Quantitative in vivo Imaging of Low Concentrations of Iron Oxide Nanoparticles with Adiabatic Preparation Pulses

Steven Harris[1], Liya Wang[2], Jing Huang[2], Lei Zhou[1], Hui Mao[2], and Xiaoping Hu[1]

[1]*Department of Biomedical Engineering, Georgia Institute of Technology / Emory University, Atlanta, GA, United States,* [2]*Department of Radiology, Emory University, Atlanta, GA, United States*

Introduction

Adiabatic pulse preparation can be used to localize and quantify superparamagnetic iron oxide (SPIO) nanoparticles for cellular and molecular imaging [1]. While an adiabatic full passage preparation pulse normally inverts the magnetization, spins diffusing near the strong, microscopic magnetic field gradients near the nanoparticles are not able to follow the adiabatic passage. The failure of the adiabatic condition for these spins results in a decrease in the net magnetization after the preparation pulse that is proportional to the number of spins failing the adiabatic condition. It has been shown that by comparing images acquired with and without the adiabatic preparation pulse an adiabatic contrast can be generated that is linearly increasing with increasing iron oxide nanoparticle concentration [1]. While the adiabatic frequency sweep may produce contrast from other off resonance components, a magnetization transfer (MT) compensated approach has been proposed using a zero passage preparation. Since the average diffusion distance of the spins during the preparation pulse increases with the square root of the pulse duration and the total power doubles with the application of two adiabatic full passages, Figure 1 shows that by doubling the full passage contrast and subtracting the zero passage contrast we may produce a contrast that is less sensitive to MT and more specific to the diffusion of the spins near the nanoparticle that is the mechanism of the adiabatic contrast.

While many methods have been proposed for generating increased signal from SPIO nanoparticles [2], most rely on changes in the macroscopic magnetic field and may require calculating the volume of increased signal for contrast quantification. In this work, the adiabatic pulse preparation technique is used to quantify SPIO nanoparticles throughout the mouse liver *in vivo*, and *ex vivo* organ iron measurement is used to confirm that the adiabatic contrast remains linear correlated with increasing iron concentration *in vivo*.

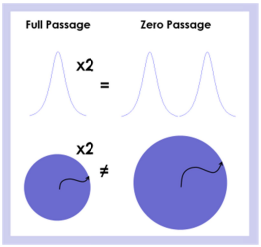

Figure 1: Since from full to zero passage the diffusion distance does not double with the doubling of the preparation pulse power, the two effects can be decoupled.

Methods

A 10 msec hyperbolic secant adiabatic full passage [3] prepared Turbo Spin Echo (TSE) sequence was implemented on a 3 Tesla Siemens Magnetom Trio (Siemens Medical Solutions, Malvern, PA). The adiabatic zero passage pulse consisted of two adiabatic full passages applied back-to-back. The adiabatic full passage contrast image was calculated by taking the normalized difference of images acquired with and without adiabatic pulse preparation, and the MT compensated image was calculated by doubling the full passage contrast and subtracting it from the zero passage contrast. Varying concentrations of SPIO nanoparticles were used to confirm the linear correlation of the adiabatic contrast with iron concentration for imaging parameters: TR: 5 sec, TE: 14 msec, Turbo Factor: 4, Field of view: 90 mm x 90 mm, Matrix: 128 x 128.

Female balb/c mice (4-6 weeks) were divided into groups of three and received doses of 1, 2.5, 4, or 5 mg/kg amphipilic triblock copolymer coated iron oxide nanoparticles with core size 15 nm and zeta potential -30 mV (Ocean NanoTech, Springdale, AR). The nanoparticles were administered by tail vein injection and allowed to circulate and accumulate in the liver for 24 hours prior to imaging (average blood half time 8-10 hours). Animals were anesthetized by ketamine/xylazine and images were acquired through the liver. Spin-echo images were used to select a region of interest within the liver, and all image analyses were performed in MATLAB (MathWorks, Natick, MA). Following image acquisition, the animals were sacrificed, and the liver tissue was digested in nitric acid. The iron concentration was determined using a calibration curve of standard iron solutions, 1,10-phenanthroline and spectrophotometry. This value was then subtracted from a baseline liver iron concentration of 0.32 mg_{iron}/g_{tissue} to yield a normalized iron concentration specific to the nanoparticles.

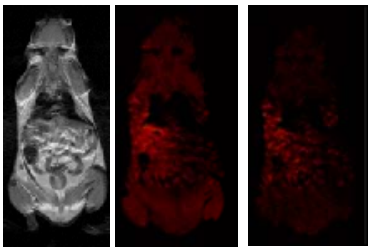

Figure 2: Spin-echo image of animal (left), and adiabatic contrast image merged with spin-echo image highlighting liver (center). MT compensated approach appears to decrease contrast from tissue outside the liver (right).

Results and Discussion

While orignailly implemented in a spin echo sequence, the adiabatic pulse preparation technqiue can be applied to a TSE sequence to reduce total imaging time to be compatible with *in vivo* imaging. Accelerated image acquisition apporaches can be used without effecting the contrast quantification, since the contrast is defined by the preparation pulse, which is very short compared to the imaging time. Figure 2 shows that after the SPIO nanoparticles circulate and accumulate in the liver the adiabatic contrast image shows increased contrast intensity in the liver region. On the far right pannel, the proposed MT compensated approach shows that while the liver area remains bright the background contrast in the other tissues is reduced. This approach may produce a contrast that is more specific to the iron oxide nanoparticles. With the overall goal of quantitative molelecular imaging, Figure 3 shows that the contrst measrued in the liver is linearly correlated with the measured *ex vivo* iron concentration (Full passage contrast: $R^2 = 0.7366$ and MT compensated contrast: $R^2 = 0.7398$). While previous phantom and *in vitro* studies showed a much higher linear correlation, the inhomogeneous distribution of the nanoparticles in the liver may confound the correlation of the image contrast from a single slice with the overall organ iron content. While the zero crossing of the MT compensated contrast appears negative, similar to phantoms studies as the MT effects are not uniformly addative, it is important to note that extendnig the linear fit for the full passage contrast yields a zero crossing for the contrast at a zero iron nanoparticle concentration.

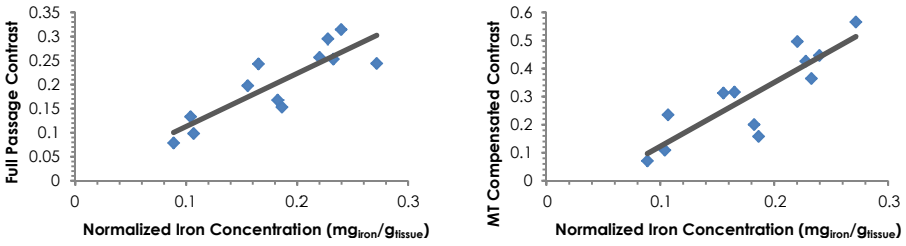

Figure 3: Adiabatic full passage (left) and MT compensated (right) liver contrast showing a linear correlation with tissue iron concentration by biochemical analysis.

Conclusion

The adiabatic pulse preparation approach for imaging SPIO nanoparticles produces a contrast *in vivo* that is linearly increasing with increasing iron content as measured *ex vivo*. The low iron concentrations used suggest that this approach may be suitable for further *in vivo* quantitative molecular MR studies.

Acknowledgements: This work was supported by NIH grant U01HL080711 and the Georgia Research Alliance.

References: [1] Harris S et al. *Proc ISMRM 2010*; 18:4933. [2] Liu W et al. *NMR Biomed* 2008; 21:242-50. [3] Garwood M, DelaBarre L. *J Magn Reson* 2001; 153(2):155-77.