SPIOs and Low Molecular Weight Gd Chelates Are Synergistic for Direct Visualization of Advanced Liver Fibrosis

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Object or Purpose of Study:

Super-paramagnetic iron oxides (SPIOs) and low-molecular weight gadolinium (Gd) chelates both increase the visibility of liver fibrosis on magnetic resonance (MR) images (1,2,3). SPIOs preferentially accumulate in and cause signal loss in non-fibrotic liver; Gd chelates preferentially accumulate in and cause signal enhancement in fibrosis. Thus, SPIO-enhanced and Gd-enhanced images both show advanced fibrosis as diffuse reticulations of higher signal than background liver. The reticulations are not seen in normal liver parenchyma, which is of homogeneous signal intensity on contrast-enhanced MR images. Because SPIOs and Gd chelates increase fibrosis visibility by different mechanisms, we hypothesized that the two agents would be synergistic. The purpose of this study was to compare the visibility of advanced fibrosis on unenhanced, Gd-enhanced, SPIO-enhanced, and combined (SPIOs + Gd) contrast-enhanced MR images.

Materials, Methods and Procedures:

This was a retrospective study of 58 consecutive cirrhotic patients who underwent spoiled gradient recalled echo (GRE) imaging of the liver at 1.5T with (a) no contrast agents, (b) Gd only, (b) SPIOs only, and (d) combined Gd and SPIOs. For each type of contrast enhancement, four breath-hold GRE sequences were analyzed: (a) 2D acquisition, TR/TE = 140/4.6 msec, flip angle (FA) = 70º (n=58 patients), (b) 2D acquisition, TR/TE = 110/8.8 msec, FA = 70º (n=11); (c) 2D multi-echo acquisition, TR/TE = 122/2.2-14.6 msec, FA = 45º (n=5), and (d) 3D acquisition, TR/TE = 4.5-5.5/1.3-1.6 msec, FA = 15-20º (n=32). Images were 8 mm (2D acquisitions) or 3 mm (3D acquisitions) thick and were obtained without gaps. MR images were evaluated qualitatively and, in 10 patients who underwent liver transplantation, compared directly to gross pathology. Also, multiple regions of interest were measured on fibrotic and non-fibrotic tissue and were averaged for each patient. Contrast-to-noise ratio (CNR) of fibrosis to background liver was calculated and compared with Bonferroni-corrected pairwise Wilcoxon tests. Tests were regressed on echo time for the multi-echo sequence.

Results:

With all sequences, combined contrast-enhanced images showed fibrosis with high clarity as a meshwork of high-signal 1-3 mm thick reticulations surrounding 2-5 mm low-signal regions, which corresponded to fibrosis and regenerative nodules on pathology (**Figure 1**). Fibrosis was less visible on SPIO- and Gd-enhanced images and was not visible, without direct comparison to enhanced images, on unenhanced images. CNR of combined contrast images exceeded CNR of SPIO-enhanced ($P<0.05$ to $P<0.0001$ for all comparisons) and Gd-enhanced ($P<0.0001$) images, and CNR of SPIO-enhanced and Gd-enhanced images exceeded CNR of unenhanced images ($P<0.05$ to $P<0.0001$) (**Figures 2 and 3**). For the multi-echo sequence, CNR peaked at TE values of 7.3 to 9.8 msec (**Figure 4**) and, for all TEs, was higher for images acquired with combined contrast enhancement than for images acquired with no contrast enhancement or with a single contrast agent.

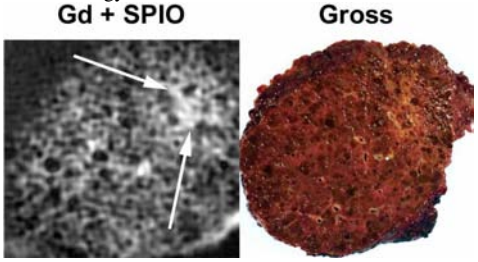
Significance of the Conclusions:

SPIOs and Gd chelates are synergistic in demonstrating advanced liver fibrosis on spoiled GRE images. The effect is robust and was confirmed on four different GRE sequences utilizing a spectrum of imaging parameters. In cirrhotics, combined contrast MR imaging directly visualizes fibrosis with high clarity

References:

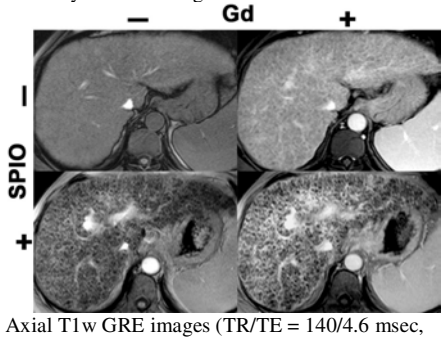
1. Lucidarme O., et al., *Eur Radiol* **13**:467-474 (2003)
2. Semelka R.C., et al., *JMRI* **13**:385-391 (2001)
3. Aguirre D.A., et al., *Radiology* **In press** (2005)

Fig 1. Fibrosis on Combined Contrast Enhanced MR and Pathology



High-signal reticulations on the axial combined contrast enhanced (Gd + SPIO) MR image (TR/TE = 140/4.6 msec) correspond to fibrosis on the gross pathology section. Low-signal regions on MR image correspond to regenerative nodules. Notice confluent fibrosis on MR image (arrows) and gross specimen.

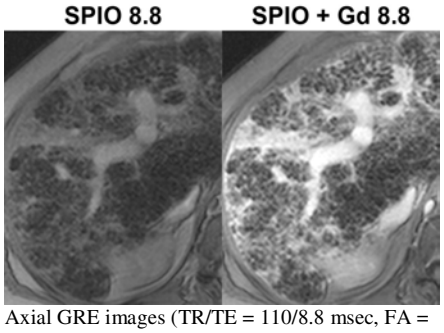
Fig 2. Effect of contrast agents on fibrosis visibility on GRE images with TE = 4.6 msec



Axial T1w GRE images (TR/TE = 140/4.6 msec, FA = 70°) without contrast agents (top left), with SPIOs (bottom left), with Gd (top right), and with both SPIOs and Gd (bottom right).

The combined contrast enhanced image shows fibrosis with the highest clarity.

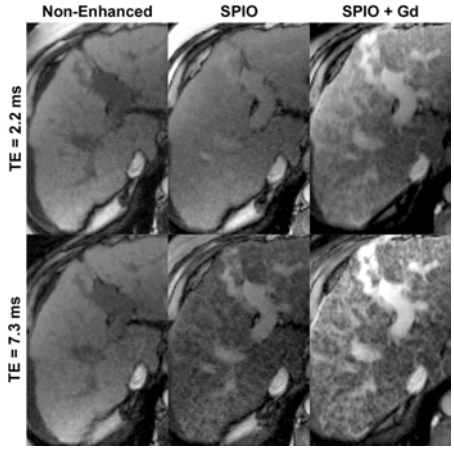
Fig 3. Effect of contrast agents on fibrosis visibility on GRE images with TE = 8.8 msec



Axial GRE images (TR/TE = 110/8.8 msec, FA = 70°) with SPIOs (left) and with combined contrast enhancement (SPIO + Gd)(right).

Fibrosis visibility is higher on combined contrast enhanced image..

Fig 4. Effect of contrast agents on multi-echo GREs.



Select axial GRE images from multi-echo sequence (FA = 45°) with TE of 2.2 msec (top panels) and 7.3 msec (bottom panels) obtained with no enhancement (left), with SPIOs (center), and with combined contrast enhancement (SPIO +Gd) (right). The fibrosis is best seen with combined contrast enhancement.