Dynamic Contrast-Enhanced MRI of Mouse Cirrhotic Liver: A Pilot Study

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Target Audience: DCE-MRI practitioners, gastroenterologists.

Purpose:

Liver cirrhosis constitute a final common pathway for a myriad of liver diseases including Hepatitis B, C and fatty liver, resulting in significant morbidity and mortality. The problem is the lack of good non-invasive tool that can accurately predict early onset fibrosis and progression to cirrhosis. Accumulating evidence indicates that one of the early pathogenetic processes in liver cirrhosis is capillarisation of liver sinusoidal endothelium or loss of fenestrae. This change is believed to alter the liver sinusoidal dynamics and result in ischemia of hepatocytes and drive the chronic process of injury. By capitalizing on the physical concepts of mono-compartment and dual-compartment kinetics, DCE-MRI is able to detect the Space of Disse to indicate whether fibrosis has occurred. Indeed, human studies have shown that patients with normal livers returned a near-zero fractional interstitial space (v_2) due to large fenestrae allowing free exchange of low-molecular weight compounds such as gadolinium-chelate contrast between the vascular space (sinusoids) and interstitial space (Space of Disse) while cirrhotic patients demonstrate a measurable value for the interstitial Space of Disse.[1,2] In this study, we would like to carry out a pilot study using DCE-MRI to assess the kinetics of mouse cirrhotic liver.

Methods:

Mice: NOD scid gamma mice (n = 6) were obtained under MTA from Jackson laboratory and bred. These mice are B cells, T cells and NK cells deleted and deficient in multiple cytokine signaling as well as defects in innate immunity. Mice were fed with thioacetamide from age of three months to induce liver cirrhosis. Scanning was performed for mice after 6 months of thioacetamide feeding and compared to similar control mice given normal drinking water. Fibrosis was validated by gross examination, H&E, sirius red, and trichrome stains.

DCE-MRI: MRI was performed on a 7T scanner (Bruker ClinScan, Bruker BioSpin MRI GmbH, Germany). A 3D VIBE sequence was used with following parameters: TR = 3.04 ms, TE = 1.23 ms, FOV = 36 × 36 mm, 128 × 128 matrix, 8 slices with thickness of 1 mm, & temporal resolution 2 s. Five sets of baseline images were acquired with α = 6° & 14°. It was followed by a dynamic sequence of 130 sets of images (α = 14°). A dose of 100 µL of Gd-DOTA (Dotarem, Guerbet SA, France) at 1 mmol/kg was injected through the tail vein after the first set of dynamic images.

Data Processing: Region of interests corresponding to the liver, major artery, and portal vein were manually outlined. Microcirculatory parameters such as blood flow (F), blood volume (v_1), and permeability (PS) were derived from the two-compartment model as described by Brix.[3]

Results:

Extravasation parameters such as v_2 (mean ± std: 8.17 ± 2.85 %) and PS (2.45 ± 1.19 mL/100mL/min) were lower in control mice than those in treated mice at 13.71 ± 7.90 % and 4.08 ± 0.29 ml/100ml/min, respectively, although the difference is not significant for v_2. The blood flow and volume in the cirrhotic liver were also lower than those found in the control mice. The contrast uptake behavior in the control mice, as shown in Figure 1, showed an immediate uptake which was followed by an immediate washout as well, which reflected the mono-compartment nature of normal liver. On the other hand, in the treated mice, the first phase of contrast uptake was followed by a plateau, which indicated further exchanges of the contrast to the existent interstitial space in the cirrhotic liver and suggested the dual-compartment nature of cirrhotic liver.

Parameter	Control	Treated
F (ml/100ml/min)	227.96 ± 4.36	195.08 ± 54.38
PS (ml/100ml/min)	2.45 ± 1.19	4.08 ± 0.29
v_1 (%)	12.73 ± 4.37	9.70 ± 5.38
v_2 (%)	8.17 ± 2.85	13.71 ± 7.90

Conclusion:

In this pilot study, we managed to show the difference in extra
DCE-MRI can be used to differentiate different stages of fibros

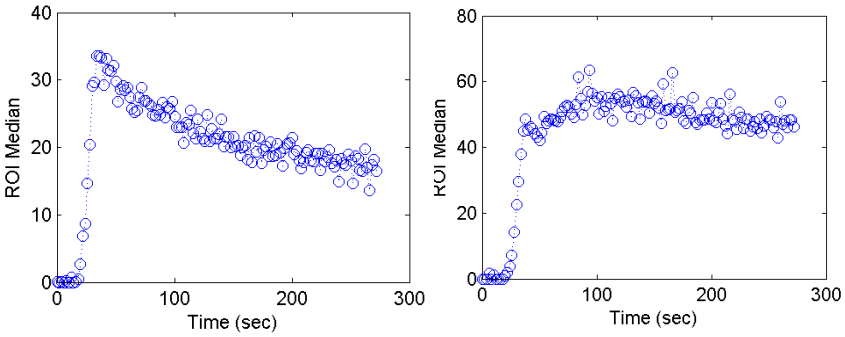

Fig. 1. Signal concentration in the liver of a control mouse (left) and treated mouse (right)

References

1. Koh TS, et al. Radiology 249:307-320.
2. Koh TS, et al. Eur Radiol 19:1184-1196.
3. Brix, et al. Radiology 210:269-76.