Liver perfusion quantification with MR-DCE imaging at 3.0 T for liver fibrosis assessment in patients with chronic liver diseases

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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 and 40,000 deaths per year in France and in USA respectively (1,2). The studies investigating the mechanism of hepatic fibrogenesis have shown the reversible aspect of liver fibrosis and have led to the emergence of more effective treatment strategies. However, an early detection and a clinical follow-up of liver fibrosis are still required. While liver biopsy is the gold standard for the diagnosis of chronic liver diseases, inherent risk, interobserver variability and sampling errors makes liver biopsy unusable for the clinical follow up. Thus, a clinical need in the development of non-invasive methods for liver fibrosis assessment has emerged. At 1.5 T, human *in-vivo* studies have demonstrated that liver perfusion imaging using a MR dynamic contrast enhanced method (MR-DCE) has the potential to detect and assess vascular modifications associated to liver fibrosis (3,4). Nevertheless, such methods required the knowledge of the relationship between signal intensity and contrast agent concentration. Authors have used either *in-vitro* pre-calibrations based on scan preparations with variable concentration of Gd^{3+} or preparations with variable T_1-values. Our objective was to validate a MR protocol at 3.0 T for liver perfusion quantification using MR-DCE imaging with an auto-calibrated procedure for tracer concentration quantification. Validation was performed *in-vivo* on a prospective study including patients with chronic liver diseases.

Material and methods

Subjects: Fourteen subjects (6 W, 8 M; mean age: 41.0 ± 15.4 years; mean weight: 73.6 ± 17.4 Kg) with chronic liver diseases were prospectively enrolled. Liver fibrosis was histologicaly quantified with METAVIR and Brunt quantification in patients with viral hepatitis and NAFLD respectively. ***MR acquisition:*** Dynamic MR acquisition was performed on a 3.0 T Discovery MR 750 *(GEHC, Milwaukee, WI, USA)* with a 3D LAVA sequence employing the autocalibrating reconstruction for cartesian imaging with an accelerating factor of 3. Acquisition, parameters were: TR/TE, 1.9/0.8 ms; 9° flip angle; 128 × 160 acquisition matrix (256² rebuilding); 480² mm² FOV; 2/3 partial K-space filling, 24 cm slab thickness including 48 coronal slices of 5 mm thickness rebuilt with a ZIP 2 interpolation algorithm. Temporal resolution was 1.8 s. Dynamic acquisition started simultaneously with contrast medium injection *(Multihance, Bracco s.p.a, Milano, Italy)* and lasted 180 s in free-breathing. Before injection, a triple-angle (3,6,9°) pre-contrast acquisition was performed with the same parameters as used for dynamic acquisition. Injection rate was 6.0 $mL.sec^{-1}$and posology was 0.2 $mL.Kg^{-1}$. ***Images processing***: First, image misregistrations induced by respiration motions were corrected by an automatic registration method using the normalized mutual information as similarity measure and an affine transformation fitted with the quasi-Newton algorithm. Next, images acquired with the triple angle precontrast acquisition were used to compute a T_1 pre-contrast map (Fig.1). Because dynamic acquisition flip angle is the same as the third angle of the T_1 pre-contrast acquisition, then Multihance™ concentration were deduced for each instant using the knowledge of plasmatic R_1 relaxivity-value at 3.0 T and 37°C: 5.5 $L.mmol^{-1}.s^{-1}$ (5). Arterial and portal input functions were measured from 5-by-5 pixels square-shaped ROIs placed on abdominal aorta (close to coeliac trunk) and main portal vein respectively. Both input functions were then normalized by one minus the large vessels hematocrit (Hct_L = 0.42) and interpolated using spline functions. Time activity curves extracted from 4 square-shaped ROI, each of 11 by 11 pixels placed on hepatic parenchyma were normalized by one minus the small vessels hematocrit (Hct_S = 0.25) and adjusted to a 5-parameters dual-input one compartment model with a non linear least-square fit using the Levenberg-Marquardt algorithm. This model is including arterial and portal delays as well as quantitative perfusion parameters: arterial perfusion, portal perfusion and Mean Transit Time (MTT). To reduce local minima problem, optimization algorithm was ran with a grid of pseudo-random starting coefficients generated between two threshold values. Each fit procedure was done with 1000 different initializations. Hepatic Perfusion Index (HPI) was calculated as the arterial perfusion to total perfusion ratio. Regional Blood Volume (RBV) was calculated as RBV = MTT × Total perfusion.

Results

Histological results were: 4 NASH (2 scored Brunt 2 and 2 scored Brunt 3), 2 NAFLD (scored Brunt 0), 6 viral hepatitis (1 scored F0, 2 scored F1, 2 scored F2 and 1 scored F3) and 2 cholangiopathies without fibrosis. Using these results, three groups were constituted: no fibrosis, for subjects with METAVIR F0 or Brunt 0; non-advanced fibrosis, for subjects with METAVIR < F2 or Brunt < 2, advanced fibrosis for subjects with METAVIR ≥ F2 or Brunt ≥ 2.

Tab.1*: MR quantified perfusion parameters stratified according to fibrosis severity.*

Fibrosis severity	**No fibrosis** *(n=5)*	**Non-advanced fibrosis** *(n=3)*	**Advanced fibrosis** *(n=6)*
Arterial perfusion *(ml.min^{-1}.100g^{-1})*	34.1 ± 8.1	51.9 ± 9.5	34.8 ± 19.0
Portal perfusion *(ml.min^{-1}.100g^{-1})*	101.3 ± 26.1	69.5 ± 10.9	28.9 ± 12.9
Total perfusion *(ml.min^{-1}.100g^{-1})*	135.4 ± 24.1	121.4 ± 20.1	63.7 ± 26.3
HPI *(%)*	25.9 ± 8.2	42.7 ± 1.8	53.0 ± 13.9
MTT *(s)*	5.2 ± 1.4	5.7 ± 1.0	11.3 ± 4.2
RBV *(ml.100g-1)*	11.8 ± 4.3	11.5 ± 3.1	10.9 ± 3.7

MR quantified perfusion parameters stratified according to fibrosis severity are summarized in Tab.1. Portal perfusion decreased according to fibrosis severity inducing an increase of hepatic perfusion index. Portal and total perfusion decreases were found significant between no fibrosis and advanced fibrosis group ($p<0.01$) as well as between non-advanced fibrosis and advanced fibrosis ($p<0.05$). HPI increase between no fibrosis group and non-advanced fibrosis ($p<0.05$) as well as between no fibrosis group and advanced fibrosis ($p<0.01$) were also found significant. MTT was constant between no fibrosis and non-advanced fibrosis group but was modified at advanced fibrosis. Indeed, MTT increases were significant between no fibrosis group and advanced fibrosis ($p<0.01$) as well as between non-advanced fibrosis and advanced fibrosis ($p<0.05$).

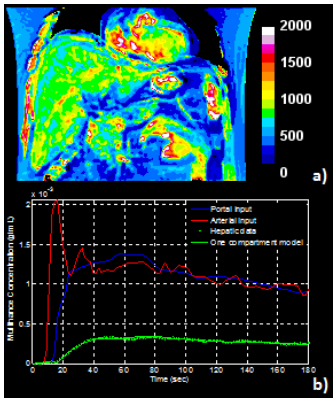

Fig.1: *T_1 precontrast map in ms (upper) and example of portal input, arterial input and experimental hepatic data adjusted to the 5-parameters dual input one compartment model (lower).*

Discussion

Results show that to quantify liver perfusion with MR-DCE imaging is feasible at 3.0T. Perfusion parameter variations observed confirm the existence of hemodynamic changes associated with fibrous damage and are consistent with previous results obtained at 1.5 T (4). Collagen deposition occurring in liver fibrosis contributes to portal perfusion decrease. A buffer response in the liver is able to counterbalance this phenomenon by increasing arterial perfusion leading to an increased of hepatic perfusion index. For advanced-cases, fibrosis contributes to MTT increase of the tracer. In this study, fat overload did not modify liver perfusion in patients with NAFLD scored brunt 0 suggesting that liver steatosis do not seem to constitute as a confounding factor in liver fibrosis assessment using MR-DCE imaging. Quantitative perfusion parameters such as HPI, MTT, total and portal perfusion could be relevant biomarkers to make the distinction between the absence of fibrosis, non-advanced fibrosis, and advanced fibrosis in patients with chronic viral hepatitis as well as in patients with NAFLD.

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