In Vitro Relaxivities Studies of Gadolinium Carbon Nanotubes at 3T

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Introduction

Gadolinium loaded ultra-short single wall carbon nanotube was recently proposed to be a high r1 relaxivity superparamagnetic MR contrast agent (1-3). However, the performance of these agents at clinical high field MRI is unknown. In this paper, we present the r1/r2 relaxivities results of Gadonanotubes based on in vitro phantom imaging at 3T. Gadonanotubes with different surfactant coatings were tested and compared to a commercial gadolinium chelate (Gd-DTPA) and monocrystalline iron-oxide (MION), which is another class of superparamagnetic MR contrast agent.

Methods

Phantom Samples Preparation

The Gd^{3+}@US-tubes (Gadonanotubes) were synthesized following a previously published procedure (1). Briefly, the procedure involved the soaking of ultra-short single walled carbon nanotubes (US-tubes, 20-50nm in length and 1.0nm in diameter) in aqueous Gd^{3+} solution followed by sonication. The Gd^{3+}-loaded US-tubes were then washed extensively with HPLC grade water to ensure the absence of external Gd^{3+} ions. The Gadonanotubes as produced were dispersed in 1.0% Pluronic F108 (biocompatible surfactant) solution for the relaxivity studies.

Due to their hydrophobic nature, the nanotubes exist in the form of bundles. Hence, portions of US-tubes were reduced using Na^0/THF to yield individual US-tubes (5). These individual nanotubes were loaded with Gd^{3+} in the same way as above. 10 mg of these nanotubes were dispersed in 1.0% solution of pluronic F108 and used for relaxivity studies. Another 10 mg of these gadonanotubes were refluxed with Carboxy dextran (MW 10K) solution to yield dextran-coated individual gadonanotubes.

Three Gadonanotube phantoms were prepared. They are a) Individual Gadonanotube at 0.083 mM Gd concentration in 1.0% Pluronic F108 solution (Individual Gadonanotube), b) Bundled Gadonanotube at 0.104 mM Gd concentration in pluronic solution (Bundled Gadonanotube), and c) Individual Gadonanotube at 0.0265 mM Gd concentration with dextran coating (GadoDex). These Gadonanotube phantoms were tested against d) dextran-coated MION-47 (CMIR, MGH, Boston, MA) phantom at 3mM Fe concentration diluted with physiological saline and e) 20mM Gd Magnevist phantom diluted with physiological saline along with two substrate phantoms from 1.0% Pluronic F108 solution and physiological saline. All the solution phantoms were cylindrical in shape with 1cm diameter and 1cm height with the cylinder axis parallel to the main magnetic field.

In Vitro Phantom Studies at 3T

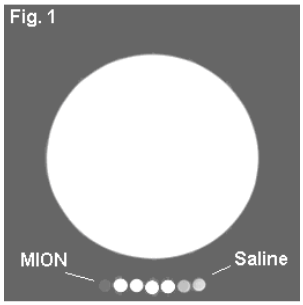
All the in vitro MRI experiments were conducted using GE 3T Signa MRI system (General Electric, Milwaukee, WI). The setup of the experiment is shown in Fig. 1. All the phantoms are lined up at the bottom, started from the left to right: MION-47, Bundled Gadonanotube, GadoDex, Magnevist, Individual Gadonanotube, 1.0% Pluronic F108 solution and saline. A standard ball-shaped quality assurance phantom from the manufacturer was used to ensure proper shimming. Hahn spin-echo sequence was used to image all the phantoms to study their r1 relaxivities with TE=10ms, TR=33ms, 50ms, 66ms, 150ms, 350ms and 500ms. A 5mm single slice image covering all the phantoms was obtained for each TR for relaxivity calculation. Circular ROIs were defined for each phantom to measure the mean image intensity. Background noise effect was removed by subtracting the mean phantom image intensity with mean image noise. A non-linear fitting module in Matlab (Mathworks, Natick, MA) was used to fit the T_1 of each phantom based on the signal form $S=S_0*(1-\exp(-TR/T_1))$. Similar imaging experiments were conducted to evaluate the r2 relaxivities of the phantoms by Hahn spin-echo sequence with TR=500ms, TE=10ms, 11ms, 12ms, 13ms, 14ms, 15ms, 25ms, 50ms, 75ms and 100ms. T_2 of each phantom were obtained by linear fitting $\log(S)=\log(S_0)-TE/T_2$. To evaluate the r2* relaxivities of the phantoms, gradient-echo sequence was used with TR=500ms, TE=5ms to 20ms. To capture the rapid transverse relaxivity of the MION phantom, gradient-echo images were acquired every 0.5ms from TE=5ms to 7ms. T_2* of each phantom were obtained similarly by linear fitting $\log(S)=\log(S_0)-TE/T_{2*}$.

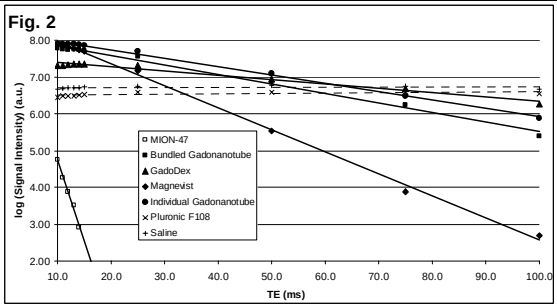
Results

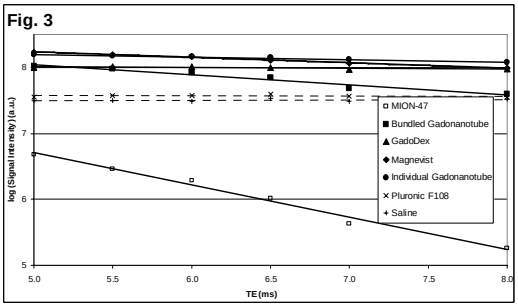
In the r1 analysis, we cannot detect r1 values reliably for any of the Gadonanotube phantoms due to the slow longitudinal recovery beyond 300ms at the concentration level of our phantoms. The r1 relaxivities of MION-47 and Magnevist were determined to be 4.53 $mM^{-1}s^{-1}$ (95% CI [3.69 5.75]) and 1.5 $mM^{-1}s^{-1}$ (95% CI [1.29 1.94]) respectively. In the r2/r2* relaxivity analysis, the log signal intensity of the phantoms were plotted against TE for spin-echo and gradient-echo imaging in Fig. 2 and Fig. 3 respectively. The r2 and r2* relaxivities of all the phantoms are summarized in Table 1.

Table 1: r2 and r2* relaxivities of Gadonanotubes, Magnevist and MION-47

	MION-47	Bundled Gadonanotube	GadoDex	Magnevist	Individual Gadonanotube
r2 ($mM^{-1}s^{-1}$)	143.77 (R^2=0.9912)	245.83 (R^2=0.9935)	428.93 (R^2=0.9766)	2.98 (R^2=0.9979)	270.68 (R^2=0.9966)
r2* ($mM^{-1}s^{-1}$)	161.37 (R^2=0.9875)	1454.81 (R^2=0.9586)	298.11 (R^2=0.4571)	4.45 (R^2=0.9984)	436.14 (R^2=0.9762)







Discussion and Conclusion

The r1 and r2 relaxivity of MION-47 at 3T is very similar to Resovist (4), which is another type of iron oxide nanoparticles. Our r1 measurement of Magnevist is slightly lower than others (4), which can be attributed to the fast r1 relaxivities at 20mM concentration and the dilution in saline instead of water. Nevertheless, the r2 of Magnevist is consistent with literature (4). The r2 relaxivity of dextran-coated Gadonanotubes is about two times stronger than bundled/individual Gadonanotubes. Bundled Gadonanotubes have at least three times higher r2* relaxivity compared to individual Gadonanotubes and about ten times stronger r2* relaxivity compared to iron oxides already in the market (4). Gadonanotubes may be a promising MR contrast agent for in vivo cell tracking.

References

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