WASSR imaging of αvβ3 targeted USPIO at 2.35T on U87 mice tumors : feasibility study

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Introduction

Off Saturation Resonance (ORS) is a recent tool [1] to investigate USPIO with high contrast, sensitivity and true spatial localization. In this study, we purpose to adapt a modified ORS sequence, WASSR (WAter Saturation Shift Referencing [2]), initially applied on CEST contrast, to investigate *in vitro* and *in vivo* detection of a targeted USPIO at a clinical field.

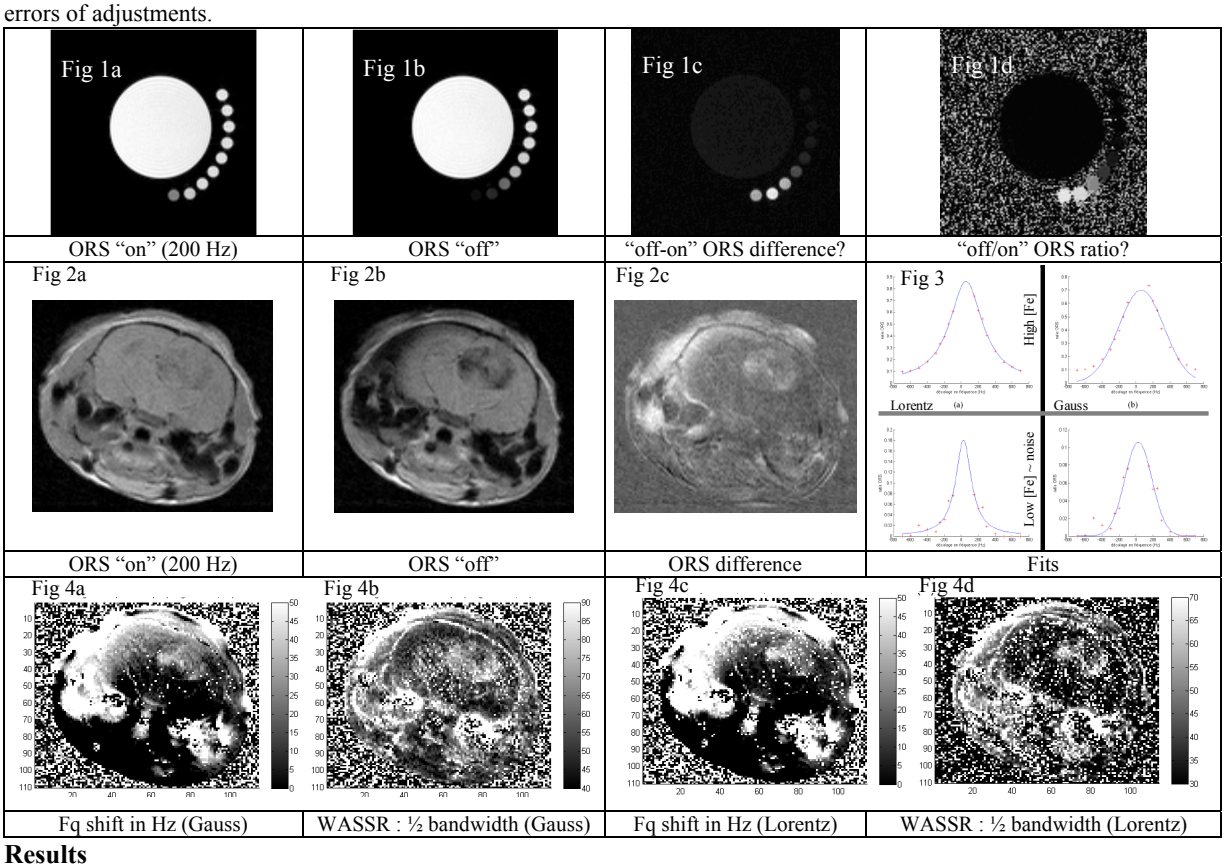
Material & Methods

Contrast agent *:* non-targeted USPIO [P904, Guerbet Research] phantoms were performed, ranging 0.1 µM to 1 mM, to check sensitivity. In vivo experiments were performed with P3420, an αvβ3 molecular imaging USPIO.

In vivo model : P3420 was iv injected at 100µmolFe/kg in U87 brain tumor mice, known to overexpress αvβ3 integrin [3].

MR acquisitions *:* Spin echo sequence was carried out on a 2.35T BioSpec scanners [Bruker, Ettlingen, Germany]. *In vitro* off resonance B1 saturation pulses were twelve 40 ms Gaussian off resonance RF pulses, corresponding to 2.5µT. WASSR shift frequencies ranged between +/- 600 Hz (100 Hz step). *In vivo* off resonance B1 RF pulses were checked to minimize Specific Absorption Rate (SAR) and Magnetization Transfer (MT) effect due to proteins, and to maximize SNR. *In vivo* off resonance B1 was tested at 0.1, 0.3 and 3µT. For *in vivo experiments,* WASSR shift frequency ranged between +/- 150 Hz (30 Hz step).

Post Processing *:* Post processing was performed with Matlab software (MathWorks) to produce ORS "off/on" ratios and WASSR maps (B0 frequency shift, half bandwidth). Fit's functions (Lorentz and Gaussian) were compared to minimize errors of adjustments.



Results

In vitro: *In vitro* MRI underlines high contrast level and sensitivity (fig1). Detection threshold of USPIO is around the micromolar of iron, corresponding to 300pM of USPIOs. This concentration is consistent to endogenous receptor concentrations. ORS ratio avoids relaxation effects visible at higher concentration as compared to ORS difference.

In vivo : Due to respectively MT and SNR considerations, low USPIO detection was performed at 2 and 0.1 µT. Images obtained at 0.3µT B1 provides optimized USPIO detection (fig2&4). As expected, direct ORS imaging suffers of B0 inhomogeneities (fig2). In WASSR, frequency dependence is adjusted to estimate these inhomogeneities and to quantify relation between signal and iron concentration (fig4). In case of high or moderate SNR obtained in phantoms, data are better fitted and described by Lorentz function. In case of more noisy data (*in vivo*), Gaussian function provides better accuracy and robustness.

Conclusion : This preliminary study shows the ability of the WASSR sequence to provide an original approach for *in vivo* USPIO imaging combining high level of contrast enhancement, accurate sensitivity, quantification and appropriate spatial resolution. This sequence is consistent to *in vivo* applications at clinical fields, but has to be adapted to consider endogenous magnetization tranfert and SAR effects.

References: [1] Khemtong et al., Canc Res (2009), 69:1651-58. [2] Kim et al., MRM. (2009), 61:1441-50. [3] Hsu et al., Mol Imaging Biol (2006), 8: 315-23