3D-liver perfusion MR imaging with MS-325 blood pool contrast agent to evaluate liver fibrosis

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Introduction

Liver fibrosis is an important cause of mortality and morbidity in patients with chronic liver diseases. Fibrosis can lead to cirrhosis from which the complications involve 15,000 deaths per year in France [1]. Recently, the studies about the mechanism of hepatic fibrogenesis have shown the reversible aspect of liver fibrosis and have allowed the emergence of more effective treatment strategies. However, an early detection and a clinical follow-up of liver fibrosis are still needed. The histology after liver biopsy is the gold standard but has inherent risk, interobserver variability and sampling errors. It has been demonstrated that liver perfusion imaging has the potential to detect and assess vascular modifications associated with liver fibrosis [2]. However, this procedure requires an adapted MRI sequence with high temporal resolution and the knowledge of the relationship between signal intensity and contrast agent concentration.
Our objective was to prospectively evaluate estimated-perfusion parameters based on 1.5T-MR dynamic acquisition with the MS-325 paramagnetic blood pool agent for liver fibrosis diagnosis in comparison with histological findings.

Material and method

Sixteen patients with chronic liver diseases (10 men, 6 women; mean age, 52.4 ± 14.8 years; mean weight, 78.3 ± 11.4 Kg) were prospectively enrolled in this study during a 9-month period from September 2008 to June 2009. From these patients, 4 were scored F0; 3 were scored F1; 4 were scored F2; 1 was scored F3 and 4 were scored F4 according to METAVIR classification.
MR-dynamic acquisition was performed on a 1.5 T Magnetom Symphony *(Siemens Medical Solutions, Erlangen, Germany)* with a 3D VIBE T_{1w} (TR/TE, 2.87/1.22 ms; flip angle, 12°; 192 x 256 matrix; 300 x 400 mm FOV; 650 Hz.pixel^{-1} bandwidth; 6/8ème partial K-space filling, 2 iPAT r-factor, 6.4 cm slab thickness, 4 mm slice thickness in coronal plane). MS-325 *(Epix pharmaceutical Inc.)* paramagnetic blood pool agent was used. At clinically relevant concentration it is highly bound to Human Albumin Serum (HAS). This property involves the increasing of agent molecular weight and r_1 relaxivity by Receptor-Induced Magnetization Effect (RIME) [3]. MR-acquisition started simultaneously with contrast agent injection (1.0 mL.sec^{-1} injection rate; 0.12 mL.Kg^{-1} posology,) and was continuously performed in free breathing during 2 min. Thanks to the knowledge of r_1 relaxivity value (19 mM^{-1}.s^{-1}) in our experimental conditions and by scanning several concentration of copper sulfate (0.3 to 7.0 g.L^{-1}), a relationship between MS-325 concentration and signal intensity was established. Due to respiratory motion; image volumes were co-registered by an automatic rigid image translation-based method. Quantitative perfusion parameters (Arterial and Portal blood flow, Hepatic Perfusion Index (HPI), Mean Transit Time (MTT) and Regional Blood Volume (RBV)) were obtained from experimental data using a 5-parameters dual-input-one-compartment model using Levenberg-Marquardt fit algorithm. Input coefficients were generated by a Monte-Carlo method using an in-house developed software using Matlab *7.5 (Mathworks, Natick, Mass)*. Patients were stratified according to the fibrosis stage and quantitative perfusion parameters significance for fibrosis stage discrimination was assessed with the Mann-Whitney test.

Results

Quantified perfusion parameters are summarized in Table 1. Arterial blood flow increased with fibrosis stage (from 21.5 ± 9.1 to 46.5 ± 15.8 mL.100g^{-1}.min^{-1}) whereas portal blood flow decreased (from 95.1 ± 43.6 to 19.7 ± 4.3 mL.100g^{-1}.min^{-1}). It involved a significant increase of HPI ($p<0.03$) with fibrosis stage (from 18.9 ± 1.8 to 62.6 ± 14.3%). MTT are constant from stages F0 to F2 (mean: 7.0 ± 2.5 sec) and increase significantly ($p<0.03$) for stages F3 and F4 (10.6 and 16.3 ± 0.5 sec respectively). Total blood flow was constant from stages F0 to F2 (mean: 120.1 ± 50.7 mL.100g^{-1}.min^{-1}) and decrease dramatically for F3 and F4 (83.6 and 66.2 ± 10.2 mL.100g^{-1}.min^{-1} respectively). HPI and portal blood flow were found relevant parameters to discriminate between F2, F3 and F4 ($p<0.03$), MTT and total blood flow between F2, F3 and F4 are significantly different ($p<0.03$ and $p<0.05$ respectively), Arterial blood flow allowed to separate only F2, F3, F4 stages with F0 and F1 stages ($p<0.03$).

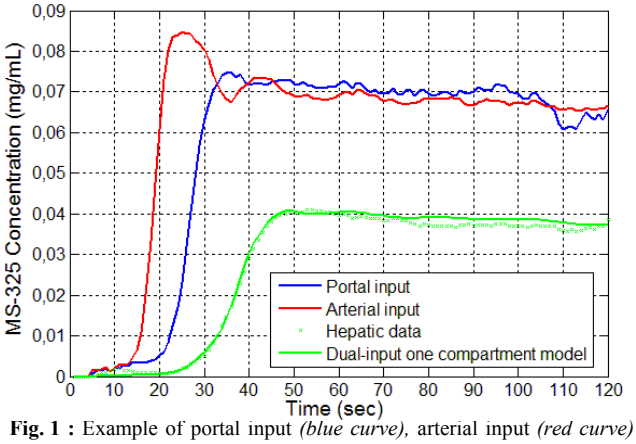

Fig. 1 : Example of portal input *(blue curve)*, arterial input *(red curve)* and experimental hepatic data *(green point)* adjusted to the model with a non-linear least-square fit in a patient with F2 METAVIR stage.

Table 1. Mean (standard deviation) of quantitative perfusion parameters in 15 patients stratified with respect to liver fibrosis stage.

METAVIR stage	F0	F1	F2	F3	F4
Arterial blood flow *(mL.100mg^{-1}.min^{-1})*	21.5 (9.1)	35.7 (21.4)	46.0 (28.2)	42.1	46.5 (15.8)
Portal blood flow *(mL.100mg^{-1}.min^{-1})*	90.6 (34.2)	95.1 (43.6)	71.5 (24.1)	41.5	19.7 (4.3)
Total blood flow *(mL.100mg^{-1}.min^{-1})*	112.1 (43.2)	130.8 (63.9)	117.5 (44.3)	83.6	66.2 (10.2)
HPI *(%)*	18.9 (1.8)	26.5 (3.1)	36.9 (13.4)	50.4	68.8 (14.8)
MTT *(sec)*	8.7 (3.7)	6.3 (3.0)	6.0 (0.9)	10.6	16.3 (0.5)

Discussion

Portal blood flow decrease could be explained by the resistance involved by collagen deposition in the space of Disse. A hepatic buffer response allowed maintaining a relevant total blood flow until stage F3 by an increase of the arterial blood flow and HPI. This response was not sufficient for stages F3 and higher where portal blood flow is too low. Small values of MTTs could be explained by a lower diffusion of MS-325 in extra-vascular space due to its higher molecular weight compared to conventional paramagnetic contrast agent. In the context of fibrosis, high molecular weight of MS-325 complex appears well suited due to its sensibility to liver sinusoid permeability changes. It could however involve quantification errors because of r_1 relaxivity value dependent on HAS-bounding rate. Small flip angle reduced saturation effects, improved sequence sensibility and reduced inflow errors. The dynamic range of measure was however limited. The use of continuous free-breathing acquisition associated to rigid-images registration increase modeling reliability with a larger number of valuable measurements during exploration. Patient comfort is also improved. In conclusion, HPI and portal blood flow could be relevant indicators for the clinical monitoring during antiviral treatments in patients with viral chronic hepatitis. These results must be confirmed with a larger number of patients per group.

References

[1] HAS – Guide affection longue durée – Cirrhoses 2008.
[2] Hagiwara M et al. Radiology 2008;246:926-34.
[3] McMurry TJ et al. J. Med.Chem. 2002;45:3465-74.