The effects of gadolinium on the hyperpolarization of [1-^{13}C]pyruvate at 3.35 T and 5 T

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Target: Researchers interested in hyperpolarization and dynamic nuclear polarization (DNP).

Introduction: When performing pre-clinical hyperpolarization studies using the dissolution DNP technique, a trace amount of a gadolinium complex is typically added to [1-^{13}C]pyruvic acid to enhance the polarization level achieved. At 3.35 T & 1.2-1.4 K (the operating conditions of the Oxford Instrument HyperSense polarizer) the inclusion of an optimal concentration (~1.5 mM) of gadolinium chloride in samples of [1-^{13}C]pyruvic acid has been reported to enhance the limiting polarization by a factor of 1.5-2[1]. Another study operating at the higher field strength of 4.6 T reported elevated polarization levels when compared to 3.35 T but also suggested that the addition of gadolinium no longer had any effect on polarization levels at this higher field strength[2]. With the development of the GE Healthcare SPINlab system, up to four samples of pyruvic acid can be polarized at one time for potential injection into humans[2]. The SPINlab operates at 5 T, and uses closed system cryogenics to cool samples to temperatures on the order of 0.8 K. We have therefore investigated whether the addition of gadolinium at a range of different concentrations has any effect on polarization enhancement in the SPINlab system (5 T & 0.8 K) and compared its effects to the enhancement seen on the HyperSense (3.35 T & 1.2-1.4 K).

Methods: Experiments were performed on a SPINlab (5 T, GE Healthcare) polarizer and on a HyperSense pre-clinical polarizer (3.35 T, Oxford Instruments). For the SPINlab experiments, 1 ml of [1-^{13}C]pyruvic acid (~1.26 g) was polarized with OX063Me (EPA), at varying concentrations of the gadolinium chelated compound, Dotarem (0, 0.5, 1.0, 1.5, and 2.0 mM). For HyperSense experiments 30.5 µl of [1-^{13}C]pyruvic acid (~40 mg) was polarized with EPA at the same concentrations of Dotarem as the SPINlab experiments. Samples were polarized until solid state NMR indicated that the limiting enhancement had been reached. The amplitude of the NMR signal was recorded as a function of time and the 'build-up' data fit to a single exponential model to determine the limiting enhancement and the apparent build-up time constant. Limiting polarization was normalized to the control at 0 mM Dotarem, to give a relative increase in polarization as a function of gadolinium concentration ([Gd^{3+}]).

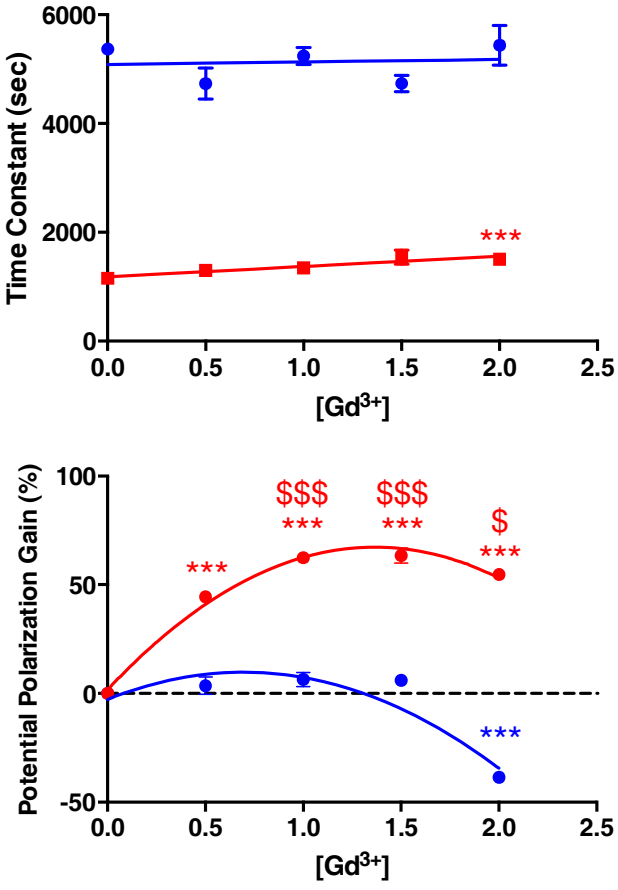

Figure 1: Build-up time constant and the relative limiting polarization value, expressed as a percentage gain at 5 T (blue) and 3 T (red). *** $p > 0.001$ compared to 0 mM. $ $p > 0.05$, $$$ $p > 0.001$ compared to 0.5 mM.

Results: As the concentration of Dotarem was increased there was a significant increase in the build-up time constant at 3.35 T / 1.2-1.4 K, but no difference was seen at 5 T / 0.8 K (Figure 1). Similarly, increased Dotarem concentrations lead to an increase in the limiting polarization at 3.35 T / 1.2-1.4 K until a maximum was reached at 1.5 mM, a relationship that was again not seen at 5 T / 0.8 K. At 2 mM [Gd^{3+}] there was a decrease in the potential polarization gain at 5 T / 0.8 K, indicating a negative effect of high Gd^{3+} concentrations that we potentially attribute to the shortening of the nuclear T_1. The SPINlab was able to generate liquid state instantaneous polarization of approximately 40-50% (in the absence of Gd^{3+}), compared with the HyperSense's 20-30% (with a [Gd^{3+}] of 1.5 mM).

Discussion: As expected, the limiting polarization value is higher at higher B / lower T. The build-up time constant also increases at higher field strengths. The addition of Gd^{3+} did not significantly alter this time constant at 5 T / 0.8 K, but increased it at 3.35 T / 1.2-1.4 K, reflecting the different dynamic equilibria at play under these different conditions. High concentrations of Dotarem (2.0 mM), which potentially reduce the nuclear T_1, reduce the limiting polarization at 5 T / 0.8 K. The addition of Gd^{3+} to [1-^{13}C]pyruvic acid samples in the SPINlab system is therefore not necessary to increase enhancement. In the preclinical setting, consistent with the concentration reported in previous studies, the addition of 1.5 mM of Dotarem to [1-^{13}C]pyruvic acid samples significantly increased the limiting polarization by an additional 60%. We anticipate measuring the rate constants of the five dynamical processes that lead to thermal mixing[4] in order to fully quantify these differences in future work, and optimally pre-polarize pyruvate for use in a clinical setting.

Conclusion: There is no need to add paramagnetic relaxation agents to hyperpolarizers operating at 5 T / 0.8 K, directly contrasting with most pre-clinical protocols operating at 3.35 T / 1.2-1.4 K.

References: [1]Ardenkjaer-Larsen, J.H. *et al*, "Dynamic Nuclear Polarization with Trityls at 1.2K", AMR 2008. [2]Jóhannesson, H. *et al*, "Dynamic Nuclear Polarization of [1-^{13}C]Pyruvic Acid at 4.6 Tesla", JMR 2009 [3]Hu, S. *et al*, "Rapid sequential injections of hyperpolarized [1-^{13}C]pyruvate *in vivo* using a sub-kelvin, multi-sample DNP polarizer", MRM 2013. [4]Serra, S. "On the role of electron-nucleus contact and microwave saturation in thermal mixing DNP", PCCP 2013.