

Ferumoxytol as a blood-pool T₂ relaxation agent for 7T phosphorus spectroscopy

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Synopsis

Ferumoxytol is a licensed carbohydrate-coated, superparamagnetic iron oxide nanoparticle indicated in the treatment of anaemia. We show that, in contrast to other agents, it predominantly reduces T₂, is confined to the blood pool for >1 hour post administration, and therefore could improve the efficiency of saturation pulses that aim to remove the 2,3-diphosphoglycerate signal from blood. This proof-of-principle study shows that Ferumoxytol could enable inorganic phosphate detection in vivo, and hence the determination of pH.

Purpose

³¹P MRS is an invaluable tool to probe myocardial metabolism.^[1] The accurate determination of the chemical shift of the inorganic phosphate (P_i) peak in ³¹P MRS enables the quantification of intracellular pH,^[2] but the determination of myocardial pH *in vivo* is challenging due to the large and spectrally overlapping 2,3-diphosphoglycerate (2,3-DPG) resonance in the blood pool, even at 7T.^[3] Whilst the use of CSI ameliorates this effect significantly, it cannot be completely removed due to partial volume and incomplete saturation effects and the presence of vasculature in the myocardium.^[4] Ferumoxytol is a carbohydrate-coated, superparamagnetic iron oxide nanoparticle indicated in the treatment of anaemia that recently has been shown to act as an effective MR negative contrast agent^[5] that is confined to the blood pool.^[6] We wished to investigate the feasibility of using Ferumoxytol as a T₂-reducing agent to suppress unwanted 2,3-DPG signal in the blood pool.

Methods

All experiments were performed with local ethical approval on a 7T Varian DDR system.

In vitro experiments: Fresh healthy human blood (3 × 2.7 mL vials) was acquired via antecubital fossa venipuncture, and stored in sodium citrate buffer (Vactutainer, BD Healthcare). A cannulation tube was inserted to allow the *in situ* introduction of Ferumoxytol at the clinically indicated dose (4 mg/kg, or [Fe]= 0.9 mM in blood). ³¹P hard pulse spectra were acquired via a single loop surface coil (TR= 512 ms; 10 kHz bandwidth; 3840 averages; $\theta_{\text{Ernst}} \approx 30^\circ$ nominal flip angle) before and after addition of Ferumoxytol. Proton T₂ was also measured by CPMG prior and post Ferumoxytol addition, and T₁ by inversion recovery in both blood and serial dilutions of Ferumoxytol in saline.

In vivo demonstration: A healthy male Wistar rat (200g) was anaesthetised (isoflurane, 2% in 2 L/min O₂) and cannulated (tail vein). As an intermediate step to investigate the cardiac half-life of Ferumoxytol, short-axis proton CINE images of the heart were acquired (51.2 × 51.2 mm² FOV; 96 × 96 matrix; 1.2 mm slice thickness; 20° FA; 4 averages; TR= 4.16 ms; TE= 1.68 mm²; 72 mm volume coil) continuously prior to and up to one hour after the administration of Ferumoxytol. A short T₁ phantom was included next to the animal as a signal reference.

Results

Ferumoxytol is an efficient relaxation agent: As illustrated in Fig. 1, Ferumoxytol reduced saline T₁ and T₂ from 1183/362 ms to 790/28 ms at the physiological concentration of 0.5 mM. In saline, this corresponds to a reduction in T₁/T₂ by a factor of 1.7/12.7. The observed behaviour was well described by a double exponential model, with short/long components of 1200/88 mol⁻¹ for T₁ and 6600/310 mol⁻¹ for T₂.

Reduction of blood pool signal: The T₂ of fresh blood decreased by nearly an order of magnitude, from 65 ms to 5.2 ms following the addition of Ferumoxytol, whereas T₁ reduced from approximately 800 ms to 400 ms. As a direct consequence, Ernst-angle hard pulse spectroscopy on whole human blood showed a reduction in all metabolites. The baseline-corrected integrated DPG peak amplitude reduced from 7 × 10⁵ to 1 × 10⁵. (Fig. 2)

Ferumoxytol is a blood-pool agent that is MR visible for > 1 hour: Repeated CINE measurements show a uniform decrease in LV and RV signal compared to that of the phantom that is statistically significant, but no change in the myocardial signal (Fig. 3, $p < 10^{-7}$ by ANOVA). Given that the received signal under these conditions is proportional to T₂ in the regime that $T_1 \gg \text{TR}$ this observed effect is consistent with a predominantly T₂ mediated effect, as has been reported elsewhere.^[7]

Discussion and Further Work

This proof-of-principle study has demonstrated that Ferumoxytol substantially reduces T₂ at 7T, and is confined to the blood pool in the *in vivo* rodent heart. The value observed at 7T of R₂ compared to R₁ is consistent with the frequency dependence of R₂ and R₁ reported for other USPIOs of 10 nm diameter at lower fields.^[8] As a direct consequence of reducing T₂ the detected phosphorous signal observed by hard pulse spectroscopy decreased by a factor of seven, despite the fact that pulse/acquire experiments are not the most appropriate sequence to maximally exploit this change. Therefore, future work will demonstrate the utility of Ferumoxytol in small animals. CSI experiments are likely to be significantly improved by the addition of Ferumoxytol as the reduction in T₂ would dramatically increase the efficiency of saturation pulses or preparation schemes such as MLEV pulses. As Ferumoxytol is licensed for use in humans, it could therefore form a translatable negative-contrast agent to enhance the ability of ³¹P-MR to resolve the inorganic phosphate peak in the myocardium without the large contaminant signal from 2,3-DPG in the blood pool, and hence determine myocardial pH. Future work will demonstrate this effect *in vivo*.

Acknowledgements

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References

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Figures

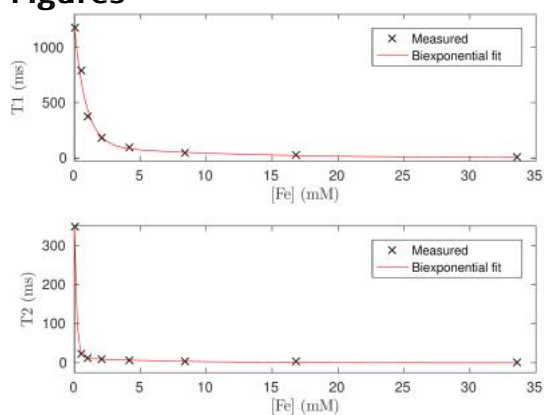


Fig. 1: T_1 and T_2 as a function of $[Fe]$ concentration at 7T in saline. Ferumoxytol addition reduces T_2 substantially more than T_1 over the physiological concentration of 0-5 mM. A double exponential fit to concentration is shown in red.

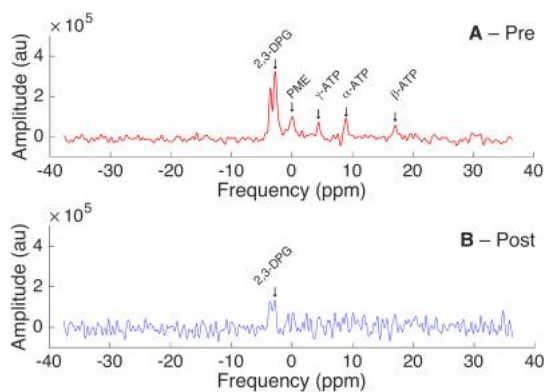


Fig. 2: Spectra acquired from whole human blood before (A) and after (B) addition of Ferumoxytol. The magnitude of the 2,3-DPG signal reduces by approximately a factor of seven, and other peaks are not observable.

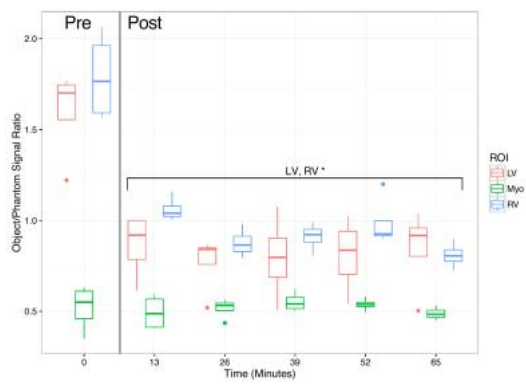


Fig. 3: Ferumoxytol decreases rat blood pool signal for a minimum of ~ 1 hour post injection, without affecting that of the myocardium. For the imaging period after the addition of Ferumoxytol, there was no significant dependence on time ($p = 0.26$ by linear model) although the addition of Ferumoxytol did substantially reduced the observed RV and LV signal intensity ($p < 10^{-7}$).