Assessment of Hepatic Perfusion With Diffusion Weighted and Dynamic Contrast Enhanced ¹H MRI in CCl₄ Treated Rat Liver

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Introduction
Liver hemodynamics play an important role in hepatic function. Several methods have been proposed for the noninvasive quantification of hepatic perfusion, including clearance of xenobiotics, single-photon emission CT, positron emission tomography, and dynamic contrast enhanced (DCE) ¹H MR [1]. Thoeny et al. [2] proposed the use of diffusion-weighted (DW) ¹H MRI for simultaneous estimation of both perfusion and diffusion without the use of an exogenous agent. The purpose of this study was to evaluate the use of DW and DCE ¹H MRI for the assessment of hepatic perfusion and diffusion parameters in a CCl₄-induced rat liver injury model. This model is widely used to study the mechanism underlying the hepatotoxic effects such as steatosis, hepatitis, fibrosis, and cirrhosis [3].

Methods
MRI experiments were performed on male Sprague-Dawley rats weighing 300-400 g (n = 7). Acute liver injury was produced by a single gavage of 2.5 ml/kg mixture of CCl₄ and corn oil (1:1). All in vivo MRI was performed on a 9.4 Tesla, 31-cm horizontal Varian bore system. DW and DCE ¹H MRI of the liver were collected with a birdcage coil (ID = 63 mm, length = 190 mm) tuned to 400 MHz. MRI experiments were performed before and 24 h after the CCl₄ treatment. Multi-slice DW ¹H MRI was collected using a modified spin-echo sequence and the following parameters: TR/TE = 1000 ms/21 ms, Δ = 6 ms, Δ = 11 ms, matrix size = 256 × 128, FOV = 80 mm × 80 mm, number of slices = 12, slice thickness = 0.5 mm, slice gap = 1.5 mm, and δ = 0, 10, 20, 30, 100, 220, 350, 600, 1000, and 1600 s/mm². Total data collection time for a set of DW ¹H MRI at the ten b values was ~23 min. After collecting DW images, 0.2 mmol/kg of Gd-DOTA was manually injected over a 30 s interval through a 26-gauge catheter placed in the tail vein. All bolus injections were performed by the same investigator. DCE ¹H MRI was obtained using a gradient-echo sequence and the following parameters: TR/TE = 10 ms/3.1 ms, matrix size = 256 × 128, FOV = 64 mm × 64 mm, number of slices = 1, and slice thickness = 4 mm. 200 images were collected over approximately 13 minutes, with 4.5 s acquisition time per image. PSI-PLOT software was used to analyze DW and DCE ¹H MRI data. DW MRI signal intensity (SI) versus b value data were fit to the following biexponential equation:

\[ SI = A_0 + A_1 e^{-bADC_{fast}} + \left(1 - A_1\right) e^{-bADC_{slow}} \]

where \( A_0 \) is signal intensity for \( b = 0 \) s/mm², ADC_fast and ADC_slow are the fast and slow ADC components which are related to tissue perfusion and random molecular diffusion of water, respectively, and \( A_1 \) is the relative contribution of ADC_fast which is related to the relative vascular volume or the signal fraction of fast moving ADC. ¹H images were reconstructed using the Image Browser software. The kinetics of contrast agent uptake were estimated by measuring the area under the curve (AUC) over the first 60 s after the contrast agent arrival, as well as by fitting the DCE MRI SI versus time data to a triexponential function [4].

Results
CCl₄ intoxication decreased body weight by 5% (P < 0.0001). Fig. 1 shows that CCl₄ treatment caused moderate multifocal infiltration of fat in hepatocytes, infiltration of lymphocytes around the portal triads, scattered or moderate hepatocellular degeneration, and mild vascular congestion (Fig. 1). After CCl₄ treatment, the liver ¹H SI with \( b = 0 \) s/mm² was almost 1.5 times higher compared to untreated liver in T₁. Plots of DW ¹H MRI signal intensity as a function of b value, before and 24 h after CCl₄ treatment, are shown in Fig. 2. The plots were biexponential in both cases. \( A_0 \) was not affected by CCl₄: 0.56 ± 0.06 (baseline) and 0.47 ± 0.08 (CCl₄). However, 24 h after CCl₄ administration ADC_fast was drastically decreased by 71%, from 27.3 ± 8.1 × 10⁻³ mm/s (P < 0.05, Fig. 2, Table). Furthermore, ADC_slow was also significantly decreased 24 h post CCl₄ treatment, from 1.2 ± 0.2 × 10⁻³ mm/s to 0.4 ± 0.2 × 10⁻³ mm/s, P < 0.05 (Fig. 2, Table).

Unlike ADC_fast (measured from DW MRI), AUC (measured from DCE MRI) did not change after CCl₄ treatment. In addition, there was no correlation (R² = 0.55) between ADC_fast and AUC values. Fig. 3 shows the fit of DCE MRI liver SI versus time data to the triexponential function: inflow (first 60-70 s), fast outflow (~ 70-200 s), and slow outflow (~ 200 – 800 s). Only the contrast agent inflow kinetics showed a decrease from 11 ± 3 s⁻¹ (baseline) to 5 ± 1 s⁻¹ (CCl₄, P < 0.05) while both fast and slow outflow components did not show any significant difference.

Discussion
The data presented here show that ADC_fast in the liver is significantly decreased 24 h after CCl₄ treatment, while the relative contribution of ADC_fast (associated with the relative vascular volume) does not change. This decrease may be because of restricted perfusion in congested microvessels as was shown by histology. A slight decrease in inflow slope detected using DCE MRI partly supports DW MRI and histology data. However, more studies of the transition from vessels to the liver representing permeability, and the transition from the liver to vessels representing washout, need to be done. CCl₄ also significantly decreases ADC_slow which can be explained by compartmental changes in liver tissue, such as cellular swelling and hepatocellular degeneration leading to a coagulative type of necrosis. The cellular swelling may also result in a decrease in extracellular space and restriction of water diffusion. In addition, our previous data [5] show that the acute effect of CCl₄ in rat liver is associated with a significant decrease in the ATP/Pi ratio in hepatocytes from 1.24 to 0.94 (P < 0.01) and a drastic increase in intracellular Na⁺ from 17 to 49 mM (P < 0.0005). These metabolic changes lead to a decrease in intracellular water diffusion that plays an important role in total tissue ADC as well [6].

Conclusion
A biexponential model for analysis of non-invasive DW ¹H MRI provides important information about toxic transformation in capillary liver tissue perfusion and water molecular diffusion. Recognition of both perfusion and diffusion components of water ADC may be important for monitoring response to therapy of liver disease, such as steatosis, fibrosis, hepatitis, and cirrhosis.