Positive Contrast with Therapeutic Iron Nanoparticles for In vivo Follow Up at 4.7T

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INTRODUCTION

The biocompatible and biodegradable properties of magnetic nanoparticles (MNP) are expected to enable the inclusion of specific molecules for drug delivery purposes. They open new clinical applications by combining a therapeutic action to the diagnostic approach [1]. The importance of positive contrast techniques is the capability to improve the sensitivity of iron detection compared to standard T2* methods. The "white marker" technique proved to be flexible and able to produce extended bright regions around magnetic disturbers [2, 3].

We report the application of this technique at a relatively high field, 4.7 T in a preliminary *in vitro* and *in vivo* study using a novel superparamagnetic nanosystem designed for local therapy.

MATERIALS AND METHODS

The contrast agent used was a polymeric based MNP consisting of magnetite crystals, with 12 nm in size conferring a superparamagnetic behaviour incorporated as a complex with oleic acid in a matrix of PLLA (poly L-lactic acid) polymer. An in vitro study was performed on an agar gel phantom containing a range of MNP dilutions. For the in vivo part, ten female OF1 mice were used. Animals were submitted to a high pressure injection of contrast agent suspension of 0.25 mmolFe/L in the left calf muscle. The MRI in vitro protocol included a T2* weighted gradient echo sequence: TE/TR = 10/300 ms, flip angle 25°, number of excitations = 4, matrix 256 x 256, 3 non contiguous slices with 1.11 mm thickness, spatial resolution 0.156x0.156 mm. The standard value, for negative contrast imaging was kept at -50 %, to avoid gradient imbalance and noise augmentation. For positive contrast imaging the amplitude of the rephasing gradient was varied between -100 % and 0 %. *In vivo* images were acquired in coronal sections using the same protocol and a spatial resolution of 0.234×0.234 mm. MRI was performed immediately after the injection and repeated 24 and 72 hours later.

RESULTS

Concerning the *in vitro* study, a maximum contrast enhancement (CE) of 31.3% was obtained with the positive contrast method (Figure 1).

The *in vivo* gradient echo negative contrast images clearly showed a signal loss at the injection site due to the strong r2 relaxivity of the contrast agent (*r1* = 1.7±0.1 $mM^{-1}s^{-1}$ and *r2* 228.3±13.1 $mM^{-1}s^{-1}$). A good correlation between the bright regions obtained from gradient compensation and the injection site can be seen in the superimposed images of Figure 3. The time variation of signal intensity was measured for both methods and a contrast decrease was observed after 3 days. As shown in figure 2 the loss of contrast was more pronounced for the gradient compensation method from 55.2±15.4% to 30±14.6% compared to the standard one from -64.9±2.9% to -55.5±5.15% and was correlated with the iron concentrations of 0.25 mmolFe/L at day 0 and of 0.012±0.0017 mmolFe/L detected in calf muscle samples from day 3.

DISCUSSION

We have shown that the gradient compensation method can be efficiently used at a relatively high field strength that, to the best of our knowledge, has not been reported before [3]. Compared to the standard gradient echo the method shows the ability to discern between high concentrations (Figure 1).

The combined negative and positive contrast protocol allowed good quality images to be obtained that offered a good characterisation for the in vivo localization of MNP and their follow up (Figure 3).

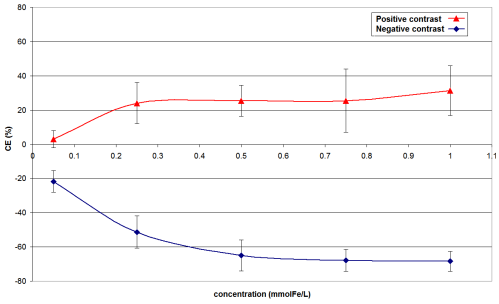

Figure 1. Graphical representations showing the concentration effect on the relative contrast enhancement for the positive and negative contrast imaging.

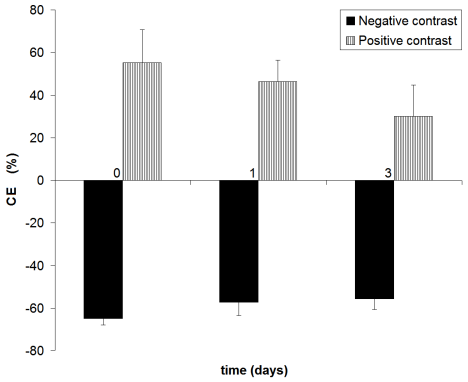

Figure 2. In vivo contrast enhancement values showing a more pronounced decrease over time for the positive contrast method.

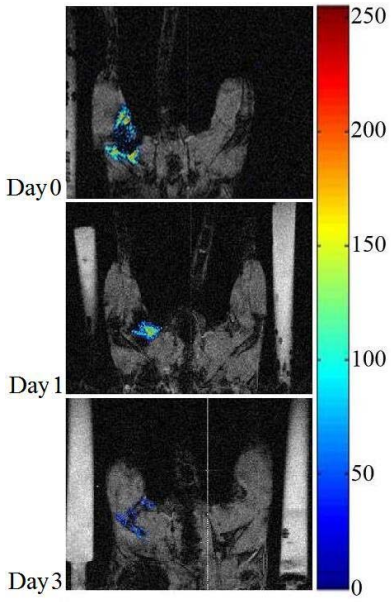

Figure 3. T2* weighted gradient echo images showing a good correlation between the injection site and the bright signal regions presented on a colour scale.

References:

1. Hamoudeh M. et al., International Journal of Pharmaceutics, 2007
2. Seppenwoolde J.H. et al., Magn Reson Med, 2003
3. Mani V. et al., Magn Reson Med, 2006