic and tissue iron overload is mandatory. The quantitative assessment of iron burden using magnetic resonance imaging (MRI) is becoming more and more available throughout the world and allows measurements of averaged iron distribution through the whole liver parenchyma (Clark PR 2000). The assessment of the transverse relaxation rates R2 (spin echo) or R2* (gradient echo) with the MRI exploits the perturbation of the proton resonance by the paramagnetic tissue property (R2) or by the additional dephasing effect from local magnetic fields (R2*). Demonstrating the feasibility of fetal liver and spleen iron quantification in utero by MRI may add valuable information to this disease.

Material and Methods

The study was approved by the local animal protection authorities. The ewes were then intubated after the intravenous administration of 1g of barbiturate (Trapanal®, ALTANA Pharma, Konstanz, Germany), and were subsequently anaesthetized by means of artificial ventilation with 1% isoflurane (Forene®; Abbot, Wiesbaden, Germany) with a 2:1 mixture of O2/N2O (O2, 2 L/min: N2O, 1 L/min). 13 healthy fetal sheep (gestational age 112-122 days) underwent MRI on 1.5 T imager. First of all, an initial T2-weighted turbo-spin-echo (T2 TSE) sequence was applied for general anatomical orientation (TE 90 msec; TR around 4 seconds - the exact value depended on the number of slices needed to cover the area of interest). Liver and spleen R2* measurements using a breath triggered (ewe) multi-echo sequence (TE 4.6-54.1 ms, 12 echoes, TR 578 ms, flip angle 20°, pixel bandwidth 283Hz/pixel) **(Figure A & B)**.

Data were primarily analyzed by CMRtools (Version 2007, Cardiovascular Imaging Solutions Ltd, Cambs, UK), which yields signal intensities (SI ± SD) within a delineated ROI and allows export to other software platforms. Pixel profiles were assessed by the free-ware DICOM reader Osiris (Version 4.19, University Hospital of Geneva). A mono-exponential model for the proton signal intensities as function of echo time TE was applied, in order to fit the unknown signal amplitude SI (TE=0), the transverse relaxation rate R2*, and the constant signal level offset SIo. This was performed according to equation 1 by Levenberg-Marquardt algorithm (SlideWrite V6.1, Advanced Graphics Software Inc., Encinitas CA, USA).

$$SI(TE) = SI(0) \cdot \exp(-R2^* \cdot TE) + SIo \qquad (1)$$

For R2* > 100 s-1 (T2* < 10 ms), usually a 3-parameter fit of SI(0), R2*, and SIo could be used. For R2* < 100 s-1 the signal intensity + SD of the nearby lung tissue was used to estimate the signal level offset SIo because the 3-parameter fit to averaged data from a ROI usually fails. The transverse relaxation rate R2* was determined from a mono-exponential fit with constant signal level offset (SILO) to the echo-time dependent signal intensities (SI) averaged over one liver and spleen slice (thickness 5.5 mm).

Results

All obtained images were of very good quality, fetal livers and spleens could easily be identified. Fetal liver R2* ranged from 28.7-36.6 s-1 (SD±0.4 - 3.1), R2* of the fetal spleens ranged from 37.4-51.0 s-1 (SD±1.7-2.4) **(Table 1)**. The corresponding liver iron concentration (LIC) was below 50 in two and 130±12 µg/gwet weight in one fetus. The corresponding spleen iron concentration (SIC) ranged from 141-308 µg/gw.w. (SD±14-53). Calibration of R2* was adopted from human liver and spleen iron measurements (Wood et al. 2005) .

	Liver				Spleen			
	R2* [s-1]	SD	**LIC** ± SD [mg/gd.w.]		R2* [s-1]	SD	**SIC** ± SD [mg/gd.w.]	
Sheep 1	29.3	1.9	**0.946**	0.062	40.2	2.2	**1.223**	0.066
Sheep 2	25.6	1.2	**0.852**	0.039	41.3	3.2	**1.252**	0.096
Sheep 3	22	0.8	**0.761**	0.028	35.1	1.3	**1.092**	0.041
Sheep 4	34.1	3.8	**1.068**	0.12	70	5.2	**1.98**	1.47
Sheep 5	19.5	1.1	**0.697**	0.038	44.4	1.8	**1.33**	0.053
Sheep 6	39.6	1.6	**1.207**	0.049	26.9	1.4	**0.885**	0.046
Sheep 7	19.6	0.1	**0.7**	0.002	40.3	2.2	**1.224**	0.068
Sheep 8	30.6	0.3	**0.979**	0.011	20.4	0.7	**0.721**	0.024
Sheep 9	19.9	0.6	**0.708**	0.023	36.2	1.8	**1.122**	0.056
Sheep 10	20.3	0.2	**0.717**	0.006	33.7	1.6	**1.058**	0.049
Sheep 11	22.3	0.4	**0.769**	0.013	37.6	1.9	**1.158**	0.057
Sheep 12	29.9	1.2	**0.96**	0.038	41.5	2.7	**1.256**	0.081
Sheep 13	113.5	3.9	**3.086**	0.107	51.5	2	**1.51**	0.058

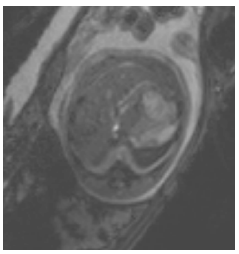

Figure A: Identification of fetal liver and spleen in transversal plane

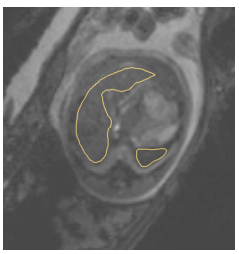

Figure B: Placing the ROI in the liver and in the spleen for R2*.measurement

Conclusion

Feasibility of intrauterine liver and spleen iron quantification by MRI was successfully demonstrated in a fetal sheep model. Transferring the intrauterine quantification of fetal LIC and SIC in sheep to human pregnancies with suspected fetal siderosis could enable early diagnosis and therapy with improvement of neonatal prognosis. Transferring the successful intrauterine quantification of fetal LIC and SIC in sheep to human pregnancies with suspected NH could enable early diagnosis and thus therapy with improvement of prognosis.

Key words: Magnetic Resonance Imaging, Liver, Pregnancy, Diagnosis