Off Resonance Spectroscopic Imaging of Iron Oxide Nanoparticles at Dilute Concentrations and High Field Strengths

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Introduction: Superparamagnetic iron oxide nanoparticles have been used in molecular imaging both to label cells as well as to detect specific molecular targets on their surfaces. Generally, T_2* weighted imaging techniques have been used to image these nanoparticles, which generate strong negative signal enhancement in the areas where they are present. While these T_2* weighted techniques have proven to be highly sensitive, capable of detecting contrast agent concentrations in the picomolar range, concerns have been raised about the linearity of the signal changes caused by these contrast agents. Specifically, the ability to correlate changes in signal intensity with the number of iron-oxide labeled stem cells has been questioned. Recently, Off-Resonance Spectroscopic Imaging (ORSI) techniques, first demonstrated by Cunningham *et al* (Mag. Reson. Med. v53, p999-1005, 2005), have been proposed as an alternative mechanism with which to image iron-oxide nanoparticles. These ORSI sequences generate bright contrast in the vicinity of iron oxide and have been shown to detect labeled stem cells with high linearity at low field strengths (1.5 Tesla). However, the performance of these sequences at higher field strengths and in the presence of lower concentrations of iron oxide than those seen in labeled stem cells is not yet known. In particular, no detailed studies have been performed to study of the dependence of the maximal induced chemical shifts and the relaxation times on the iron-oxide concentration. Such information is crucial for understanding and optimizing the ORSI technique. In addition, to date no one has exploited the potential of ORSI techniques to selectively image different contrast agents and to suppress susceptibility artifacts. The aims of our study were thus to (1) characterize the performance of ORSI at field strengths ranging from 4.7 to 14 Tesla, (2) examine the sensitivity of ORSI at concentrations of iron oxide that might be seen when surface targeted probes are used, and (3) to develop sequences to selectively image susceptibility agents with different induced chemical shifts.

Materials and Methods: We have developed a variant of the ORSI technique that uses an “on-resonance” water suppression pulse with a variable frequency bandwidth and a subsequent spin-echo detection sequence, with a wide detection bandwidth, to image the “off-resonance” water molecules. Monocrystaline Iron Oxide Nanoparticle (MION) concentrations ranging from 2-64 ug Fe/ml were imaged. For the 14 Tesla acquisitions, the samples were placed in 3 mm o.d. NMR tubes and then placed in a 15 mm centricon tube filled with water. Both the chemical shift and the reduction in T_2 and T_1 relaxation times induced by these iron oxide particles were studied. The effect of varying the water suppression bandwidth on the detectability of various concentrations of iron oxide was also studied. The water suppression bandwidths used to image the phantom at 14 Tesla ranged from 50 to 500 Hz.

Results and Discussion: T_1/T_2 relaxation times of 1650/33 ms, 1501/28 ms, 1026/11 ms, 752/6 ms, and 460/4 ms were measured at 14 Tesla for MION concentrations of 2, 4, 8, 16, and 32 µg Fe/ml, respectively. Representative images, acquired at 14 Tesla, of MION samples containing 8, 16 and 32 ug Fe/ml are shown in Figure 1. The images are from left to right: T_2 weighted spin-echo image of the phantom, and ORSI images of the phantom with water suppression bandwidths of 50, 75, 125, 250, and 375 Hz, respectively. By varying the water suppression bandwidth different MION concentrations could be selectively imaged. Of note, susceptibility artifacts due to air bubbles were substantially suppressed at water suppression bandwidths greater than 250 Hz. At the minimum 50 Hz water suppression bandwidth (dictated by the “on resonance” water linewidth), no ORSI signal was observed for MION concentrations of <8 µg Fe/ml, indicating that their respective MION induced chemical shifts must be less than 50 Hz, even at 14 Tesla. This establishes a lower bound MION detectability limit in fluid solution for ORSI of ~8 µg Fe/ml. The very short T_2 relaxation times measured at 14 Tesla for high MION concentrations requires the use of very short TE’s and suggests that lower magnetic field strengths may be desirable to detect high MION concentrations by ORSI.

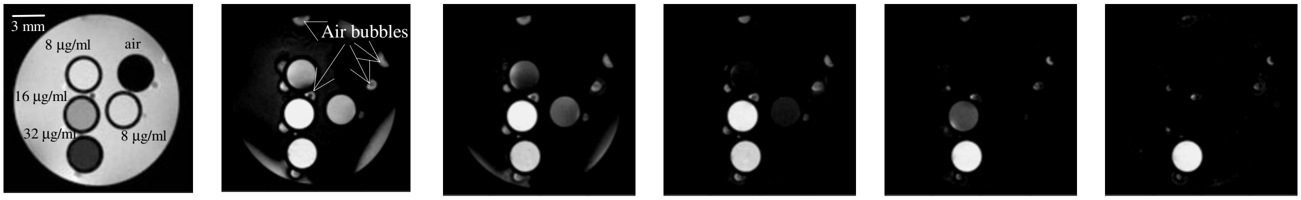

Figure 1: MION phantom consisting of 3 mm NMR tubes filled with air or with 8, 16, or 32 µg/ml of MION. The NMR tubes are immersed in a water bath. Spin-echo and off-resonance spectroscopic images were acquired on a 14 Tesla Bruker Avance scanner. (A) Spin-echo image were acquired with TE/TR = 10/4000 ms. Off resonance spectroscopic images were acquired with TE/TR = 3.5/1000 ms and water suppression bandwidths of (B) 50, (C) 75, (D) 125, (E) 250, and (F) 375 Hz.

Conclusions: In addition to providing bright image contrast for susceptibility based contrast agents, ORSI provides a technique to selectively image different susceptibility contrast agents with different susceptibility induced chemical shifts. The maximal resolvable MION based chemical shift, at 14 Tesla in fluid solution, is 50 Hz, corresponding to a minimum detection limit for ORSI of 8 µg Fe/ml of MION. A role for ORSI imaging of labeled stem cells at low field strengths appears to be emerging. The utility of the technique at higher field strengths and for the detection of more dilute concentrations of iron oxide will require extensive further study.