T1 and T2* Relaxation Rates of Four Gadolinium Based Contrast Agents in Whole Human Blood at First-Pass Concentrations: Non-Linearities and their Impact on Optimizing Contrast-Enhanced MRA

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Introduction Dynamic contrast-enhanced MR angiography (CE-MRA) is an increasingly established and reliable diagnostic imaging modality. Multiple technological advances have been made; most primarily related to hardware/data acquisition improvements (*e.g.* faster gradients, better coils, parallel imaging, view-sharing). Increasing attention, however, is being focused on the properties of the gadolinium-based contrast agent (GBCA) used, most importantly R_1 and R_2* relaxation ($1/T_1$ and $1/T_2$*) and how to most efficaciously exploit it. Recent work examining GBCA's in human blood [1] (to be discussed) has brought to light two effects that mute the often assumed "linear" relationship between R_1 relaxation rate and GBCA concentration (the slope of which is described as the agent's "r_1"): 1) protein binding, and 2) finite kinetics for water exchange across the RBC membrane. These effects are not well understood with respect to their impact on CE-MRA. Our intent is to explore the R_1 and R_2* relaxivities of GBCA's in whole human blood at concentrations consistent with first-pass CE-MRA, and apply the results to improving CE-MRA.

Methods Whole human blood at physiologic temperature, pH, and oxygen tension was separately doped at blood concentrations ranging from 1 - 18 mM with four different GBCA's; gadoteridol (ProHance, Bracco), gadobenate (MultiHance, Bracco), gadobutrol (Gadavist, Bayer), gadofosveset (Ablavar, Lantheus). R_1 and R_2* were measured in whole blood and plasma (same specimen, eight hours settling) using Look Locker [TR/TE/ΔTI/α/NSA/#TI = 1000/1.95/5.0/8^0/3/128] and multi-echo FFE [TR/TE/ΔTE/α/#echoes = 200/1.5/2.4/350/32] sequences at 1.5 and 3.0T (Philips Achieva). The plasma R1 data for gadobenate and gadofosveset were fitted with a two component macromolecule binding model using established binding constants [1], and these fittings were incorporated into a two-site-exchange [2SX] model to predict from known quantities the GBCA concentration ([GBCA]) dependence of whole blood ^1H_2O R_1 as the system transitions from the fast-exchange limit (FXL) to the fast-exchange regime (FXR) with increasing [GBCA] [1,2]. The analytic predictions were compared to experimental blood data. Fittings of R_2* *vs.* [GBCA] were performed for both blood and plasma. The combination of these datasets allows for prediction of blood ^1H_2O R_1 and R_2*, which in turn can be translated to expected vascular signal intensity for each GBCA for any physiologic situation ([Hct, [albumin]) and scanning protocol (B_0/TR/TE/α). Simulations were performed using MatLab (Mathworks).

Findings Plasma fittings conformed to the expected linear R_1 [GBCA]-dependence for the non protein-binding agents gadoteridol and gadobutrol at both field strengths. Using a two component macromolecule binding model, good nonlinear fittings were obtained for gadobenate and gadofosveset, establishing discrete "free" and "bound" r_1 values (r_{1f} and r_{1b} respectively; $r_{1b} >> r_{1f}$). This demonstrated near complete saturation of primary albumin binding sites for [GBCA] > 0.5-1mM, with slope ~r_{1f} above this concentration. The 2SX model predicts a nonlinear [GBCA]-dependence of whole blood R_1, and nearly perfectly matches data (Fig. 1). [Note, the curve is not a fitting, rather a prediction using known quantities.] There is some Hct-dependence for all agents; approximately 5-6% decrease per 10% Hct increase over the physiologic range (Fig. 1), but only minimal dependence on [albumin] at higher [GBCA] (>5mM). Plots of R_2* *vs.* blood [GBCA] were remarkably linear, but demonstrated much higher r_2* in blood vs. plasma, ranging 15-22 (s^{-1}/mM) at 1.5T and 28-32 (s^{-1}/mM) at 3T (highest in all cases for gadofosveset). Combining the protein-binding and 2SX results with expected Hct and [albumin] values, R_1 can be predicted for any [GBCA], as can R_2*. This gives full latitude to predict expected signal intensity for the 3D spoiled gradient (SPGR) CE-MRA sequence.

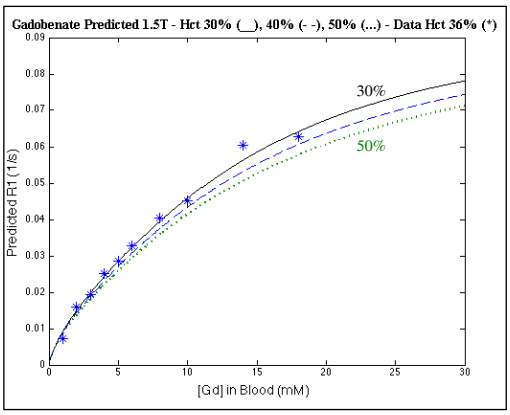

Figure 1. R1 *vs.* [Gd] at 1.5T; Gadobenate in blood. Predicted 2SX modeling demonstrating non-linearity R1 vs. [gadobenate] (deviation from linear line) and predicting some Hct dependence. Experimental data for Hct 36% matches well, validating model (similar excellent matching other GBCA at both B_0).

Discussion CE-MRA is an intrinsically non-linear technique. First, as demonstrated, blood R_1 increases non-linearly with [GBCA] consequent to RBC finite water exchange kinetics (Fig. 1), with additional non-linearity due to interaction of some GBCA's with serum albumin. Second, the signal intensity (SI) from the SPGR sequence is non-linear with respect to R_1, increasing as ~$R_1^{1/2}$ [3] while simultaneously attenuated by T_2* effects per $e^{-TE\ R2^*}$. This has important implications for CE-MRA, where GBCA's are injected relatively fast (often 2mL/s), and depending on patient physiology, may achieve peak blood concentrations of >10-20 mM. Simulations of SPGR SI using our predictive R_1 and R_2* modeling (Figs. 2, 3) allow insight into optimal injection strategies; note from Fig. 2 a definite peak SI for each GBCA, with a loss of SI (for this particular regime) with injection rates > 0.5-0.75mmol/s. More realistically, changing the abscissa to the duration over which an approved GBCA dose is injected (Fig. 3), a better comparison between agents can be made. A final important consideration concerns time-varying intravascular signal (*ie.* due to decay of first pass [GBCA]) during acquisition). This is known to cause artifacts - primarily blurring – which can degrade quality [4, 5]. Thus maintaining a relatively constant arterial GBCA concentration over the entire acquisition period is important, and optimal CE-MRA becomes a balance between appropriate management of the injection rate (*i.*e. managing R_1 and R_2*) and the injection duration (*i.e.* managing the bolus shape). The combination of these effects points to slower GBCA injection rates than are often currently used.

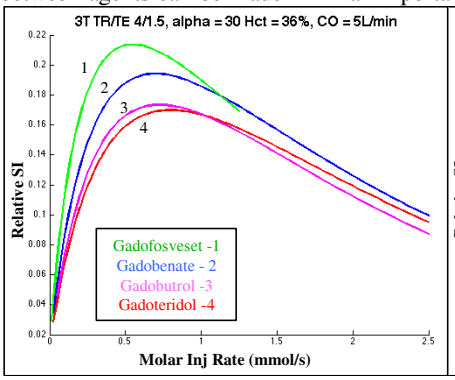

Figure 2. Predicted SI *vs.* injection rate for each of the four GBCA's under investigation; modeled at 3T with TR/TE = 4/1.5 ms, α = 30^0, cardiac output = 5L/min.

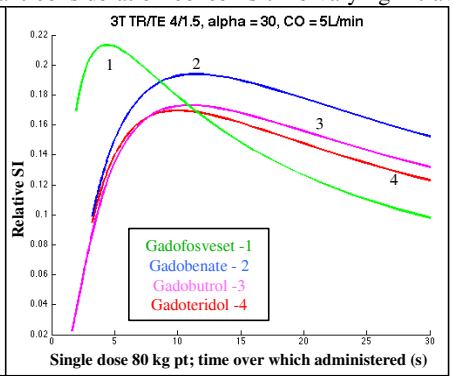

Figure 3. Predicted SI *vs.* injection duration for a single FDA approved dose for each of the four GBCA's under investigation; modeled at 3T for 80kg patient, TR/TE = 4/1.5 ms, α = 30^0, cardiac output = 5L/min.

References

1) Wilson et al. MRA Club 2012, Utrecht, NL. Paper 5.2.
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