

# Relaxivities of Conventional and Protein-Binding Gd-Based Contrast Agents in Human Blood and their Implications for Dosing in CE-MRA

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## Introduction

With the recent proliferation of several “high relaxivity” protein-binding Gd-based contrast agents and their subsequent adoption for CE-MRA, it is important to fully understand the relaxivity properties of these agents when imaged in blood at the relatively high arterial concentrations inherent to CE-MRA – not the typical circumstances under which  $r_1$  and  $r_2$  relaxivities are measured in the literature (typically measured in plasma at much lower concentrations) (1,2). The practical nature of this becomes apparent considering studies such as Schneider et al. (3), a dose ranging study of the high relaxivity agent gadobenate (Bracco Diagnostics) where 84 patients undergoing CE-MRA (DSA comparator) showed significantly better accuracy at a dose of 0.1 vs. 0.2 mmol/kg. Our aim was to better understand the  $r_1$  and  $r_2^*$  relaxivities of Gd contrast agents in whole human blood, with particular attention to understanding why higher doses/injection rates may actually be detrimental.

## Methods

This was an IRB approved phantom study. Whole human blood was doped with 3 different Gd agents, gadoteridol (ProHance, Bracco Diagnostics), gadobenate (MultiHance, Bracco), gadofoveset (Ablavar, Lantheus Medical), at concentrations of 0, 1, 1.5, 2, 3, 5, 7.5, 10, 15, 20 mmol. These were placed in 6 ml HDPE vials embedded in 2% agarose gel. Four additional phantoms contained gadoteridol in normal saline (NS) at concentrations of 0, 1, 3, 10 mmol. The phantom was inverted several times every 5-10 minutes throughout the study to avoid hematocrit layering. Imaging was performed at both 1.5T and 3.0T (Achieva, Philips Medical, Best, the Netherlands) in order to calculate  $T_1$  and  $T_2^*$  using the following sequences: Look Locker (IR-T1-TFE-EPI, TR 1sec, TE 5.4ms, FA 8°, EPI factor 3,  $\Delta T_1$ =15ms), Multi-Echo FFE (TR 200ms, TE1=1.5ms,  $\Delta T_E$ =2.4ms, FA 35°). In addition, CE-MRA 3D  $T_1$ -FFE images were obtained at different TE’s (1.1-3.5ms) to look at simulated CE-MRA signal intensity vs. [Gd].

Regions of interest (ROIs) were placed in each imaged phantom and mean signal intensity measured. Data fits determined  $R_1$  and  $R_2^*$  using Matlab (Mathworks, Natick, MA) and the standard correction for Look Locker. Relaxivities  $r_1$  and  $r_2^*$  were evaluated based on the slope of the  $R_1$  or  $R_2^*$  vs. [Gd] data.

## Findings

For all Gd concentrations,  $R_1$  was greatest for gadofoveset and least for gadoteridol, with gadobenate falling in the middle (Figure 1), as predicted by their commonly reported relaxivities (2). Also as expected,  $R_1$  decreased at higher field strength (Figure 2). Relaxivity ( $r_1$ , defined as the regional slope of  $R_1$  vs. [Gd] - Figure 1) appears non-linear, with an inflection point at approximately 3 mmol (arrow, Figure 1). Less than 3 mmol, the slope ( $r_1$ ) of gadofoveset > gadobenate > gadoteridol. Beyond 3 mmol, the slopes for all agents become nearly equal, and similar to that of gadoteridol in NS.

$R_2^*$  measurement demonstrated a surprising initial decrease in  $R_2^*$  (ie increase in  $T_2^*$ ) as [Gd] increased at both field strengths up to approximately 2 mmol, most notable for gadoteridol > gadobenate > gadofoveset (Figure 3). Beyond this  $R_2^*$  increases, with  $1/R_2^*$  ( $T_2^*$ ) being on the order of 6 ms or less for [Gd] > 10 mmol at 1.5T (4 ms at 3.0T). Gadoteridol in NS behaved linearly over the entire range with  $r_2^*$  values of 4.9/4.6 mmol<sup>-1</sup> s<sup>-1</sup> at 1.5 and 3.0T respectively.

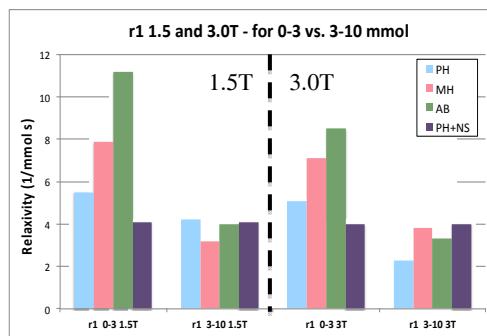
Analysis of 3D MRA SI data (Figure 4) demonstrates the benefit of the high relaxivity agents gadobenate and gadofoveset at lower [Gd], but the lack of improvement for higher [Gd] (generally ~ 5 mmol), with signal loss seen for [Gd] greater than this.

## Discussion

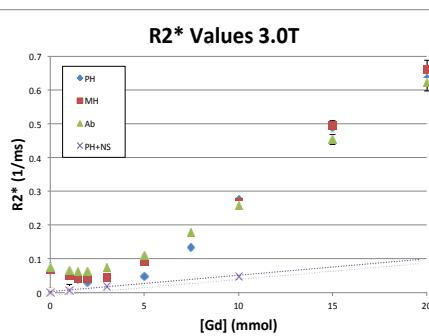
Most literature values of  $r_1$  and  $r_2$  relaxivity are a) measured in plasma or serum, and b) based on [Gd] ranges of  $\leq 1$  mmol (1,2). For first pass MRA, expected [Gd] concentrations (typical injection rate of 2 mL/s) are on the order of 12 mmol (0.5M agents); i.e. falling into a non-linear range of  $r_1$ . The observed  $r_1$  inflection point at ~3 mmol (Figure 1) is most pronounced for the protein-binding agents gadobenate and gadofoveset (and very minimal for gadoteridol), likely reflecting the point at which albumin binding sites are effectively saturated. Beyond this, the “relaxivity” differs very little from that of conventional relaxivity agents (iso-slopes in Figure 1). The observed  $R_2^*$  effects likely relate to the paramagnetic properties of the deoxygenated blood used for this study, with rapid water exchange across the erythrocyte leading to shortened  $R_2^*$  at low concentrations of paramagnetic Gd, making it very difficult to define a  $r_2^*$  in blood. This effect is likely of little consequence for CE-MRA (and is being sorted out with further investigation using oxygenated blood), however the longer  $R_2^*$  at higher “CE-MRA-type” concentrations decreases SI at dosages/flow rates commonly administered.

Fully understanding the properties of different Gd contrast agents, particularly those with protein binding properties, in blood at typical CE-MRA concentrations is vital to use the contrast to best advantage for CE-MRA.

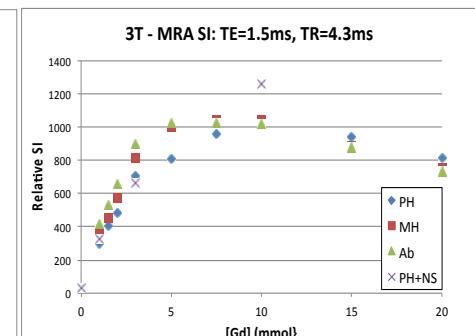
**References** 1) Pintaske et al. Invest Radiol 41(3):213-221 (2006). 2) Rohrer et al. Invest Radiol 40(11): 715-724 (2005) + Erratum Invest Radiol 2006. 3) Schneider G et al. J Magn Reson Imaging. 2007;26:1020-1032.



**Figure 2.** Relaxivity ( $r_1$ ) measured as slope of  $R_1$  vs. [Gd] (see Figure 1) over the range 0-3 mmol ( $r_1$  0-3) and 3-10 mmol ( $r_1$  3-10) at both 1.5T and 3.0T. PH+NS = ProHance in normal saline – linear throughout both ranges.



**Figure 3.** Measured  $R_2^*$  values in whole blood at 3T vs. [Gd] demonstrating initial decrease, followed by increase. The dashed line shows the perfect linearity of [Gd] vs.  $R_2^*$  for ProHance in normal saline.



**Figure 4.** Relative signal intensity (SI) for 3D CE-MRA sequence vs. [Gd] – typical TR/TE 4.3/1.5 ms. Note the flattening of SI vs. [Gd] at 5mmol (7.5 mmol for gadoteridol) with subsequent loss of SI beyond. This effect is more pronounced for longer TE (not shown).