High Relaxivity Contrast Reagents Allow Detection of Erythrocyte Transcytolemmal Water Exchange

Gregory J Wilson, Charles S Springer, Jr., Mark Woods, Sarah Bastawrous, Puneet Bhargava, and Jeffrey H Maki

1Radiology, University of Washington, Seattle, WA, United States, 2Advanced Imaging Research Center, Oregon Health and Science University, Portland, OR, United States, 3Chemistry, Portland State University, Portland, OR, United States, 4Radiology, Puget Sound VAHCS, Seattle, WA, United States

Introduction: The kinetics of the equilibrium (steady-state) exchange of water molecules across cell membranes have been studied by non NMR techniques (isotope labeling) for almost 60 years [reviewed in (1)] and by NMR methods for 40 years [reviewed in (2) and (3)]. For erythrocytes, there is consensus that water exchange across the cell membrane is anomalously facile (4), though the reason is still not clear (5). It has been known for 20 years that it is sufficiently fast to be hardly detectable in T2-weighted blood. H2O signals obtained at practical plasma concentrations of monomeric Gd(III) chelate contrast reagents (CRs) that do not interact with macromolecules (6-8). For high relaxivity CRs (e.g., CRs that interact with serum albumin), the blood plasma longitudinal relaxivity (T1) is considerably elevated (9), perhaps increasing the signal-to-noise (SNR) sufficiently to allow robust detection of this exchange process in blood.

We have titrated approved CRs that do (gadobenate dimeglumine and gadofosveset trisodium) and do not (gadoteridol and gadobutrol) interact with albumin into each whole blood separately. We have determined H2O T1, T2, and T1* values for these samples at 1.5 and 3T. To illustrate our results and our analysis, we report here the T1 determinations for gadobenate dimeglumine (MH, MultiHance, Bracco Diagnostics) at 3T. These show clear evidence for the effects of equilibrium transcytolemmal water molecule exchange in blood at physiological temperature.

Methods: A 3.0T Achieva MRI scanner (Philips Healthcare, the Netherlands) was used, with an 8 channel SENSE head coil. The phantom sample consisted of two trays, each with 35 6 mL (13 x 55 mm) HDPE tubes embedded in 2% agar gel. These were filled with fresh, whole blood that was 99% O2 saturated, at physiologic pH, 3.3 g/dL albumin content, 36% hematocrit, 37°C, and periodically agitated to prevent RBC settling. In 10 of the tubes for each agent, 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)]. The H2O T1s values were measured in whole blood using a Look-Locker sequence [TR/TE/ΔT/TE0/NSA/FTI = 1000/1.95/5.08/3/128]. After eight hours of settling, the measurements (T1s) were repeated for the plasma supernatants.

Results: Figure 1 shows the [CR]-dependence [CR concentration in mmol(CR)/L(plasma) in this instance] of the longitudinal relaxation rate constant R1p [= (1/T1p)] for MH in plasma at 3T: the points (squares) are the measured values. [The error bars represent the confidence intervals resulting from the Look-Locker fitting.] The nonlinearity at low [CR] is evidence for MH-albumin interaction [reviewed in (11)]. For a rapid CR macromolecule (M) binding equilibrium with 1:1 stoichiometry, Equations [1-3] can be used to describe the data (12):

where R1b is the binding equilibrium constant, [CR]M, [CR]b, and [M] are equilibrium plasma concentrations, [M] and [CR] are total concentrations, τM is the relaxivity of CRM, and R1p is RI in the absence of CR. Fitting the data with Eqs. [1] - [3] yields the solid curve (setting K1 = 1.5 (mM)-1(13), [M] = 0.497 mM for human serum albumin (HSA) in plasma - and R1b = 0.6 s-1, returns τM = 13.22 (mM)-1s) and τM = 4.52 (mM)-1s). The agreement of the curve with the data, and the relaxivities with the literature (13), is outstanding. [The dashed linear asymptote demonstrates the nonlinearity.] Most likely, the interaction of MH with HSA involves more than 1:1 stoichiometry, the curve with the data, and the relaxivities with the literature (13), is outstanding. [The dashed linear asymptote demonstrates the nonlinearity.]

Discussion: The effects reported here are less obvious with gadodiamide ([ProHance] or gadobutrol [Gadavist], but are more pronounced with gadofosveset trisodium [Ablavar] because of its interaction with albumin and resultant greater T1 relaxivity enhancement (9,11). The τ parameter takes on much greater significance since it was recently discovered to have a metabolic component (10). Our results suggest that samples such as these can be used to investigate the reason why τ is so small for erythrocytes (4,5). For example, does a mechanism involving active trans-membrane water cycling (10) play a role? These results also have a bearing on the performance of Contrast-Enhanced MR Angiography (CE-MRA), where first-pass blood CR concentrations [CR] may approach 15-20 mM. The deviation from FXL relaxivity that may be errantly assumed at these concentrations (Fig. 2) leads to an over-prediction of vessel signal intensity. In conjunction with T1* effects, this implies diminishing returns for CE-MRA performed at high [CR] (i.e., rapid CR injections).

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References: