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

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Introduction: Accurate characterization of contrast reagent (CR) relaxivity in arterial whole blood is necessary for optimization of contrast enhanced MR angiography (CE-MRA) [1]. 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 in whole blood plasma. Limited 1.5 and 3.0T ^1H_2O T_2 and T_2* values [2] and some T_1 values [3] have been reported previously. This work explores the underlying mechanism of fast T_2* relaxation in oxygenated whole blood.

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 six mL (13 × 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. 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)}. ^1H_2O T_2 and T_2* values were measured in whole blood using a 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. ROI signal intensity data was fitted with a mono-exponential decay curve using non-linear least squares (Matlab, Natick, MA). After 6 hours of settling, the measurements were repeated for the plasma supernatants.

Results: Relaxation rate constant R_2 (≡ $1/T_2$) *vs.* [CR] is approximately linear in both whole blood and plasma (**Figure 1**). R_2', the rate constant for RF-refocusable transverse relaxation (≡ R_2* - R_2), is highly elevated in whole blood compared to plasma, and approximately twice as fast at 3.0T compared to 1.5T (**Figure 2**). R_2' in whole blood is approximately the same for all four contrast agents.

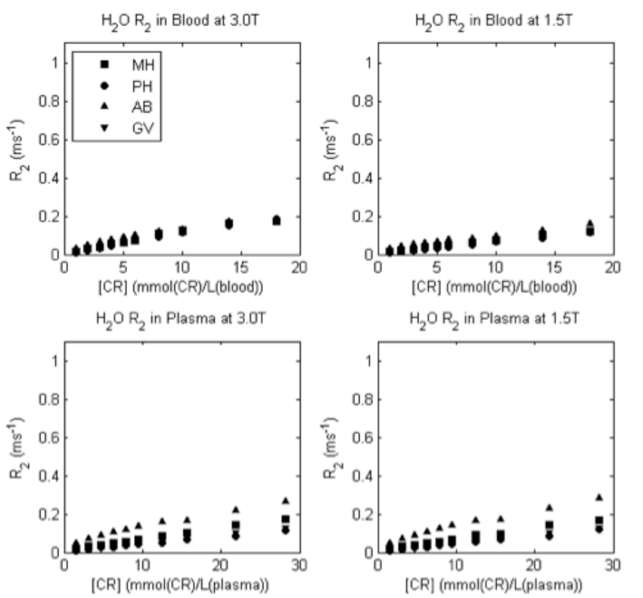

Figure 1. Measured R_2 in oxygenated whole blood (top) and plasma (bottom) at two field strengths. R_2 increases approximately linearly with [CR] in both whole blood and plasma, and exhibits CR-specific relaxivities in plasma.

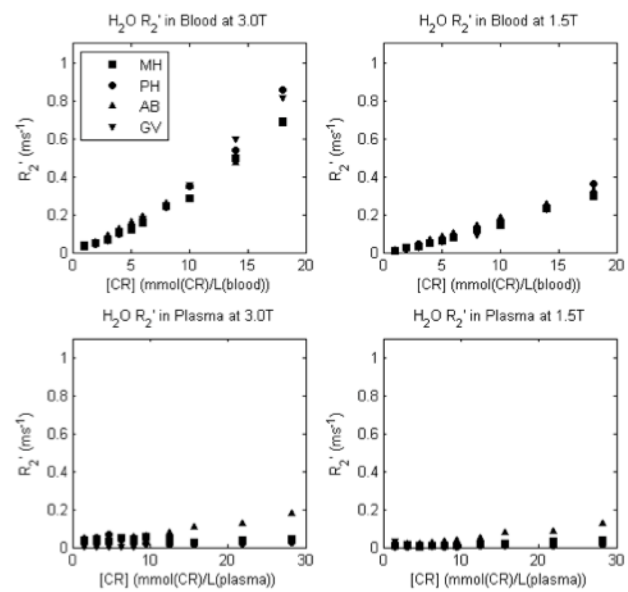

Figure 2. Measured R_2' (difference between R_2* and R_2) in oxygenated whole blood (top) and plasma (bottom) at two field strengths. R_2' in whole blood is very high, appears to have super-linear dependence on [CR], and increases linearly with field strength.

Discussion: The fast RF-refocusable transverse relaxation suggests static dephasing is the dominant mechanism in whole blood. This is likely a result of the exclusion of CR from red blood cells (RBC) leading to microscopic magnetic field inhomogeneities; CR in the plasma space creates a bulk magnetic susceptibility (BMS) difference between RBCs and the surrounding plasma. While dipole-dipole ("hyperfine") interactions likely dominate the non-refocusable (R_2) relaxation and show plasma relaxivity variation between CRs, R_2' data show very little difference for the various CRs. BMS depends much more on the concentration of CR than on its chemical nature. BMS frequency shifts (Δω) are constant in dimensionless ppm units, but spin dephasing depends on the absolute Δω value: hence the greater effect at 3T. Monte Carlo simulations have predicted dephasing due to the microscopic BMS inhomogeneities (including variation in blood oxygenation) [4]. They modeled RBCs as 3 μm radius spheres (of low BMS; when fully oxygenated) surrounded by (the high BMS) CR-containing plasma. The water molecules diffused through the resulting microscopic plasma inhomogeneities (accounting for Δω "motional narrowing"), and the accumulated phase variations resulted in signal loss. The model predicted a quadratic [CR]-dependence of R_2' (with minimum corresponding to BMS "matching" of deoxygenated RBC with the surrounding CR in plasma). Our data follow a similar trend, including R_2' relaxivity values on-the-order-of 40 s^{-1}/mM at 3.0T and 20 s^{-1}/mM at 1.5T.

In contrast enhanced MR angiography (CE-MRA), first-pass blood [CR_T] may approach 15 - 20 mM. Large R_2* 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 increasing CR dose or injection rate, and lead to optimized dosing strategies for CE-MRA.

References: **1.** Schneider G, *et al., JMRI* **26**:1020-32 (2007); **2.** Wilson GJ, *et al.*, *PISMRM* **21**:4459 (2013); **3**. Wilson GJ, *et al*., *PISMRM* **21**:3066 (2013); **4.** Blockley NP, *et al*., *MRM* **60**:1313-1320 (2008).