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

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\textbf{Introduction:} Accurate characterization of contrast reagent (CR) relaxivity in arterial whole blood is necessary for optimization of contrast enhanced MR angiography (CE-MRA) \cite{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 \textsuperscript{1}H\textsubscript{2}O T\textsubscript{2} and T\textsubscript{2}\textsuperscript{*} values \cite{2} and some T\textsubscript{1} values \cite{3} have been reported previously. This work explores the underlying mechanism of fast T\textsubscript{2}\textsuperscript{*} relaxation in oxygenated whole blood.

\textbf{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\textsubscript{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] values of 1, 2, 3, 4, 5, 6, 8, 10, 14, and 18 mM [mmol(CR)/L(blood)]. \textsuperscript{1}H\textsubscript{2}O T\textsubscript{2} and T\textsubscript{2}\textsuperscript{*} values were measured in whole blood using a multi-echo TSE [TR/ΔTE/#TE = 2000/6.7/32], and multi-echo FFE [TR/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.

\textbf{Results:} Relaxation rate constant R\textsubscript{2} (≡ 1/T\textsubscript{2}) vs. [CR] is approximately linear in both whole blood and plasma (Figure 1). R\textsubscript{2}', the rate constant for RF-refocusable transverse relaxation (≡ R\textsubscript{2} - R\textsubscript{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\textsubscript{2} in whole blood is approximately the same for all four contrast agents.

\textbf{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\textsubscript{2}) relaxation and show plasma relaxivity variation between CRs, R\textsubscript{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\textsubscript{BMS}) are constant in dimensionless ppm units, but spin dephasing depends on the absolute value: hence the greater effect at 3T. Monte Carlo simulations have predicted dephasing due to the microscopic BMS inhomogeneities (including variation in blood oxygenation) \cite{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 inhomogeneities (accounting for Ak (“motional narrowing”)), and the accumulated phase variations resulted in signal loss. The model predicted a quadratic [CR]-dependence of R\textsubscript{2}' (with minimum corresponding to BMS “matching” of deoxygenated RBC with the surrounding CR in plasma). Our data follow a similar trend, including R\textsubscript{2}' relaxivity values on-the-order-of 40 s\textsuperscript{-1}/mM at 3.0T and 20 s\textsuperscript{-1}/mM at 1.5T.

In contrast enhanced MR angiography (CE-MRA), first-pass blood [CR\textsubscript{1}] may approach 15 - 20 mM. Large R\textsubscript{2}' may yield diminishing returns for CE-MRA performed at high [CR\textsubscript{1}] (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.


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