

Towards detection of sub-micromolar contrast agent concentration with hyperpolarized 6-lithium

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Introduction

At room temperature ⁶Li has longitudinal relaxation times T_1 on the order of several minutes in both H₂O and D₂O [1,2]. These long relaxation times make ⁶Li highly sensitive to sufficiently potent contrast agents if their effect on the signal would be observed after a sufficiently long relaxation time TR (on the order of 100 s). However, observing the signal after these long TRs make most NMR studies too long for *in vivo* purposes. In hyperpolarization experiments on the other hand, long relaxation times are desired since they will allow the polarization to remain for a longer time. We therefore sought to determine the effect of contrast agents on ⁶Li T_1 and the feasibility of detecting low contrast agent concentrations.

Materials and Methods

We chose to monitor the signal difference in the ⁶Li NMR signal between the two compartments: one with a small amount of contrast agent doped D₂O and one with the same amount of pure D₂O. TR = 100 s was selected, which should allow for contrast generation while the signal also had not disappeared yet. This means that the ratio of the longitudinal magnetization decay C of these compartments allows us to calculate the required amount of contrast agent according to:

$$C = \frac{e^{-TR \cdot R_{1,app}}}{e^{-TR \cdot R_1}} = \frac{e^{-(TR \cdot [CA] \cdot r_1 + TR \cdot R_1)}}{e^{-TR \cdot R_1}} = e^{-TR \cdot [CA] \cdot r_1}, \quad (1)$$

where R_1 is the longitudinal relaxation rate ($= 1/T_1$), r_1 the longitudinal relaxivity, $R_{1,app}$ the apparent R_1 and [CA] the concentration of contrast agent.

The first series of experiments aimed at finding a contrast agent that had a high r_1 for ⁶LiCl when dissolved in both H₂O and D₂O. To this end r_1 of several commercial contrast agents was determined in a 9.4T 31 cm bore actively-shielded animal spectrometer (Varian/Magnex) using an inversion recovery sequence consisting of an adiabatic 180° and 90° pulses.

The second step was hyperpolarizing the lithium. Hyperpolarization of enriched ⁶LiCl (95% pure) was generated by the dynamic nuclear polarization (DNP) [3] method, using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) as a radical catalyst. Helium-driven high pressure transported the D₂O-steam dissolved liquid from the cryostat to the 9.4T magnet, where the liquid was collected in a separator that removed the high pressure. The separator was connected to a T-junction that was in turn connected to two catheters which lead to the imaging phantom. One catheter leading to the phantom was filled with 0.05 ml D₂O doped with 10 μM GdDOTP, while the other was filled with 0.05 ml pure D₂O. The phantom consisted of a 25 mm diameter water-filled cylinder that contained two 5 mm diameter cylinders (see inset of Fig. 1). Since the volume of one of the inner cylinders was 1 ml, the final contrast agent concentration was not more than 500 nM. The acquisition was done with 120 separately stored repetitions of a 1D projection that consisted of a 32 point gradient recalled echo (TE = 1095 ms) with an adiabatic 10 degree BIR-4 pulse every 5 s. The direction of the gradient is shown under the inset of figure 1.

Results and Discussion

After observing that uncharged Omniscan has a smaller relaxivity than negatively charged Magnevist (see table 1), the strongly negatively charged GdDOTP (Macrocylics, Dallas, TX) was tested. This resulted in $r_1 = 11 \text{ s}^{-1} \text{ mM}^{-1}$. Using eq. 1, if we take TR=100 s and $r_1 = 11 \text{ s}^{-1} \text{ mM}^{-1}$, the required [CA] would be ~40 nM.

⁶LiCl polarized with a time constant of 450 seconds. The enhancement factor at 1.2 K in the 3.35 T cryostat was ~150 (equivalent to ~13000 at room temperature in a 9.4T magnet). Following dissolution and injection into the phantom, a stack plot of the projections can be seen in Fig. 1. An exponential decay fit of projections gives $T_1 = 120 \pm 2$ and 125 ± 1 s for the left and right curve, respectively. The distortion of the profiles was most likely caused by the presence of small air bubbles.

The integrated signal of the two projection peaks corrected for the flip angle attenuation is plotted in Fig. 2. The integral of both projection peaks were normalized to be able to evaluate the signal difference 100 s later. This signal difference after 100 s was 10-30% (n=3), suggesting via eq. 1 that the concentration was approximately 50 nM. Most likely this is caused by the sub-optimal design of the T-junction, which allowed air bubbles to separate the contrast agent from the hyperpolarized fluid. From a high-average thermal equilibrium acquisition we estimated that the enhancement factor in the phantom was at least 2000.

Conclusions

We conclude that (a) contrast agents with high relaxivity for ⁶Li can be designed, (b) that ⁶Li can be polarized well above thermodynamic equilibrium and (c) that the decay of hyperpolarized magnetization is sensitive to small concentrations of CA on the order of μM or below. (d) The extreme sensitivity of the hyperpolarized ⁶Li to minute amounts of paramagnetic agents points to its potential application as a sensitive agent for determining the blood oxygenation level *in vivo*.

Acknowledgements

Supported by Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations; NIH grant R01NS42005 and SNSF grant 200021-109479.

References

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Table 1. Overview of the contrast agents and their ⁶Li relaxivity r_1

	Charge	r_1 (s ⁻¹ mM ⁻¹)
Omniscan	0	0.10 ± 0.01
Magnevist	-2	0.33 ± 0.03
GdDOTP	-5	11 ± 1

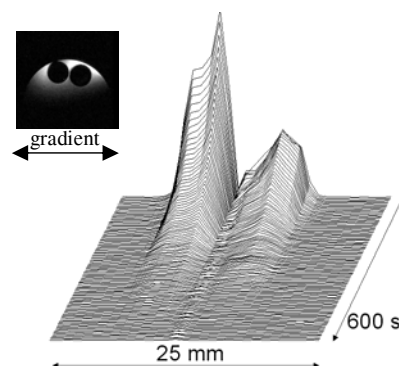


Figure 1. Stack plot of the signal decay in the projection through the two cylinders. Left the contrast agent doped cylinder. Inset: an image of the phantom made with the surface coil, where both cylinders contained D₂O and thus do not generate signal.

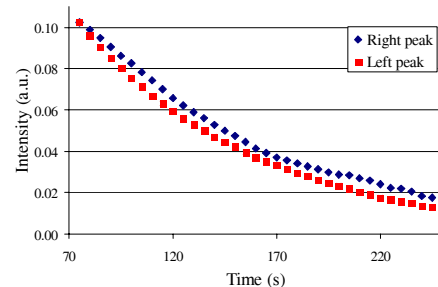


Figure 2 Plot of the normalized integrated intensity over time with a 14% signal difference between the two cylinders 100 s later.