**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 R₁ and R₂* relaxation (1/T₁ and 1/T₂*) 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 R₁ relaxation rate and GBCA concentration (the slope of which is described as the agent’s “R₁*”); 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 R₁ and R₂* 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 separated doped at blood concentrations ranging from 1 - 18 mM with four different GBCA’s; gadoteridol (ProHance, Bracco), gadoxate (MultiHance, Bracco), gadobutrol (Gadavist, Bayer), gadofosveset (Ablavar, Lantheus). R₁ and R₂* were measured in whole blood and plasma (same specimen, eight hours settling) using Look-Locker [TR/TE/T1/NSA/#TI = 1000/1.95/5.0/8/3/128] and multi-echo FFE [TR/TE/ATE/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 H₂O R₁, as the system transitions from the fast-exchange limit (FSL) to the fast-exchange regime (FXR) with increasing [GBCA] [1,2]. The analytic predictions were compared to experimental blood data. Fittings of R₁ vs. [GBCA] were performed for both blood and plasma. The combination of these datasets allows for prediction of blood H₂O R₁ and R₂*, which in turn can be translated to expected vascular signal intensity for each GBCA for any physiologic situation ([Hct, [albumin]]) and scanning protocol (B₁/TR/TE/α). Simulations were performed using MatLab (Mathworks).

**Findings** Plasma fittings conformed to the expected linear R₁ [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” r₁ values (r₁f and r₁b respectively; r₁b >> r₁f ). This demonstrated near complete saturation of primary albumin binding sites for [GBCA] > 0.5-1mM, with slope ~r₁f above this concentration. The 2SX model predicts a nonlinear [GBCA]-dependence of whole blood R₁, 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 R₂* vs. blood [GBCA] were remarkably linear, but demonstrated much higher r₂* 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, R₁ can be predicted for any [GBCA], as can R₂*. This gives full latitude to predict expected signal intensity for the 3D spoiled gradient (SPGR) CE-MRA sequence.

**Discussion** CE-MRA is an intrinsically non-linear technique. First, as demonstrated, blood R₁ 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 R₁, increasing as ~R₁¹/₂ [3] while simultaneously attenuated by T₂* effects per e⁻¹/T₂*². This has important implications for CE-MRA, where GBCA’s are injected relatively fast (often 2mL/s), and depending on patient physiology, becomes a balance between appropriate management of the injection rate (i.e. managing R₁ and R₂*) 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.

**References**