Deuterium prolonged relaxation reveals the macromolecular content in MRI

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Introduction. Recently, the deuterium oxide (D_2O) has been used as a negative contrast agent for perfusion imaging by indirectly monitoring the infused deuterium via the conventional protonium imaging. [1] It is also noticed that the H/D isotope exchange effect of deuterium can prolong the T_1 and T_2 relaxation of protonium. In this study, we aimed to further investigate the contrast mechanism in an environment with organic macromolecules. The interaction of macromolecules, such as bovine serum albumin (BSA), has been reported to change the relaxivity of Gd-based contrast agent. [2] Since the H/D isotopes will also exchange on the macromolecules [3], it is anticipated that the relaxivity provided by deuterium would be also altered. Therefore, the T_1 and T_2 of H_2O/HDO/D_2O solution phantoms with various BSA concentrations were measured by a MRI scanner to investigate the macromolecular effect.

Materials and methods. All experiments were conducted on a 4.7T Bruker Biospec 47/40 MRI scanner with protonium RF coils. The BSA (Sigma-aldrich, USA) was dissolved into H_2O/HDO/D_2O solutions to five concentrations: 0%, 5%, 10%, 15% and 20% in 1-ml tubes. Five different H_2O/HDO/D_2O solutions are formulated by diluting 0, 10, 20, 30, 40 and 50% of D_2O (99.8%, Cambridge Isotopes, USA) with deionized H_2O, and then placed into a 50-ml centrifuge filled with deionized H_2O. T_1 and T_2 of phantoms were measured through IR-EPI and MSME sequences, respectively. The imaging parameters for IR-EPI were as follows: TE/TR= 54/20000ms, Matrix size= 128x128, TI= 50 to 3650ms with intervals of 600ms; MSME sequence: TE/TR= 15/2000ms, echo= 15 to 225ms with intervals of 15ms. In this study, D_2O relaxivity r_1 and r_2 (unit: $mM^{-1}sec^{-1}$) of all BSA phantoms were measured as $R_{1,2} = R_{(0)\,1,2} + r_{1,2} \cdot [D_2O]$, where $R_{1,2}$ (unit: s^{-1}) are reciprocals of the $T_{1,2}$ and $R_{(0)\,1,2}$ denotes the relaxation of BSA solutions without the influence of D_2O. All acquired data were processed by Matlab script.

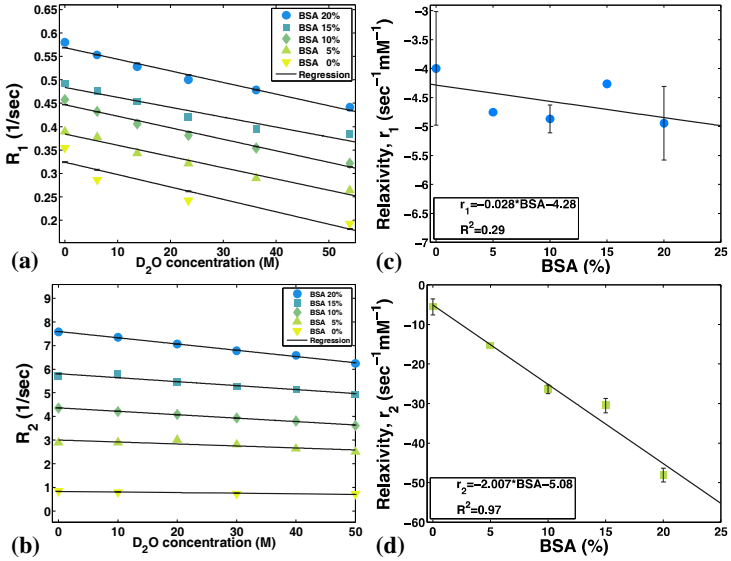

Fig 1. (a)(b) R_1 and R_2 relaxationrates of BSA phantoms as a function of D_2O concentration. (c)(d) The r_1 and r_2 relaxivities of D_2O as a function of BSA concentration. It is noted that the r_2 has a negative slope with BSA in (d).

Results. Fig 1. (a) and (b) show the relaxation rates R_1 and R_2 as a function of D_2O concentrations, respectively. All of the slopes are negative, which means the isotope effect of deuterium prolongs relaxation times. Furthermore, the r_1 and r_2 relaxivity of D_2O are plot as a function of BSA concentration in Fig 1. (c) and (d), respectively. It is noted that the r_1 relaxivity of D_2O is nearly irrelevant to BSA concentration (R^2=0.29), while the r_2 relaxivity has a linear correlation with BSA concentration (R^2=0.97). The regression line can be fitted as r_2=-2.007*[BSA]-5.08.

Discussion and Conclusion. In previous report, the negative relaxivity of D_2O on protonium imaging is attributed to the isotope exchange effect. Because of the less interference from deuterium than protonium, the protonium on the HDO molecule has longer relaxation times. In this study, we further found that this contrast mechanism is sensitive to the macromolecular content in the environment. This mechanism is still not clear, and further study is needed. It is speculated to be related to the change of bound water and the H/D isotope exchange on the macromolecule. In NMR studies, the H/D isotope exchange effect on spectroscopy has been used to investigate misfold proteins, which are abnormally aggregated in brain of patients with Alzheimer's disease. [3] In our results, we demonstrate that T_1 and T_2 relaxation can provide information of the macromolecules. Therefore, we may use the T_1 and T_2 image contrast of MRI to extract molecular information after administration of D_2O contrast agent *in vivo*. Furthermore, it is possible to utilize the R_1 change for calibrating regional D_2O concentration, and then use the R_2 change for quantification of the effect of macromolecules. In conclusion, we demonstrated that employing D_2O as a contrast agent for protonium MRI is potentially valuable for future MR molecular imaging.

References. [1] Wang, F.N. et al., *NMR Biomed*, **26**(6): 692-698, 2013. [2] Hassan, B.E. et al., *NeuroImage,* **54**:S176-S179, 2011. [3] Ma, B. and Nussinov, R., *J. Biol. Chem.*, **286**(39): 34244-34253, 2011.