Overcoming the low relaxivity of gadofosveset at high field with spin locking

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Introduction: Gadofosveset trisodium (Ablavar, Lantheus Medical Imaging, previously marketed as Vasovist, Schering AG, Germany) is a small-molecule gadolinium (Gd) contrast agent that acquires macromolecular properties on binding to serum albumin. Over 90% of the agent binds at low concentrations in human serum (1); binding facilitates a significantly higher (up to tenfold) longitudinal relaxivity at low magnetic field strengths (2). The longitudinal relaxivity of the bound gadofosveset molecule (r_{1bound}) peaks at around 0.5 T, with a substantial decrease at higher fields (3). The longitudinal relaxivity of free (unbound) gadofosveset (r_{1free}) is slightly higher than conventional small-molecule Gd-based agents such as gadopentetate dimeglumine, and shows only a moderate decrease with field strength (4), leading to a convergence of r_{1bound} and r_{1free} at high fields. In spin locking (SL) experiments a 90° excitation pulse is followed by an RF pulse (phase shifted by 90° to the excitation pulse), applied for a duration of time (TSL), locking the spins in the rotating frame of reference. Magnetisation relaxation in the presence of this SL field (B_{1L}) is characterised by the time constant $T_{1\rho}$. $T_{1\rho}$ is influenced by the strength of the SL field, which is commonly in the μT range, rather than the main magnetic field (B_0). The interaction times associated with SL at very low fields give this technique an increased sensitivity to macromolecules (5). The purpose of this study was to determine the potential impact of albumin binding on $T_{1\rho}$ for *in vitro* gadofosveset solutions at high B_0. It is hypothesized that by combining the macromolecular sensitivity of SL with the albumin-binding affinity of gadofosveset, a large contrast-induced change in $T_{1\rho}$ may be achieved at field strengths where the T_1 effects of gadofosveset are very similar to those of conventional Gd-based agents. Although other studies have utilised SL in conjunction with small-molecule contrast agents (e.g. (6)), a literature search found no published studies assessing the effect of gadofosveset on $T_{1\rho}$.

Methods & Results: *In vitro* solutions of gadofosveset (Vasovist) at concentrations ≤ 5 mM in phosphate-buffered saline (PBS), representing unbound gadofosveset, and in bovine serum albumin (BSA, 4.5% w/v), representing a physiological combination of bound and unbound agent, were imaged at 4.7 T and 37°C, along with solutions containing equivalent concentrations of gadopentetate (Magnevist, Bayer Healthcare Pharmaceuticals, Germany) in BSA. A spin locking pulse (B_{1L}) of 90 μT (3.8 kHz) was applied for 14 durations (TSL) between 0.01 and 200.0 ms, followed by a RARE readout. A mono-exponential three-parameter nonlinear fit was applied to the measured signal intensity (SI) data to determine the fully recovered SI (S_0) values and relaxation rates, $R_{1\rho}$ ($1/T_{1\rho}$),including a parameter (a) to account for residual magnetisation in the y axis due to the SL pulse: $SI = S_0 . e^{-TSL.R1\rho} + a$. R_1 ($1/T_1$) values were also determined from a separate RARE saturation recovery sequence, using eight repetition times (TR) and a mono-exponential two-parameter nonlinear fit: $SI = S_0.(1 - e^{-TR.R1})$.

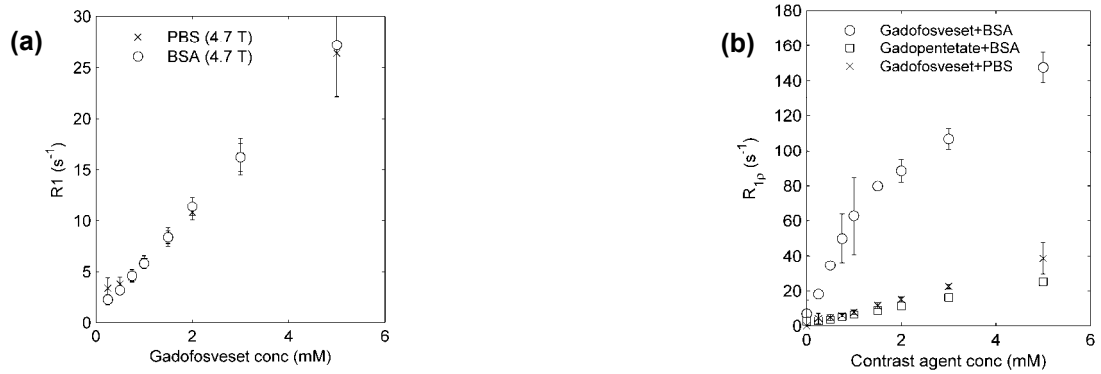

Figure 1: (a) R_1 values for gadofosveset in BSA (circles) and in PBS (crosses); (b) corresponding $R_{1\rho}$ values at B_0 = 4.7 T, B_{1L} = 90 μT, including gadopentetate in BSA (squares). Error bars represent 95% confidence intervals.

Discussion: At 4.7 T gadofosveset binding is shown to have little influence on R_1 (Fig. 1a), with solutions of gadofosveset in BSA and PBS displaying similar characteristics. However, gadofosveset $R_{1\rho}$ values are significantly higher in the presence of serum albumin (Fig. 1b). As $R_{1\rho}$ values for gadopentetate in BSA are comparable to those for gadofosveset in PBS (Fig. 1b), it is likely that the macromolecular binding of gadofosveset has a much larger influence on $R_{1\rho}$ than the presence of albumin alone. This study demonstrates the feasibility of a novel method for combining the albumin-binding properties of gadofosveset with the macromolecular sensitivity of SL to generate improved contrast modification at high field strengths. In addition, the distinct responses of bound and free gadofosveset suggest a potential opportunity for additional tissue characterisation *in vivo*. It should be noted that it was not necessary to consider potential tissue heating issues for this *in vitro* study; optimal SL parameters would require further investigation prior to implementation in a clinical setting.

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References: **1.** Lauffer RB et al. Radiology 1998;207(2):529-538. **2.** Eldredge HB et al. Invest Radiol 2006;41(3):229-243. **3.** Muller RN et al. Eur J Inorg Chem 1999(11):1949-1955. **4.** Rohrer M et al. Invest Radiol 2005;40(11):715-724. **5.** Aronen HJ et al. Magn Reson Imaging 1999;17(7):1001-1010. **6.** Muthupillai R et al. Radiology 2004;232(2):606-610.