

A new technique for the detection of liver damage by evaluation of impaired exocytotic activity of Kupffer cells; an experimental study of gadolinium chloride-induced liver injury in rats

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Introduction: Superparamagnetic iron oxide (SPIO) exhibits specific uptake by Kupffer cells (KCs) via phagocytosis. Once compartmentalized into the phagolysosomes of KCs, SPIOs are subsequently broken down and released from KCs within one week. Reflecting this process, the signal intensity of the liver is reduced after the administration of SPIO [1] and then gradually recovers on T₂*-weighed MRI. To our knowledge, few studies have focused on the correlation between the rate of signal recovery on SPIO-enhanced MRI and the exocytotic function of KCs. Our preliminary study [2] demonstrated that signal recovery was significantly delayed in rats that underwent the administration of gadolinium chloride (GdCl₃), which specifically injures KCs [3] prior to SPIO. The delayed recovery was probably caused by SPIO remaining in KCs due to the decrease in exocytotic function, even though only a small amount of SPIO has accumulated in KCs because of the decreased phagocytotic function. Our hypothesis is that if KCs are labeled by SPIO prior to damage, MRI could selectively evaluate the exocytotic function of KCs. This study, therefore, investigated whether SPIO-enhanced MRI could demonstrate the delayed recovery of hepatic signal intensity in rats that received SPIO administration prior to the induction of KC damage by GdCl₃ administration.

Materials and Methods: The institutional animal experimental committee approved the protocol of this animal experiment. Male Wistar rats (230-250 g) were intravenously injected with 8 μmol Fe/kg BW of ferucarbotran (Resovist; Bayer Shering Pharma, Osaka, Japan). The next day, 6 of the rats were intravenously injected with 3.8 and 7.5 mg/kg BW GdCl₃ and assigned to the mild and severe injury groups. Three other rats were injected with normal saline and served as the control group. In addition, 6 rats injected with GdCl₃ alone (3.8 and 7.5 mg/kg BW) were enrolled. Respiratory-gated T₂*-weighted MR images (TR/TE = 450/11 ms, FA = 30°, 80 mm FOV, 256 x 160 matrix, 2 mm slice thickness, 4 NEX) were obtained on days 0, 1, 8, 15, and 22 after SPIO administration using a 3 Tesla whole-body scanner (Signa HDx; GE Healthcare, Milwaukee, WI) equipped with a dedicated small animal coil. Signal intensity was measured in observer-defined region-of-interests on the liver parenchyma and paraspinal muscles. Differences in liver signals relative to paraspinal muscle (relative intensity; RI) were assessed at each time point and compared among control, mild injury, and severe injury groups using Tukey's test.

Results: Figure 1 shows examples of MR images in the control and severe injury groups. Signal intensity of the liver in the control group was restored at day 8, whereas that in the severe injury group remained relatively low. Figure 2 shows the plot of RI at each time point. RI in the mild injury group was restored on day 15. RI in the severe injury group showed a gradual recovery; however, it remained significantly lower on day 22 compared with those in the other two groups at the same time point. Figure 3 shows the plot of RI in rats injected with GdCl₃ alone. RI in rats injected with 3.8 mg/kg BW GdCl₃ was slightly reduced 10 minutes after GdCl₃ administration and there was no significant change between day 1 and day 22. RI in the rats injected with 7.5 mg/kg BW GdCl₃ did not show any significant change between day 1 and day 22 either.

Discussion: A single administration of GdCl₃ produced slight hypointensity on T₂*-weighted images as shown in Figure 3 presumably due to susceptibility effects from gadolinium ions or a slight iron deposition caused by GdCl₃ [4]. The signal reduction by GdCl₃ alone accounted for less than 0.2 in RI. Therefore, it did not completely explain the prolonged hypointensity in the severe injury group. Since the rate of recovery from the initial hypointensity up to day 8 was slow in both the mild and severe injury groups compared with the control group, we considered that the prolonged hepatic hypointensity after SPIO administration is likely to reflect the decreased exocytotic function of KCs. This finding implies the ability to evaluate the impaired exocytotic function of KCs by KC labeling with SPIO prior to the occurrence of liver damage would be useful for the early detection of liver damage. The possible application of this technique is early diagnosis of drug- or radiation-induced liver diseases in which KCs damage precedes hepatocytes damage.

Conclusion: SPIO-enhanced MRI demonstrated a delayed recovery of hepatic signal intensity in rats injected with SPIO prior to Kupffer cells damage.

References: [1]Invest Radiol 2002; 37 :292-298 [2]Proc. ISMRM 2010; 18: 2625 [3]J Leukoc Biol 1992; 52: 296-302 [4]Biochimie 2010; 92: 1343-1353

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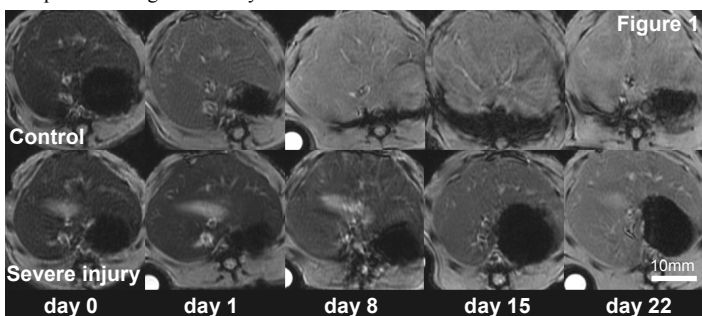


Figure 1 Axial T₂*-weighted MR images in the control and severe injury groups.

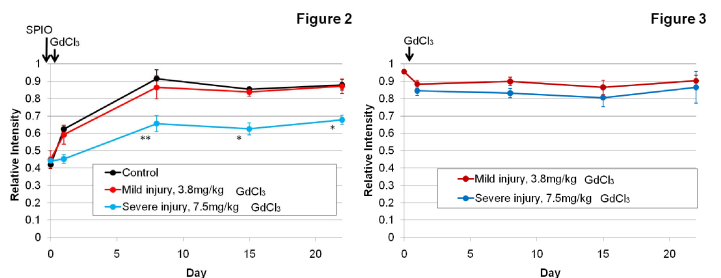


Figure 2 Relative intensity of the liver in the control, mild injury, and severe injury groups. Data are means ± SE (n=3). *p<0.05, **p<0.01 versus control rats on Tukey's test.

Figure 3 Relative intensity of the liver in the rats injected with GdCl₃ alone. Data are means ± SE (n=3).