

Molecular MRI of Liver Fibrosis

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Introduction

Dramatic increases in the incidence of obesity, diabetes, and the metabolic syndrome are increasing the prevalence of chronic liver diseases. Liver fibrosis occurs in advanced stages of most types of liver injury such as hepatitis C, alcoholic liver disease and nonalcoholic steatohepatitis. Prognosis, surveillance, and treatment decisions in patients with chronic liver disease rely on a precise estimation of the degree of fibrosis. While, liver biopsy is the gold standard for assessment of fibrosis, it is invasive and has potential complications. Because fibrosis is characterized by excess deposition of type I collagen in the parenchyma, we hypothesize that an imaging agent providing a non-invasive measure of elevated collagen would have broad applications in the early assessment and quantification of fibrosis prior to irreversible cirrhosis and carcinogenesis while potentially monitoring response to therapy.

Methods

Rats were either given a toxin, diethylnitrosamine (DEN), 50 mg/kg i.p. weekly for 8 weeks in order to induce liver fibrosis or PBS as a control. Animals were imaged at 4.7T one week following the last DEN administration (i.e. week 9). Imaging was performed prior to and immediately following i.v. EP3600 administration. EP3600 is a type I collagen-targeted Gd-based contrast agent similar to a probe reported recently that assessed cardiac fibrosis [1,2]. Inversion recovery (IR) spin echo imaging (TR/TE/TI=4000/5.5/700ms) provided the best contrast. The inversion time was set to null the signal of the liver prior to contrast administration. Regions of interest were drawn through the liver and also in the air outside the rat. Signal to noise ratio (SNR) is signal in liver divided by the standard deviation of the signal in the air (noise). %SNR increase was calculated as $(\text{SNR}_{\text{post}} - \text{SNR}_{\text{pre}})/\text{SNR}_{\text{pre}} \times 100\%$. Liver collagen levels were quantified by measuring hydroxyproline (Hyp) content using a colorimetric assay. Trichrome was used to stain for fibrosis.

Results

Livers of DEN-treated animals were moderately fibrotic as assessed by histology. The fibrotic animals showed a significant ($p<0.01$) 2-fold higher hydroxyproline liver concentration than animals given PBS. Anatomical imaging (Fig 2A, 2D) showed no gross morphologic differences between fibrotic and control animals. The fibrotic animals ($N=4$) showed marked and significant ($p<0.01$) signal enhancement at 20 min post EP3600 compared to PBS controls ($N=4$), Fig 1. An example is shown in Fig 2. The IR images taken pre (B, E) and post EP3600 (C, F) are windowed identically.

Fig. 1 Signal was significantly ($p<0.01$) increased at 20' post EP-3600 injection in fibrotic animals compared to controls.

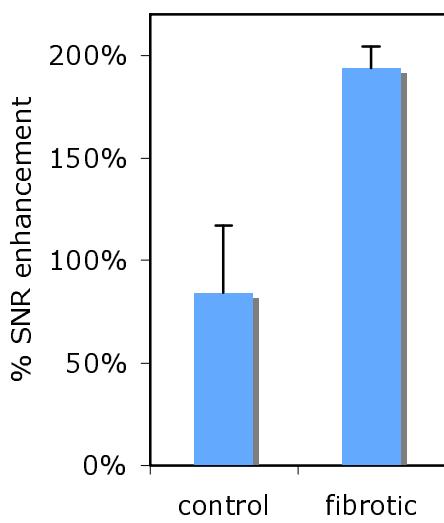
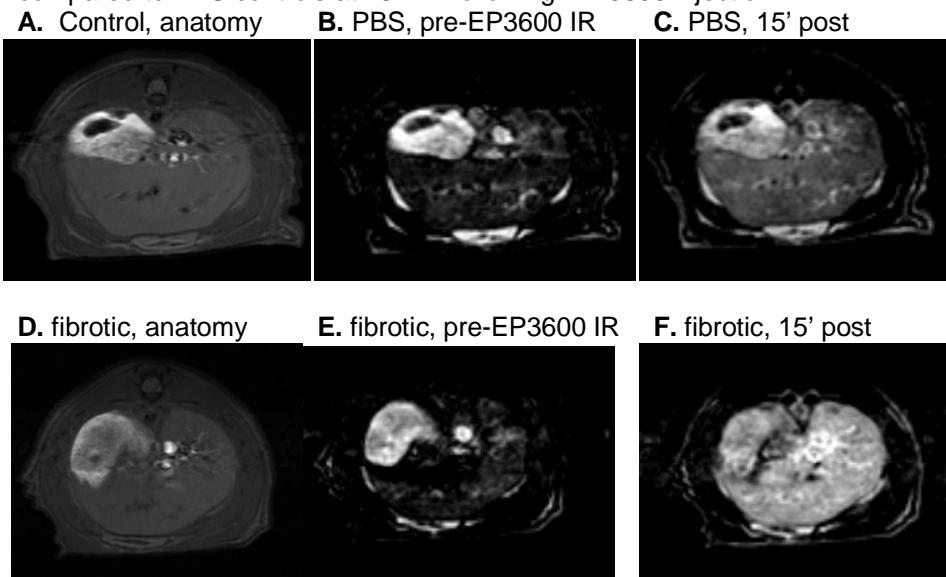


Fig. 2 Increased signal enhancement in liver of fibrotic animals (bottom) compared to PBS controls at 15 min following EP-3600 injection.



Conclusions

Molecular MRI using the collagen-targeted, Gd-based contrast agent EP-3600 is able to identify rats with moderate liver fibrosis. Work is ongoing to determine if liver fibrosis can be accurately staged and quantified using molecular MRI.

References: ¹Caravan et al. Angew. Chem. Int. Ed. 2007, 46:8171. ²Helm et al. Radiology 2008, 247:788