Ferumoxytol Enhanced 2D & 3D Phase Contrast MRI in dialysis fistulas

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Background: The FDA recently approved a superparamagnetic iron oxide product (ferumoxytol, AMAG) for anemia treatment in patients undergoing dialysis. This product is also a very promising MRI contrast agent for medical applications in which Gadolinium agents are contra-indicated [1]. In the specific application of dialysis fistula assessment, accurate blood flow measurements are essential, as blood flow is an indicator of fistula function. It is thus important to know if the use of ferumoxytol will affect flow measurements. Use of Gd improves 3D flow visualization [2] and has no effect on flow measurements [3]. In comparison, ferumoxytol has a higher r2* relaxivity that could potentially induce strong intravoxel dephasing leading to errors in flow measurements. **The objective** of this study was to evaluate the effect of ferumoxytol on 2D and 3D PC-MR flow imaging.

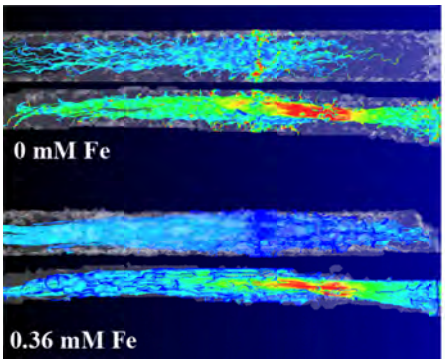

Fig1. Streamline visualization in a flow loop with stenosis, pre and post ferumoxytol.

Materials and Methods:

Phantom experiments were done on a flow loop containing water circulating under steady state conditions in a sealed tube surrounded by a static water phantom (Figure1). Ferumoxytol was added in increasing concentrations to the circulating water, and both 2D and 3D velocity measurements were repeated for every concentration.

6 patients with upper extremity dialysis fistulas were included in the study. Ferumoxytol was diluted with saline (~1:5) and administered intravenously as single or double dose for estimated blood concentrations of 0.4 and 0.8 mM Fe.

Imaging was performed at 1.5T (Siemens Avanto, Erlangen Germany) before and after contrast administration. *Through plane velocities* were measured with a 2D PC-MRI sequence: TR/TE = 29.5/4.1 ms, VENC = 150-250 cm/s FA = 30°, voxel 0.78×0.78×5mm^3, BW = 391Hz/pixel, NA = 3. *All three velocity components* were measured with a 3D PC-MRI sequence: TR/TE = 114.4/4 ms, VENC = 150-250 cm/s FA = 15°, voxel 1.3×1.3×1.1mm^3, BW = 651Hz/pixel, NA = 1.

SNR and flow measurements were performed offline. Data was corrected for background phase errors by subtracting the time averaged velocity map of a "flow off" experiment. In vivo data was corrected for first order eddy currents by subtracting a linear fit of the time averaged velocity map of the static tissue of the arm. Due to the highly off-center location, patient data was also corrected for gradient field nonlinearities [4]. 3D visualization (EnSight, CEI, NC, USA) was used to compare 3D flow characteristics before and after contrast administration.

***Simulations*:** Signal intensities of laminar blood flow were simulated using a theoretical description of the signal in a spoiled gradient echo sequence [5]. The effect of increasing concentrations of ferumoxytol on blood relaxation was included in the simulation.

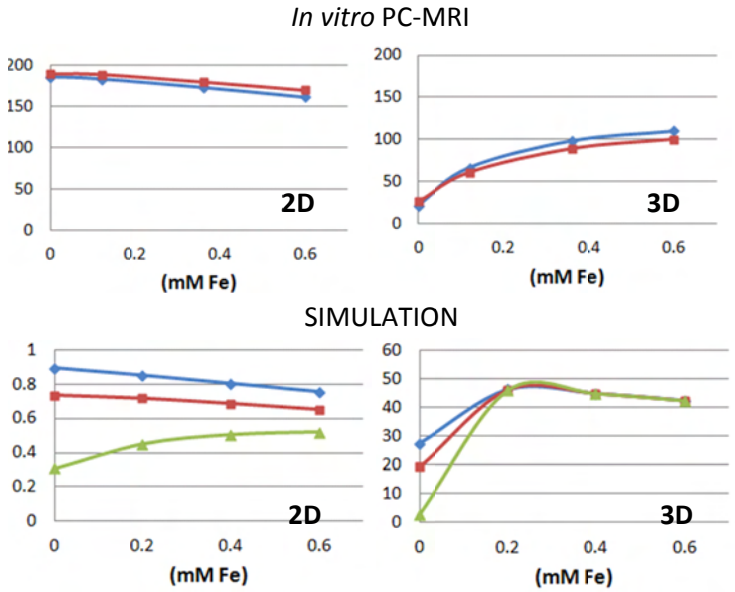

Fig1. Top row: In vitro SNR plots for 10(■) and 25(●) cm/s; Bottom row: Simulated signal intensities (au) for 2(▲), 15(■) and 25(●) cm/s.

Results:

2D PC-MRI with ferumoxytol resulted in a decrease in SNR *in vitro* (Figure2 left). No significant variation was obtained for flow values. *In vivo* contrast administration resulted in a significant decrease of arterial SNR in all patients (* p=0.03, ANOVA with Bonferroni post-hoc). This effect was variable for the venous SNR. Similarly to the *in vitro* results, *in vivo* flow measurements did not vary with contrast administration.

3D PC-MRI with ferumoxytol resulted in a general increase in SNR (Figure2 right) *in vitro*. Furthermore, it greatly improved 3D streamline visualization (Figure1). Flow measurements showed no variation between the different ferumoxytol concentrations. *In vivo*, SNR values measured post contrast were higher than pre-contrast values (Table1). Differences in venous SNR were statistically significant (* p=0.04, ANOVA with Bonferroni post-hoc).

Table1. In vivo SNR values for 2D and 3D PC-MRI

Concentration (mM Fe)	2D	0	0.4	3D	0	0.4	0.8
Artery		167±59	83±42*		20±5	25±3	21±2
Vein		97±42	70±38		15±6	23±3*	22±4

These results were validated by simulation data showing similar variation trends for SNR as a function of velocity and ferumoxytol concentration (Figure2 bottom row). Furthermore, for 2D PC-MRI an increase in SNR for slow moving spins (< 5 cm/s) was obtained over the range of investigated concentrations. This explains the variable effect of venous SNR, where very small velocities can be found in highly dilated vessels.

Discussion:

We have shown here that ferumoxytol, if administered in relatively low concentrations, does not affect PC-MRI flow measurements. However, the velocity dependent effect on SNR needs to be considered. For the investigated concentration range, the T1 effect is dominant when spins experience a large number of RF pulses allowing the magnetization to reach steady state. The T2* effect is dominant for spins that experienced a very small number of RF pulses, in the case of fast moving spins in the 2D acquisition. Based on these results it is preferable to perform 2D measurements before USPIO administration and 3D measurements post contrast.

References: 1. Neuwelt E et al, KidneyInt (2009)75:465–474; **2.** Bock J et al, MRM (2010)63(2):330-8; **3.** Heverhagen JT et al, EJR(2002)44(1):65-9; **4.** Markl M et al, MRM(2003)50:791–801; **5.** Gao, MedPhys(1988)15:809-814.