Diffusion Enhanced Sensitivity of bSSFP Quantification of Micron-Sized Superparamgnetic Iron Oxide

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Introduction

MRI cellular trafficking using superparamagnetic iron oxide (SPIO) is an area of intense research with broad applications in regenerative medicine and immunology research, however a practical quantitative approach that is *both* sensitive and specific to SPIO has yet to be presented. Quantification in cellular imaging studies is vital to investigate comparative efficacies for regenerative medicine and immunomodulatory therapies. Conventional spin echo (SE) sequences provide SPIO quantification that is very SPIO-cell specific because of inherent refocusing of background magnetic field inhomogeneities (imperfect shim), however SE sensitivity to SPIO labeled cells is unfortunately as much as 70 times less sensitive than gradient echo (GE) techniques [1]. Conversely, GE sequences offer optimal SPIO sensitivity, but artifacts created by field inhomogeneities greatly reduce GE's SPIO specificity. Most recently, balanced steady state free precession (bSSFP) has demonstrated potential to be the best approach to cellular density imaging, having both SPIO sensitivity comparable to GE acquisitions [2], and preserved specificity from SE-like refocusing of background field inhomogeneities [3]. The potential for SPIO labeled cell quantification using bSSFP was demonstrated, in principle, using a phantom model of SPIO loaded cells and analytic expressions for transverse relaxation rate enhancement [2]. A linear dependence between the transverse relaxation rate enhancement measured using bSSFP ($\Delta R_2^{(bSSFP)}$) and the local magnetic dose (LMD) was demonstrated for Gd-DTPA doped gel containing polystyrene microspheres [2].

To date, no bSSFP sequence practical for quantitative SPIO cellular density imaging applications has been evaluated, and no assessment using SPIO contrast agents has been reported. In this work, we have studied two candidate bSSFP sequences for quantification of $\Delta R_2^{(bSSFP)}$. The first, segmented inversion recovery (IR) bSSFP has been proposed for quantifying T_1, T_2 and M_o by Schmitt et al. [4], and we have adapted the technique for SPIO quantification ($\Delta R_2^{(IR)}$). A second approach, using variable echo time bSSFP acquisitions (VT), was also analyzed for SPIO quantification ($\Delta R_2^{(VT)}$). We show that ΔR_2 estimates from both sequences, $\Delta R_2^{(IR)}$ and $\Delta R_2^{(VT)}$, demonstrate 2-3 times greater sensitivity than ΔR_2 from CPMG acquisitions, and with excellent linearity to varied concentration of micron sized particles of iron-oxide (MPIO). The mechanism of this sensitivity enhancement is shown to be from diffusion effects in the MPIO samples.

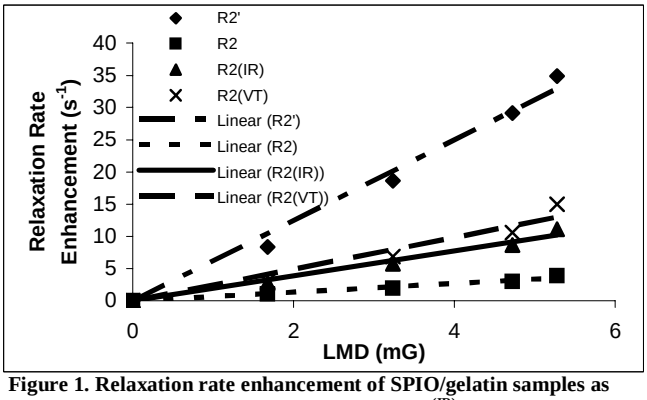

Figure 1. Relaxation rate enhancement of SPIO/gelatin samples as quantified by GE (R_2*), SE (R_2), IR bSSFP ($R_2^{(IR)}$) and VT bSSFP ($R_2^{(VT)}$). bSSFP relaxation rates are significantly greater than R_2, and well correlated to LMD, a measure of SPIO concentration.

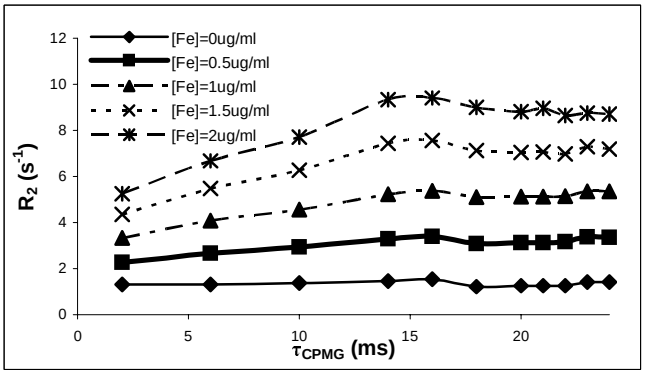

Figure 2. R_2 sensitivity to varied τ_{CPMG} for CPMG acquisitions using MPIO/gelatin samples with a range of iron concentrations. Diffusion sensitivity is consistent with Luz-Meiboom predictions.

Methods

Acquisitions were performed on a 4-T Varian/Siemens whole-body scanner on a model of cells containing MPIO, where the MPIO were freely suspended in gelatin. In contrast to SPIO nanoparticles which require compartmentalization of a large number of particles within a cell for detection, MPIO particles were chosen because of their large iron-content which allows single particles to be detectable using MRI. A 5-cm diameter cylinder containing 5mm OD NMR tubes having a range of MPIO concentrations (0-2 μg/ml) were used. 2D IR-prepped α/2-catalyzed bSSFP parameters were: 6x6 cm FOV, 128x128, 10 mm slice, 10/5 ms TR/TE, 200 echoes along IR train, 6 s segment delay and 2 phase cycled acquisitions. R_2 quantification from IR recovery rate was estimated as described by Schmitt [4]. Similarly, 2D α/2-catalyzed VT bSSFP acquisition parameters were: 6x6 cm FOV, 128x128, 10 mm slice, TR/TE ranging from 10/5 ms to 50/25 ms, 500 catalyzation pulses and 2 phase cycles. VT bSSFP R_2 values were quantified by an exponential fit of the signal with varied TE. ΔR_2 enhancement relative to gel references were compared to ΔR_2 values obtained from a non-localized CPMG sequence (SE) of individual tubes, and ΔR_2^* values extracted from a multi-echo FLASH imaging sequence (GE) of the cylindrical phantom. CPMG acquisitions were repeated for a range of 180°-180° spacings, τ_{CPMG}, to assess the role of diffusion. The amount of SPIO per phantom was estimated using an MRI susceptometry technique [1] to quantify the local magnetic dose (LMD).

Table 1 SPIO quantification sensitivities as calculated from the slopes of the relaxation rate enhancement versus LMD.

Sequence	MPIO Relaxation Rate Enhancement Sensitivity (s^{-1}/mG)
GE	6.7 ± 0.5
SE (τ_{CPMG}=10ms)	1.2 ± 0.006
IR bSSFP (TR=10ms)	2.0 ± 0.1
VT bSSFP (TR=10ms)	3.1 ± 0.1

Results & Discussion

Figure 1 shows that the transverse relaxation rate enhancement quantified by IR and VT bSSFP is two to three times higher than SE, but a third to a half that of GE (see **Table 1**). The enhanced sensitivity to MPIO of $\Delta R_2^{(IR)}$ and $\Delta R_2^{(VT)}$, compared to ΔR_2 from spin-echo estimates, may reflect the enhanced diffusion sensitivity to MPIO micro-field gradients for bSSFP acquisitions. The role of diffusion is supported by ΔR_2 sensitivity to τ_{CPMG} variation for CPMG measurements shown in **Figure 2**, as well as by GE relaxivity being below the static dephasing prediction of 10.78 $s^{-1}mG^{-1}$ [1], for conditions of negligible diffusion (see **Table 1**). Additionally, the elevated sensitivity of $\Delta R_2^{(VT)}$ compared to $\Delta R_2^{(IR)}$ relaxivity (3.1 vs 2.0 $s^{-1}mG^{-1}$) is analogous to the elevated diffusion sensitivity of single echo spin-echo compared to CPMG acquisitions of fixed τ_{CPMG}. All observations are consistent with a diffusion contrast mechanism.

Conclusions

The potential to quantify MPIO labeled cells using IR and VT bSSFP acquisitions for low cell density applications is supported in this work by the accurate quantification of iron content using MPIO suspensions. The 2-3 fold improvement in sensitivity for bSSFP compared to SE is consistent with enhanced diffusion sensitivity to MPIO micro-field gradients, consistent with the reports of others studying bSSFP diffusion sensitivity [5]. Although $\Delta R_2^{(IR)}$ and $\Delta R_2^{(VT)}$ sensitivities to MPIO are significantly less than ΔR_2* from GE acquisitions, bSSFP acquisitions have spin-echo like specificity to MPIO through refocusing of background tissue inhomogeneities, and great potential for producing quantitative SPIO labeled cellular density maps for low density, cellular trafficking applications.

References

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