A field comparison of r1 and r2* relaxivities of Gd-DTPA in aqueous solution and whole blood: 3T versus 7T

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INTRODUCTION: Gd-DTPA (Magnevist™) is one of the most widely used MRI contrast agents (CAs) today. The relaxation enhancement of Gd-DTPA depends on its relaxivity which in turn depends on factors like magnetic field strength, macromolecular content, pH and temperature.[1, 2, 3, 4] Knowledge of relaxivity is essential in many MRI areas. The Gd-DTPA concentration ([Gd]) is calculated from signal enhancement in DCE-MRI studies using r_1 relaxivity value assuming a linear relationship between [Gd] and longitudinal relaxation rate (R_1). While r_1 relaxivity has been shown to slightly decrease [1] with increasing field strength, r_{2*} relaxivity increases and can dominate signal changes especially at higher CA concentrations. In addition, the strong effect of compartmentalization on T_{2*} shortening can also change the shape of the contrast enhancement curve in tissue and thus the quantification of pharmacokinetic parameters in DCE MRI studies. [5] By knowing the r_1 and r_{2*} values and hence the calibration curve for blood and aqueous solution one can potentially determine [Gd] in vivo for human blood and extravascular extracellular space. The goal of this study was to measure r_1 and r_{2*} relaxivity of Gd-DTPA in bovine blood and aqueous solution at 3T and 7T. To our knowledge this is the first time that the r_{2*} characteristic for blood has been measured at 7T.

METHODS: Commercially available formulation of Gd-DTPA (Magnevist, Bayer Healthcare Pharmaceuticals Inc. Wayne, NJ) having a concentration of 0.5 M was mixed with bovine blood and aqueous solution (pH 7) in 50 ml centrifuge tubes to obtain final concentrations of 20, 10, 5, 2.5, 1.0, 0.5, 0.25, 0.12, 0.06, 0.03, 0.01 and 0.008 mM by serial dilution. Bovine Blood was obtained from a slaughterhouse (Dakota Premium Foods, St Paul, MN). Bovine erythrocytes have similar shape, size, and water permeability as human cells [6].The blood was treated with Heparin (Elkins-Sinn, Cherry Hill, NJ) and used within 2 days. Sodium Azide was added to the blood samples as a preservative. Aqueous solutions of pH 7 were made using 1 M HEPES buffer solution (Sigma Aldrich, Switzerland).Thirteen test tubes of Gd-DTPA solutions were placed inside a plastic container which in turn was put in a plastic trough. Both the container and the trough were filled with 0.45% saline solution. This was done to ensure field homogeneity over the phantom, for loading the transmit coil and for efficient heat transfer from the water bath hoses. All studies were performed at a constant temperature of 37±1°C maintained by surrounding the plastic container with hoses from a heated bath (Thermo Scientific Neslab RTE-7 Digital One). The complete phantom setup is shown in figure 1. The temperature was monitored using a thermistor (YSI 400 series) and DigiSense (Cole-Parmer) Temperature Controller. All 3T measurements were performed on a Siemens Magnetom Trio scanner. Signal detection was achieved using a 12 channel head coil. RF transmission was performed using the scanner body coil. All 7T measurements were done on a Magnex 7T, 90 cm bore magnet with Siemens console and head gradients using a trasceive head coil.

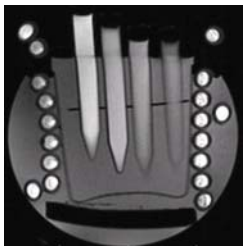

Figure 1: Gd-DTPA phantom setup. The circles are the water bath hoses.

T_1 Measurement: An IR-Turbo Flash (TFL) sequence with a slice selective π pulse was used. Other values included: TR, 10 s; TE, 1.26ms; Flip angle, 8°; Acquisition matrix, 128²; Field of view, 180mm(7T), 280mm(3T) ; Slice thickness, 3.5mm; Number of Averages, 2. The inversion time (TI) was varied from 23ms to 8850ms. Average MR signal intensities were obtained from selected ROIs in the TFL images. We assumed a negligible T_{2*} effect across each ROI after localized B_0 shimming was performed.. The T_1 values were obtained by fitting the ROI signal intensities for different TI values. A linear relationship between R_1 (R_1= $1/T_1$) and [Gd] was assumed to calculate r_1. **T_1 IR-TFL Measurement Validation**: T1 measurement done using the IR-TFL method was validated by using the inversion recovery spin echo (IRSE; TR, 3s; TE, 11ms; Flip angle, 90°; Acquisition matrix, 256²; Field of view, 300mm; Slice thickness, 5mm; Number of Averages, 1; TI, 23ms) sequence for the same measurement at 3T.A mono-exponential, three parameter curve fit program written in IDL (ITT, Visual Information Solutions, Boulder, CO) and linear fitting routines in Origin (OriginLab Corp., Northampton, MA) were used to calculate the T_1 and T_{2*} values. **r_1 Measurement:** T_1 values for lower concentrations (0-5mM) were obtained by the IR-TFL method. The DESPOT method (3D Acquisition, TR, 14ms; TE, 10ms; Flip angles, 20° and 60°; Acquisition matrix, 128²; Field of view, 300mm; Slice thickness, 2mm; Number of Averages, 1) was used to obtain the T_1 values for high concentrations (5-25mM). **T_{2*} Measurement**: A multi-echo gradient echo sequence was used. Other values included: TR, 100ms; min TE, 1.84ms(7T), 1.67ms(3T); Flip angle, 10°; Field of view, 280mm; Slice thickness, 3mm; Number of Averages, 4.**RESULTS:** The r_1 values reported in table 1 are obtained from the IR-TFL method. The TFL values differed by 3% to those obtained using the IRSE method.The errors take into consideration the error propagation from volumetric analysis, non linear fit (T_1& T_{2*} calculation) and linear fits (r_1 & r_{2*} calculation). The standard error in the fitting parameters is calculated from the square root of a main diagonal value of the variance-covariance matrix. Linear relationship between the [Gd] and R_1 was observed only till 5 mM using the IR-TFL method. The difference between the r_1 values calculated using the IR-TFL and DESPOT method was ~ 16%. As can be seen from table 1, the r_1 values for aqueous solution and bovine blood decrease with increasing magnetic field strength as expected. Table 2 shows that there exists a linear relationship between R_{2*} and [Gd] for aqueous solutions. A quadratic relationship between the ΔR2* signal and [Gd] in blood has been demonstrated by Osch et al. [7] as shown in (1) where c_1, c_2 are constants and Hct is the hematocrit level. Table 2 shows that R_{2*} relaxation rate follows a quadratic relationship with [Gd] in the case of blood given by

$$\Delta R_2^* = c_1 \cdot \frac{Hct}{(1-Hct)^2} \cdot [Gd]^2 + c_2 \cdot [Gd] \qquad (1)$$

The T_{2*} value for zero [Gd] in blood at 7T and 3T was 12.36 and 84.57 ms respectively. T_{2*} value for 10 mM [Gd] in blood at 7T and 3T was 2.02 and 7.59 ms respectively .The 7T T_{2*} value for 10 mM seems reasonable as it is close to our in vivo 7T bolus passage T_{2*} measurement (~2ms).

DISCUSSION: A linear relationship between R_{2*} of aqueous solution and [Gd] can be understood in terms of the absence of Hct and macromolecules from the solution [7]. As R_1 and R_2 rates increase linearly with Hct [8] and that Bovine Hct (32%) < Human Hct (40-53%) [9] r_1 and r_{2*}relaxivity values in human blood will be greater than values reported in this study. There is some variability in the r_1 values published in literature. As a comparison our 3T r_1 value for aqueous solution is close to that obtained by Rohrer et al. [10] (r_1 = 3.1).

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Media	3T	7T
Aqueous Solution	3.29±0.03	3.10±0.01
Bovine Blood	3.59±0.02	3.48±0.06

Table 1: Gd-DTPA r_1 relaxivity (mM $^{-1}$s^{-1}) in aqueous solution and whole bovine blood.

Media	3T	7T
Aqueous Solution	4.8	5.4
Bovine Blood	$4.8[Gd]^2+0.7[Gd]+0.5$	$1.4[Gd]^2+8.7[Gd]+26.4$

Table 2: Gd-DTPA r_{2*} relaxivity (mM $^{-1}$s^{-1}) in aqueous solution and whole bovine blood.