Ultra-short Echo Time Balanced SSFP for Highly Sensitive Detection and Quantification of Multi-resonant ^{19}F Imaging Agents for Targeted Molecular MRI

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Introduction

^{19}F-MRI [1] bears a high potential for molecular imaging allowing the direct quantification of targeted perfluoro-carbon nanoparticles (NP) [2] or labeled cells [3]. Previously, $\alpha_v\beta_3$-integrin targeted NP have been shown to detect and quantify angiogenesis in tumor models [4, 5]. Towards human translation of NP, clinically-relevant compounds like perfluoro-octyl-bromide (PFOB, CF_3-$(CF_2)_6$-CF_2Br) should be used because of their favorable safety and stability. But rich spectra and large chemical shifts (CS) add significant complexity (PFOB has 7 ^{19}F-resonances) making robust and optimal signal detection challenging. Many methods have been developed to manage CS-artifacts, but tradeoffs in SNR efficiency (selection of single resonances like CF_3 [6]) and needs for complex δB_0 or relaxation correction remain (IDEAL [7], echo-time encoding [8]). A combination of ultra-short echo time (UTE) with a balanced steady-state free precession (SSFP) pulse sequence offers a means for highly sensitive detection of multi-resonant imaging labels like PFOB. A robust technique, as presented herein, will be important for the clinical translation of NP-based targeted molecular MRI.

Methods

As shown in Figure 1, all CS components of a PFOB CF_2 line group (5 components, at 3T: 0, +/-100 Hz, +/-500Hz) stay within a phase range of +/-90 degrees for about 0.5 ms and are not yet affected by the apparent T2 relaxation (10ms). Using a UTE sequence with an echo time of 100 µs, a typical gradient performance of 200 $mTm^{-1}s^{-1}$ and a pixel bandwidth of 1 kHz, the FID readout takes about 0.6 ms resulting in a spatial resolution of about 1mm, well suited for the detection and quantification of targeted PFOB-NP. The sequence was implemented on a 3T clinical whole-body scanner (Achieva, Philips Healthcare, NL) using a ^{19}F/^{1}H dual-tuned transmit/receive solenoid coil (∅7 cm) with the following imaging parameters: 3D UTE balanced SSFP sequence with radial readout (Wong-type [9] radial trajectory), FOV=128 mm, matrix 128^3, isotropic voxel Δx=1.0 mm, α=30°, excitation bandwidth exBW=5 kHz centred on the PFOB-CF_2 line group, pixel bandwidth pBW=900 Hz, TR=2.1 ms, TE=90µs (FID sampling), T_{exp}=71 sec. For comparison, 3D sequences with cartesian k-space sampling were used with identical FOV, spatial resolution, exBW and pBW: (i) Gradient-echo, (ii) balanced SSFP and (iii) fast spin-echo (TSE). Imaging parameters: (i) α=30°, TR/TE=4.8/2.1 ms, T_{exp}=104 sec; (ii) α=30°, TR/TE=4.2/2.1 ms, T_{exp}=89 sec; (iii) α=90°, TSE/RARE factor 116, pBW=660 Hz, exBW=2830 Hz, TR=4000 ms, TE=7.4 ms, T_{exp}=1032 sec. For further comparison to line selection methods [6], the fast-spin echo sequence was also performed on the CF_3 line. Sensitivity was measured in terms of $S=SNR\times(mol/voxel)^{-1}\times T_{exp}^{-1/2}$, where SNR is the achieved signal-to-noise ratio, T_{exp} the duration of the sequence and (mol/voxel) the amount of PFOB agent within an imaging voxel.

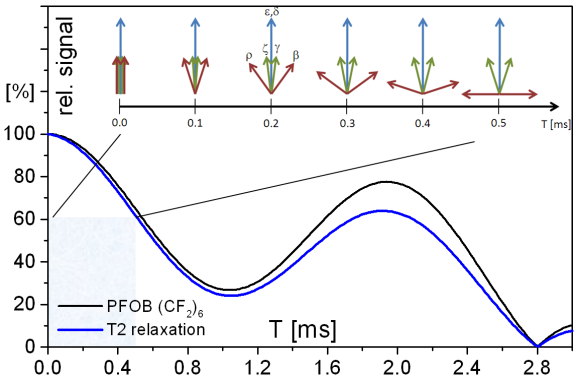

Figure 1: ^{19}F signal evolution of the $(CF_2)_6$ line group (β,γ,δ,ε,ζ,ρ) of perfluoro-octyl-bromide, without and with apparent T2 relaxation. During a fast FID readout as in the UTE-SSFP technique, the relative signal remains above 60%, which cannot be recovered for later echo times.

PFOB line(s)	Sequence	Sensitivity S [SNR×µmol^{-1}min$^{-1/2}$]
$(CF_2)_6$	gradient-echo/FLASH	12
	bal. SSFP	23
	fast spin-echo/RARE	16
	UTE-SSFP	51
CF_3	fast spin-echo/RARE	7

Table 1: Sensitivity comparison of the novel UTE-SSFP technique for ^{19}F MRI of PFOB to standard imaging sequences (GRE, balanced SSFP, fast spin-echo/RARE)

Results and Discussion

Table 1 summarizes the observed sensitivity for the investigated sequence types. With S=51 $\mu mol_{PFOB}^{-1}min^{-1/2}$, the proposed UTE-SSFP technique is superior with a sensitivity of at least twice that of other sequence types. The next best sequence is balanced SSFP with a cartesian k-space trajectory, demonstrating the value of the T1/T2 contrast, in particular for perfluoro-carbons with long T1 and for agents with shortened T2 such as those bound to molecular targets [10]. The signal gain by constructive addition of all CF_2 lines clearly over-compensates the loss in SNR-efficiency imposed by 3D radial sampling (25%) and the FID readout, which requires twice the number of k-space lines, since all start at $k_{x,y,z}$=0. For $(CF_2)_6$, the proximate CS components lead to destructive signal overlay at larger echo time (e.g. 2.8 ms) and are difficult to separate with line selection techniques. Fast spin-echo techniques are typically highly SNR efficient, but are not optimal for perfluoro-carbons like PFOB. The achievable echo times do not allow full signal combination of the CF_2-group. Selecting the CF_3 group is possible, but only uses 3 out of the 17 fluorine nuclei, as reflected in the lowered sensitivity, S=7 $\mu mol_{PFOB}^{-1}min^{-1/2}$. The UTE-SSFP technique is optimal for a short (apparent) T2 relaxation. The proposed UTE-SSFP technique can be combined with simultaneous dual-nuclei techniques [5] for efficient anatomical localization, motion correction and quantitative calibration of the non-proton signals.

Conclusion

In conclusion, a novel UTE-SSFP technique was demonstrated that allows a highly sensitive detection of multi-resonant imaging labels like PFOB.

References

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