High Concentration Relaxivities of Four Gadolinium-Based Contrast Reagents in *ex vivo* Physiologic Whole Blood and Plasma at 1.5 and 3.0T

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Introduction: In Contrast Enhanced MR Angiography (CE-MRA), reduced image quality with increasing contrast reagent (CR) dose has been reported for reagents with relatively high protein affinity (1). Possible explanations for reduced image quality include lower than expected longitudinal ($R_1 = 1/T_1$) or dominant transverse ($R_2^* = 1/T_2^*$) relaxation rate constants at high CR concentrations. Moreover, most relaxivities reported were measured in plasma rather than whole blood. To investigate relevant relaxivities, we have separately titrated approved CRs that do [gadobenate dimeglumine/MultiHance(MH) and gadofosveset trisodium/Ablavar(Ab)] and do not [gadoteridol/ProHance(PH) and gadobutrol/Gadovist/(GV)] interact with albumin into whole blood. We have determined ^1H_2O T_1, T_2, and T_2^* values for these samples at 1.5 and 3.0T.

Fig 1. ^1H_2O R_1 in Plasma at 3T

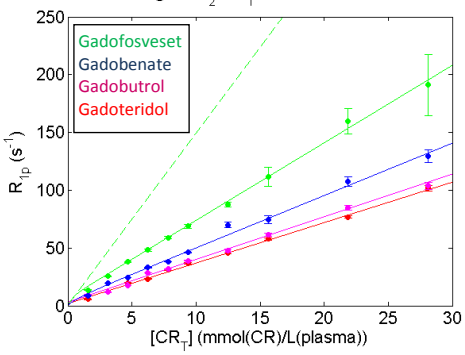


Fig 2. ^1H_2O R_1 in Whole Blood at 3T

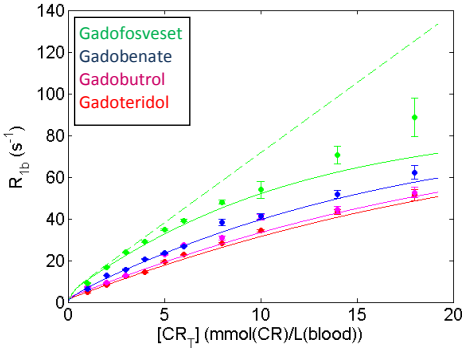


Fig 3. Apparent r_2 and r_2^* in Plasma at 3T

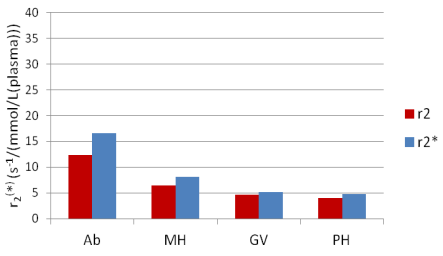
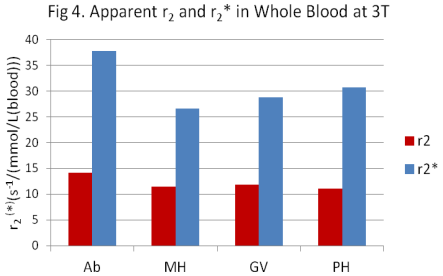


Fig 4. Apparent r_2 and r_2^* in Whole Blood at 3T



Methods: Measurements were performed on both 1.5T and 3.0T Achieva MRI scanners (Philips Healthcare, the Netherlands). The phantom consisted of two trays, each with 35 6 mL (13 x 55 mm) HDPE tubes embedded in 2% agar gel. These were filled with fresh, whole blood at 99% O_2 saturation, physiologic pH, 3.3 g/dL albumin, 36% hematocrit, held at 37°C, and periodically agitated to prevent RBC settling. The CR was added to make up [CR_T] values of 1, 2, 3, 4, 5, 6, 8, 10, 14, and 18 mM {mmol(CR)/L(blood)}. The ^1H_2O T_1, T_2, and T_2^* values were measured in whole blood using a Look-Locker sequence [TR/TE/ΔTI/α/NSA/#TI = 1000/1.95/5.0/8°/3/128], multi-echo TSE [TR/ΔTE/#TE = 2000/6.7/32], and multi-echo FFE [TR/TE/ΔTE/α/NSA/#TE = 200/1.3/1.7/35°/4/32], respectively, allowing simultaneous measurement of all samples in the phantom. After eight hours of settling, the measurements were repeated for the plasma supernatants.

Results: **Figure 1** shows the [CR_T]-dependence [CR concentration in mmol(CR)/L(plasma)] of the longitudinal relaxation rate constant R_{1p} for all four contrast agents in plasma at 3T (1.5T results were qualitatively similar to 3T). The error bars represent the confidence interval for the measured R_{1p} resulting from the Look-Locker fittings. The non-linearity at low [CR_T] (*e.g.*, < 2 mM) is likely caused by interaction with proteins, as it is most pronounced for MH and Ab. We can approximate this macromolecular (M) interaction with a 1:1 stoichiometry:

$$K_b = [CRM_p]/([CR_p][M_p]) \quad [1]$$

$$R_{1p} = r_{1bound}[CRM_p] + r_{1free}[CR_p] + R_{10} \quad [2]$$

In these, K_b is the binding equilibrium constant, [CRM_p], [CR_p], and [M_p] are equilibrium plasma concentrations, r_{1bound} is the CR relaxivity of CRM, r_{1free} is the relaxivity of unassociated CR, and R_{10} is R_1 in the absence of CR. Fitting the MH and Ab data points with Eqs. [1,2] as f([CR_T]) yields the solid curves in Fig. 1 [setting K_b = 1.5 (MH) and 12.53 (Ab) $(mM)^{-1}$ (2,3), [M_T] = 0.497 mM - for human serum albumin (HSA) in plasma, and R_{10} = 0.6 s^{-1} (3T) or 0.8 s^{-1}(1.5T)]. The dashed linear asymptote (Ab) demonstrates the nonlinearity and illustrates the oft-reported high relaxivity at lower [CR_T] (*e.g.*, < 2 mM) for albumin-interacting CRs (4).

Figure 2 shows the [CR_T]-dependence [CR concentration in mmol(CR)/L(blood)] of whole blood ^1H_2O R_{1b} for all four CRs at 3T: the points are the measured values. The solid curves are the predicted R_{1b} values using the two-site-exchange [2SX] model for intra- and extracellular water. In this model, the fast exchange regime (FXR) allowed R_{1b} is given by (5):

$$R_{1b} = (1/2)[R_{1i} + R_{1p} + \tau_i^{-1} + p_i/(\tau_i(1 - p_i))] - (1/2)\{[R_{1i} - R_{1p} + \tau_i^{-1} - p_i/(\tau_i(1 - p_i))]^2 + 4p_i/(\tau_i^2(1 - p_i))\}^{1/2} \quad [3]$$

where R_{1i} and R_{1p} are the relaxation rate constants for intra- and extracellular (plasma) ^1H_2O, respectively, and τ_i and p_i are the mean lifetime and mole fraction, respectively, of intra-erythrocyte water molecules. For our prediction, we set $R_{1i} = R_{10}$ = 0.6 s^{-1} (3T) or 0.8 s^{-1} (1.5T) and R_{1p} as the empirical fitted Fig. 1 curve [*i.e.*, R_{1p} = f([CR_T])], p_i = 0.36 for blood of this hematocrit and the consensus value of τ_i = 10 ms (6). The predicted R_1 curves agree with the experimental data very well. The smaller relaxation rate constants (at smaller [CR_T]) are well approximated by the fast exchange limit (FXL), where $|R_{1i} - R_{1p}| << (1/\tau_i + 1/\tau_p)$. In the FXL, R_{1b} is given by:

$$R_{1b} = p_iR_{1i} + (1\text{-}p_i)R_{1o} \quad [4]$$

and is the dashed curve in Fig. 2 (Ab). The FXL prediction is clearly different than the experimental data, and demonstrates the sensitivity of the data to the trans-membrane water exchange kinetics.

Figure 3 shows the apparent transverse relaxivities (r_2 and r_2^*) for each CR in plasma at 3T. These were determined by fitting, *e.g.*, the measured $R_{2p}^{(*)}$ values with $R_{2p}^{(*)} = r_2^{(*)}[CR_T] + R_{20}$, where R_{20} was fixed at 5 s^{-1} for all transverse relaxation data fitting. This is a reasonable first approximation to the data, as all R_{2p} and R_{2p}^* rate constants increased approximately linearly beyond 2 mM and throughout the measured [CR_T] range. Similarly, **Figure 4** shows the apparent transverse relaxivities in whole blood. In plasma, r_2^* values are only slightly greater than r_2 and varied between CRs. In whole blood, r_2^* values are much greater than r_2 and there is less variation among CRs. The latter suggests a dominant transverse relaxation mechanism created by the susceptibility gradients consequent to the exclusion of paramagnetic CR molecules from the erythrocytes.

Discussion: In Contrast-Enhanced MR angiography (CE-MRA), first-pass blood [CR_T] may approach 15 - 20 mM. The non-linear [CR_T]-dependence of R_{1b} in conjunction with large R_{2b}^* may yield diminishing returns for CE-MRA performed at high [CR_T] (*i.e.*, rapid CR injection rates). These results may provide an explanation for diminishing return with CR dose and lead to optimization of dosing strategies in CE-MRA.

References: **1.** Schneider G, *et al.,* JMRI 26:1020-32(2007); **2**. Henrotte, *et al.,* Contr Med Mol Imag 2:258-61(2007); **3.** Caravan, *et al.,* J Am Chem Soc 124:3152-62(2002); **4.** Rohrer M, *et al.,* Invest Radiol 40:715-24(2005); **5.** Landis CS, *et al.,* MRM 44:563-74(2000); **6.** Kuchel PW, *et al.,* BioSyst 82:189-96(2005).