Increased sensitivity of ^{19}F MR of perfluoro-emulsions using lanthanide chelates for T_1 shortening

R. Lamerichs[1], R. Wegh[1], D. Burdinski[1], S. Langereis[1], and H. Grüll[1]
[1]Philips Research, Eindhoven, Netherlands

Introduction
Since fluorine (^{19}F) does not occur naturally in the human body in significant amounts, MR imaging of ^{19}F containing compounds will has intrinsic high specificity, which is a major advantage for Molecular Imaging purposes. One of the major drawbacks of Molecular Imaging by MRI is the inherently low sensitivity. To increase the sensitivity, the use of perfluoro-compounds in emulsions containing particles with a size between 200-500 nm has been proposed [1]. However, the T_1 of these perfluoro-compounds is generally long compared to the repetition times that are typically used in MRI sequences, resulting in significant signal loss due to T_1 saturation. This phenomenon also occurs in ^{1}H imaging, in which case the signal loss can be overcome by using contrast agents that shorten the T_1, i.e. Gd-DPTA [2]. With the same compounds, the T_1 of ^{19}F compounds can also be shortened, provided they are dissolved in aqueous solutions [3]. Here we show that the T_1 of perfluoro compounds can be shortened significantly even in non-aqueous solutions by using hydrophobic gadolinium complexes that bear fluorinated ligands. With this approach a significantly increased sensitivity of ^{19}F MRI and MRS has been achieved.

Experimental
Gadolinium tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate) ($Gd(fod)_3$) was obtained from ABCR, Karlsruhe, Germany. It was mixed with perfluoro-octyl-bromide (PFOB) which was obtained from Fluorochem, Old Glossop, UK, to give a 0.16 molar solution. This stock solution was diluted with different amounts of PFOB to give the solutions (each about 400 µl) used in this work. MR imaging was performed on a Philips Achieva clinical scanner, 3T dual-quasar, Philips Medical Systems, Best, the Netherlands. T_1 values were determined using an inversion-recovery spectroscopy sequence. The images were recorded with a gradient echo sequence with RF spoiling (T_1 -FFE). A specially designed ^{19}F small-volume coil was used for both imaging and T_1 measurements.

Results and discussion
Experimental data obtained at 3 Tesla are shown in Table 1. $Gd(fod)_3$ can decreases the T_1 of PFOB significantly. The T_1 values were used to determine the r_1 as shown in Figure 1. For this specific gadolinium complex the r_1 is 1.6 $mM^{-1}s^{-1}$. This value is lower than for most water soluble chelates (about 4 $mM^{-1}s^{-1}$). The relaxation mechanism is still under investigation, but considering PFOB being a very poor ligand for metal ions it is reasonable to assume that relaxation resulting from 2nd and out-sphere interactions dominates. The T_1-weighted field-echo images are shown in Figure 3. From the line profiles it can be deduced that the signal intensity increases by a factor of about 10 for the 10 mM solution.

Conclusion
The sensitivity of ^{19}F MRI and MRS of perfluorinated organic compounds is increased significantly by T_1 shortening of the ^{19}F resonance in the presence of suitable lanthanide complexes.

References
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Sample		^{19}F T_1 at 3 Tesla
1	Pure PFOB	1318±10 ms
2	2.5 mM $Gd(fod)_3$ + PFOB	211±0.5 ms
3	5.0 mM $Gd(fod)_3$ + PFOB	109±0.7 ms
4	10.0 mM $Gd(fod)_3$ + PFOB	60±1.0 ms

Table 1. T_1 relaxation time shortening of PFOB with $Gd(fod)_3$.

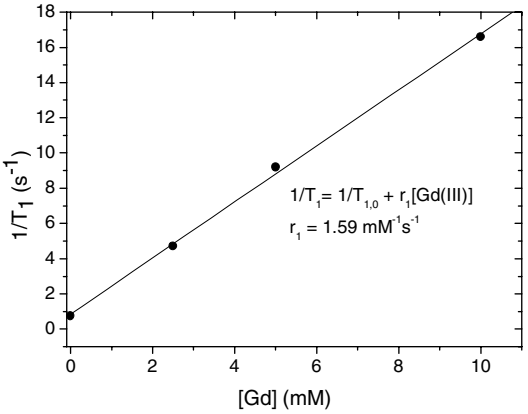

Fig. 1. Longitudinal relaxivity of $Gd(fod)_3$ in PFOB.

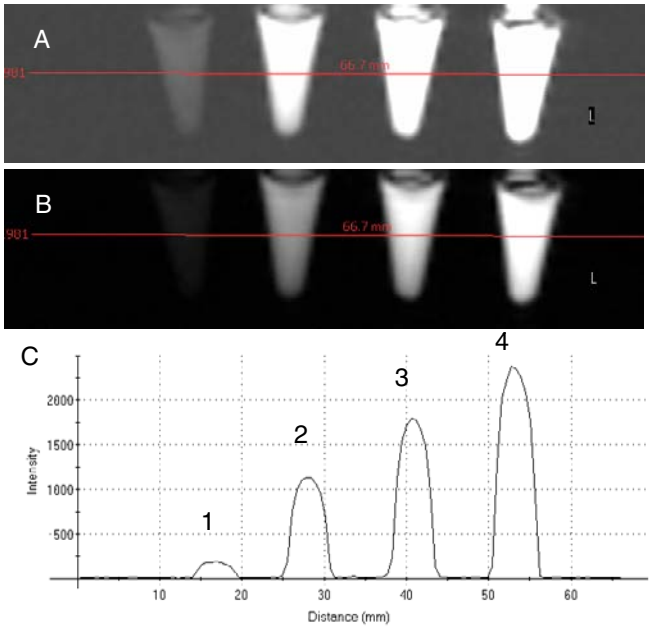

Fig. 2. T_1-FFE image of the 4 samples from table 1. A and B are the same images, but with different window setting in order to show the image of vial 1 (pure PFOB) better in A. The window levels in B are the default setting from the scanner. C shows the profile along the line indicated in the images.