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Improved Quantitative ^{19}F MR Molecular Imaging With Flip Angle Calibration and B_1 -Mapping Compensation

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Abstract

Purpose—To improve ^{19}F flip angle calibration and compensate for B_1 inhomogeneities in quantitative ^{19}F MRI of sparse molecular epitopes with perfluorocarbon (PFC) nanoparticle (NP) emulsion contrast agents.

Materials and Methods—Flip angle sweep experiments on PFC-NP point source phantoms with three custom-designed $^{19}\text{F}/^1\text{H}$ dual-tuned coils revealed a difference in required power settings for ^{19}F and ^1H nuclei, which was used to calculate a calibration ratio specific for each coil. An image-based correction technique was developed using B_1 -field mapping on ^1H to correct for ^{19}F and ^1H images in two phantom experiments.

Results—Optimized ^{19}F peak power differed significantly from that of ^1H power for each coil ($p < 0.05$). A ratio of $^{19}\text{F}/^1\text{H}$ power settings yielded a coil-specific and spatially independent calibration value (surface: 1.48 ± 0.06 ; semi-cylindrical: 1.71 ± 0.02 , single-turn-solenoid: 1.92 ± 0.03). ^1H -image-based B_1 correction equalized the signal intensity of ^{19}F images for two identical ^{19}F PFC-NP samples placed in different parts of the field, which were offset significantly by $\sim 66\%$ ($p < 0.001$) before correction.

Conclusion— ^{19}F flip angle calibration and B_1 -mapping compensations to the ^{19}F images employing the more abundant ^1H signal as a basis for correction result in a significant change in the quantification of sparse ^{19}F MR signals from targeted PFC NP emulsions.

Keywords

quantitative ^{19}F MRI; molecular imaging; RF power settings; flip angle calibration; B_1 correction; perfluorocarbon nanoparticles

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INTRODUCTION

MR molecular imaging with the use of ligand-targeted contrast agents has proven capable of noninvasively detecting the presence of cellular indicators of biological processes for many classes of pathology (1–4). Common exogenous contrast mechanisms have employed either paramagnetic or superparamagnetic readouts based on the composition of the core materials of nanoparticulate agents that function by altering the local relaxation properties of protons in T_1 or T_2/T_2^* weighted images to reveal local changes in MRI contrast indicative of a binding event (5). Of the paramagnetic agents, one of the first to become useful for a broad range of imaging applications was a perfluorocarbon (PFC) core nanoparticle (NP) decorated with several hundred thousand gadolinium atoms with the use of conventional chelating chemistries, and a smaller population of molecular targeting ligands (e.g., antibodies, small molecules, peptides, etc.) covalently coupled into a surrounding lipid/surfactant monolayer (6–9). Further model-based efforts have been pursued to quantify these sparse binding events in attempts to compute the concentrations of the targeted epitopes (10). Yet all of these approaches that rely on indirect readouts of binding through altered proton relaxation suffer from high background proton signals, susceptibility artifacts (11), potential toxicities of the contrast agent itself (12,13), and most importantly, the need for both pre- and post-contrast images to accurately delineate changes in local contrast (14,15).

For some time, it has been appreciated that the ability to create local MRI contrast based on detection of alternative nuclei such as fluorine (^{19}F) might offer a direct and quantifiable readout of molecular binding events (16–18). Fluorine exhibits well-known advantages of being a high signal nucleus with a natural abundance of its stable isotope, favorable toxicity profiles, a convenient gyromagnetic ratio close to that of protons ($\gamma = \sim 6\%$) (19), and a unique spectral signature with no detectable background at clinical field strengths (20). However, clinical development of this approach has been slowed by the need to deposit sufficient concentrations of the contrast material within a voxel to yield a detectable signal, and by the lack of imaging hardware and software (e.g., coils, multinuclear spectrometers, pulse sequences, etc.). Over the past 15 years, efforts in ^{19}F contrast agent development and imaging at 1.5 and 3T have yielded translatable solutions to many of these imaging hardware needs (21,22), while simultaneously validating the utility of the PFC-core nanoparticle agents as targetable molecular imaging probes (23–25).

However, for ^{19}F MRI to mature as a truly robust whole body detection approach for quantifying molecular binding events noninvasively, additional obstacles must be overcome. Although ^{19}F MRI is potentially quantitative in nature because ^{19}F spin density (and signal) is linearly correlated to the deposition and resultant concentration PFC NPs at a particular site in the body (17), the imaging chain of a clinical MR system comprises many steps that can confound absolute signal calibration, even when specialized transmit/receive (T/R) coils are used (26). Coil tuning and RF drive power (i.e., flip angle) settings must be calibrated and center frequency determined for ^{19}F tracers that are in miniscule concentrations lending little signal on which to perform these measures that drive not only image quality, but ultimately accuracy. ^{19}F MRI also is susceptible to imaging artifacts, such as motion, partial volume, and eddy currents, all of which can degrade image quality and produce quantification errors (21). Lastly, B_1 -field inhomogeneities that are inherent to many surface

T/R coils, which are necessary to achieve sufficient SNR in clinical settings, must be accounted for (27,28). Because the concentration of PFC NPs within a voxel is determined by a comparison to an external standard of known ^{19}F concentration, local differences in the B_1 field between the targeted region of interest and the location of the standard may lead to errors in the quantified ^{19}F signal.

The purpose of this study is to improve quantitative ^{19}F MRI of sparse molecular epitopes from perfluorocarbon nanoparticle emulsion contrast agents using ^{19}F flip angle calibration and ^1H -based B_1 -mapping compensation to the ^{19}F and ^1H data.

MATERIALS AND METHODS

Magnetic Resonance Spectroscopy

All magnetic resonance spectroscopy and imaging data were acquired on a 3T clinical whole-body scanner (Achieva, Philips Healthcare, The Netherlands) with a dual $^{19}\text{F}/^1\text{H}$ spectrometer system (21). Dual-resonant $^{19}\text{F}/^1\text{H}$ RF coils were used, which can either transmit or receive at both resonance frequencies simultaneously (29). Three dual-tuned coils were used for the MRS experiment including a single loop rectangular surface coil (7×12 cm, Philips Healthcare, The Netherlands), a custom-built semi-cylindrical coil (13 cm diameter, 15 cm length), and a custom-built single-turn solenoid coil (11.5 cm diameter, 14 cm length) (Fig. 1). Before each MRS experiment, the $^{19}\text{F}/^1\text{H}$ coils were tuned to resonate at both the fluorine and hydrogen frequencies (120.1 and 127.7 MHz, respectively at 3T) on a network analyzer (National Instruments, Austin, TX, USA) at -30 dB signal loss or better.

PFC NP Formulation and MRS Phantom Setup

A nontargeted perfluoro-15-crown-5-ether (PFCE: $\text{C}_{10}\text{F}_{20}\text{O}_5$) NP emulsion was prepared as previously published (30), which was composed of 20% (v/v) PFCE (Exfluor Research Corp., Round Rock, TX, USA), 2.0% (w/v) surfactant commixture, and 1.7% (w/v) glycerin, with water comprising the remaining balance. An MRS point source phantom was created by filling a 1 mL clear glass shell vial (6 mm inner diameter, National Scientific, Rockwood, TN, USA) with 50 mM PFCE NP emulsion in 2% agar (0.2 mL volume, 5 mm height in vial), with 2% agar comprising the rest of the volume. The phantom was positioned in a 1 L beaker filled with 275 mL 1.0% saline using a custom-built holder allowing translational movement in two directions (± 18 mm) at three different heights (9 mm, 15 mm, and 27 mm) above the surface and semicylindrical coils, and within the solenoid coil.

Power Setting Optimization and Flip Angle Calibration

Flip angle sweep experiments were performed on the ^{19}F and ^1H frequencies independently to determine optimal RF output settings for flip angle calibration. Slice-selective spectroscopic echo sampling was first performed on the ^{19}F signal as a single series, sweeping the flip angle setting from 10° to 210° in 10° -increments with the following parameters: 10 mm slice, 8 kHz excitation BW centered on single PFCE peak, TR/TE = 2000/2.6 ms, 4 NSA, scan time 4 min, automated power optimization preparation phase turned off. Peak power settings were adjusted according to the offset between real and requested 90° pulse, and the sequence was repeated in an iterative fashion until the optimal

power setting was achieved, denoted by a maximum spectral height at the requested 90° pulse (Fig. 2a).

After acquiring a similar data set at this same power setting on the ^1H channel for comparison, the process was repeated at the ^1H frequency until an optimal power setting was achieved, which was then compared to the ^{19}F setting. This experiment was repeated in triplicate with the phantom located at 15 distinct locations for each coil, with replicates occurring on separate days after detuning and retuning the coils.

Optimized RF power settings for the ^{19}F and ^1H nuclei were depicted with a 3D ball plot in MATLAB (MathWorks, Natick, MA), with both spherical radius and color representing peak power (W) for each nucleus, averaged over each replicate. A ratio of $^{19}\text{F}/^1\text{H}$ peak power at each phantom location is also visualized with a ball plot, and a global average of $^{19}\text{F}/^1\text{H}$ peak power from all locations is reported for each RF coil, termed flip angle calibration ratio.

MRI Phantom Setup and B_1 -Mapping Compensation

Two fluorine-containing phantoms were created to design and test a B_1 -mapping compensation technique to correct for RF inhomogeneities in ^{19}F MRI with $^{19}\text{F}/^1\text{H}$ dual-tuned coils. A discrete sample phantom was made with two 5 mL glass vials (inner diameter 15 mm) filled with 1.0 M sodium fluoride (NaF) in 2% agar, aligned 2 cm apart in 200 mL bottle of 1.0% saline. A homogeneous ^{19}F phantom consisted of a 300 mL glass bottle (inner diameter 6 cm) filled with 1.0 M NaF in 2% agar.

A simultaneous $^{19}\text{F}/^1\text{H}$ 2D balanced gradient echo (GRE) imaging sequence was used to generate transverse ^{19}F and ^1H images of the phantoms, with identical parameters as follows: 140 mm FOV, matrix 64×64 , 4 mm slice thickness, $2.18 \times 2.18 \times 4$ mm resolution, $\text{exBW} = 4$ kHz centered on the single NaF peak, $\text{pBW} = 500$ Hz, $\alpha = 25^\circ$, $\text{TR}/\text{TE} = 3.64/1.82$ ms, $\text{NSA} = 1000$, 3.8 min scan time. The B_1 field was mapped using an actual flip angle imaging (AFI) sequence with the following parameters for both phantoms: 140 mm FOV, matrix 64×64 , 13 4-mm slices, $2.18 \times 2.18 \times 4$ mm resolution, $\alpha = 70^\circ$, $\text{TR}/\text{TE} = 13.43/2.23$ ms, 1.0 min scan time.

To correct for RF inhomogeneities present in the simultaneous $^{19}\text{F}/^1\text{H}$ balanced GRE image acquisition, the sequence was modeled following rephased gradient echo theory as per Eq. 4.24 in Vlaardingerbroek et al. (31) as

$$M_T = M_0 \sin \alpha_{\text{nom}} \sqrt{E_2} \frac{1 - E_1}{1 - E_1 E_2 - (E_1 - E_2) \cos \alpha_{\text{nom}}}, \quad [1]$$

where α_{nom} is the nominal flip angle and $E_{1,2} = e^{-\text{TR}/T_{1,2}}$. From this signal model, a calibration factor (ρ) can be defined as

$$\rho = \sin(\text{AFI} * \alpha_{\text{nom}}) \frac{1 - E_1}{1 - E_1 E_2 - (E_1 - E_2) \cos(\text{AFI} * \alpha_{\text{nom}})}, \quad [2]$$

where AFI represents the voxel values from the B_1 map ($\alpha_{\text{requested}}/\alpha_{\text{nominal}}$). A spatially dependent calibration mask was calculated from Eq. 2 in MATLAB and used to compensate the ^1H and ^{19}F signal intensities of the molecular imaging sequence by dividing each image by ρ , on a voxel-by-voxel basis.

Statistical Analysis

MR spectroscopy and imaging data were analyzed with analysis of variance (ANOVA) or student t-tests as appropriate with MATLAB. For all statistical tests, $p < 0.05$ denotes statistical significance. Standard errors of the mean are reported for MRS and MRI measurements, and used to display error bars. Measures of ^{19}F image homogeneity were calculated as a root-mean-square value over all ^{19}F signal-containing voxels.

RESULTS

Power Setting Optimization and Flip Angle Calibration

Power settings were optimized for ^{19}F and ^1H nuclei, such that a requested 90° flip angle yielded a maximum spectral height in FA sweep measurements of a PFC NP point source phantom. Figure 2 shows a representative FA sweep that was optimized for ^{19}F (top), and the resultant ^1H FA sweep (bottom) using the same power setting (peak power = 122.9 W), which yielded a maximum ^1H spectral height at 20° .

Power settings for ^{19}F and ^1H nuclei are depicted in a 3D ball plot (Fig. 3), in which the spherical radius and color correspond to the requested peak power (W) for a point source PFCE NP phantom at 15 distinct locations in the FOV of the surface coil, averaged over three replicates. These plots exemplify the need for higher power settings to accurately measure sources farther away from a surface coil, as well as the obvious difference in optimal power settings between ^{19}F and ^1H nuclei. However, a ratio of optimum $^{19}\text{F}/^1\text{H}$ power requirements yields a spatially independent calibration value for the surface coil (1.48 ± 0.06).

Figure 4 displays the MRS phantom data for all three $^{19}\text{F}/^1\text{H}$ dual-tuned coils, with averaged measurements from all five locations at each height (9, 15, 27 mm). Optimized ^{19}F peak power was significantly different than the ^1H power requirement at each height for each coil ($p < 0.05$ in each case). Taking a ratio of $^{19}\text{F}/^1\text{H}$ power settings for the semi-cylindrical coil yielded a calibration value of 1.71 ± 0.02 , and 1.92 ± 0.03 for the single-turn solenoid coil.

B_1 -Mapping Compensation in Phantom Experiments

Figure 5 demonstrates a technique for B_1 -mapping compensation of ^{19}F MRI using the ^1H signal in a phantom containing two vials of 1.0 M NaF in agar, imaged with a simultaneous $^{19}\text{F}/^1\text{H}$ GRE sequence and a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil. Before correction, the ^{19}F image (Fig. 5a) and $^{19}\text{F}/^1\text{H}$ overlay image (Fig. 5b) exhibit the effects of the inhomogeneous RF field produced by the surface coil. Mean signal intensity in the vial closest to the coil was 2537 ± 176 arbitrary units (a.u.), while the ^{19}F signal from the identical vial 2 cm farther from the coil was 66.0% lower (863 ± 40 a.u., $p < 0.001$). The B_1 -field was mapped using the ^1H signal with actual flip angle imaging (% actual/requested

FA) (Fig. 5c), and input into Eq. 2 to create a correction ratio Fig. 5d). This factor was used to correct both ^{19}F and ^1H signal intensities, as displayed in Figure 5e&f. After correction, the mean signal intensity in the vial closest to the coil (2621 ± 156 a.u.) was not significantly different ($p = 0.85$) than that in the vial farther from the coil (2681 ± 129 a.u.).

Figure 6 shows the B_1 -field compensation applied to a homogeneous phantom of 1.0 M NaF in 2% agar. Before correction, the ^{19}F (Fig. 6a) and $^{19}\text{F}/^1\text{H}$ overlay images (Fig. 6b) display the inhomogeneity of the surface coil, with a mean signal intensity of 1145 ± 35 a.u. and a RMS value of 1320 a.u.. B_1 -mapping compensation with AFI and calculated correction ratio (Fig. 6c&d), yielded a more homogeneous corrected ^{19}F image (Fig. 6e), as measured by a mean signal intensity of 2332 ± 29 a.u. and a RMS value of 1157 a.u..

DISCUSSION

This study describes a strategy to more accurately quantify sparse ^{19}F MR signals from perfluorocarbon nanoparticle emulsions by means of ^{19}F flip angle calibration that utilizes the abundant ^1H signal, and a ^1H image-based B_1 -mapping correction to the ^{19}F and ^1H images. The requisite peak power to achieve a requested flip angle for ^{19}F and ^1H nuclei was shown to be different for three $^{19}\text{F}/^1\text{H}$ dual-tuned RF coils. However, a ratio of the two optimized power settings results in a spatially independent calibration ratio that was unique to each coil. Once established, the coil-dependent calibration ratio can be used to set the power settings for ^{19}F imaging based on the ^1H signal for all imaging with the coil, regardless of location within the field of view. For sparse fluorine signals as would be expected in clinical MR molecular imaging, power settings and calibrations cannot be performed easily on the ^{19}F nuclei a priori. However, ^{19}F flip angle calibration can be performed based on the rich ^1H signal by multiplying the ^1H -derived power settings by the calibration ratio before any ^{19}F contrast agent is even introduced.

This work also demonstrated the utility of an image-based B_1 -mapping compensation to correct signal intensities for simultaneously acquired ^1H and ^{19}F images. The deleterious effects of coil inhomogeneities on quantitative ^{19}F MRI were demonstrated in a phantom experiment where two significantly different signal intensities were demonstrated for identical fluorine samples with the use of a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil. However, the proposed B_1 -mapping compensation technique corrected the signal intensity for both the ^{19}F and ^1H images, thereby removing the effects of the inhomogeneous RF field. This method was further tested in a homogeneous fluorine phantom, which corrected for the characteristic signal drop-off observed with surface coils, as a consequence of employing the proposed B_1 correction technique to improve ^{19}F image homogeneity. This technique might not be necessary in preclinical settings, in which volumetric coils with homogeneous B_1 profiles are used to image an entire small animal with sufficient SNR. If ^{19}F MR molecular imaging is to be implemented in the clinic, with applications in human carotid or renal imaging for example, surface coils will likely be necessary to achieve enough SNR for detection, and subsequent B_1 correction as presented here will be needed for accurate quantification.

This study was performed with $^{19}\text{F}/^1\text{H}$ dual-tuned coils, which consist of the same coil elements, and hence generate the same B_1 field for both ^{19}F and ^1H nuclei (29). The

observed difference in requisite power settings between the two nuclei demonstrates the effective difference in detection sensitivity of these dual-resonant coils, because they are electrically tuned in the same manner for both nuclei. However, this difference is consistent for each coil, and allows for the determination of a specific coil-dependent calibration ratio. Notably, this property is likely unique to dual-resonant coils, which cannot be replicated with single-tuned coils or other double-frequency coils with significantly different geometry between ^{19}F and ^1H resonator elements. On the other hand, although the B_1 correction technique using ^1H -derived B_1 maps to correct ^{19}F and ^1H images also benefits from the use of dual-tuned RF coils, this technique should apply to single-tuned coils if the B_1 fields for the two nuclei are the same. In the future, additional testing with both dual-tuned and single-tuned coils would be valuable to determine translatability of this technique to such coils.

One potential limitation of this study involves the use of slice-selective spectroscopic echo sampling in the MRS experiments. While small voxel-selective spectroscopic ROIs could lead to more precise flip angle sweeps, avoiding any flip angle averaging of the ^1H spins across the slice, a slice-selective technique was chosen to closer represent in vivo power setting optimization where the exact location in the imaging plane is unknown. Furthermore, several iterations of this experimental setup using volume- and bar-selective MRS showed similar ^{19}F and ^1H FA sweeps, and resultant calibration ratios. The concentration of PFC NP emulsion in the MRS experiment (50 mM) was chosen to mimic the millimolar concentrations of targeted PFC NP observed in preclinical experiments. For the B_1 correction experimental setup, however, phantoms consisting of 1.0 M NaF were used to ensure sufficient SNR for ^{19}F detection and image processing. When this technique is applied in vivo with lower available PFC NP concentrations, image acquisition parameters and scan duration must be optimized to achieve high enough SNR for ^{19}F image formation and processing using the abundant ^1H signal. In addition, both of the experiments in this study utilized ^{19}F -containing molecules with single resonance peaks (i.e. PFCE and NaF). If other perfluorocarbons with more complex spectral characteristics like perfluorooctyl bromide (PFOB) or perfluorodecalin (PFD) are used, advanced MR sequences such as balanced UTE-SSFP (32) may be needed to achieve sufficient SNR for this technique. Finally, if the ^1H power settings are not set properly and there is insufficient ^1H signal farther away from a surface coil, the B_1 correction algorithm cannot accurately correct the ^{19}F images. As such, the slice-selective ^1H power optimization must be performed at an appropriate distance away from the coil to ensure sufficient ^1H signal throughout the region of interest.

In conclusion, this study devised and tested a new approach to overcome certain challenges for accurate quantitative ^{19}F MR molecular imaging, which comprises a combination of flip angle calibration between ^1H and ^{19}F nuclei, and B_1 -mapping compensation to offset RF inhomogeneities. Correction techniques such as this one should facilitate improved accuracy and repeatability of measurements of non-proton molecular imaging agents used in preclinical and clinical trials at routine field strengths.

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Figure 1. $^{19}\text{F}/^1\text{H}$ dual-tuned RF coils. (a) Single loop rectangular surface coil (7×12 cm, Philips Healthcare, Best, The Netherlands). (b) Custom-built 6-element semi-cylindrical coil (15 cm diameter), and (c) single-turn solenoid coil (11.5 cm diameter, 14 cm length).

Figure 2. Representative flip angle sweep (10°-210°) on ^{19}F nucleus (**top**) and ^1H nucleus (**bottom**) using the same power setting (peak power = 122.9 W) with a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil indicating correct power settings for ^{19}F , but too high for ^1H .

Figure 3.

3D Ball plot representation of optimized RF power settings (peak power, W) for ^{19}F (a) and ^1H (b) nuclei using a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil and a point source phantom of PFCE NP emulsion. (c) Ratio of optimum $^{19}\text{F}/^1\text{H}$ power setting yields a spatially independent calibration value (1.48 ± 0.06 for surface coil).

Figure 4.

Power settings (peak power, W) needed to optimize 90° flip angle for ^{19}F and ^1H signals from point source phantom at 9 mm, 15 mm, and 27 mm above $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil (a), semi-cylindrical coil (b), and within single-turn solenoid coil (c).

Figure 5.

^{19}F MRI of phantom with two vials of 1.0 M NaF in agar using a simultaneous $^{19}\text{F}/^1\text{H}$ balanced GRE sequence and a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil. Before correction, ^{19}F image (a) and $^{19}\text{F}/^1\text{H}$ overlay image (b) illustrate the inhomogeneous RF field produced by the surface coil, resulting in a mean signal intensity of 2537 ± 31 a.u. and 863 ± 7 a.u. in each vial. ^1H B_1 -field was mapped with actual flip angle imaging (% actual/requested FA) (c), and input into balanced GRE signal model to create a correction factor (d), which was used to compensate ^{19}F and ^1H signal intensities. The corrected ^{19}F image (e) and $^{19}\text{F}/^1\text{H}$ overlay image (f) demonstrate the image-based compensation technique, resulting in a mean signal intensity of 2621 ± 27 a.u. and 2681 ± 23 a.u. in each vial.

Figure 6.

^{19}F MRI of a homogeneous phantom (1.0 M NaF in 2% agar) imaged with a simultaneous $^{19}\text{F}/^1\text{H}$ balanced GRE sequence and a $^{19}\text{F}/^1\text{H}$ dual-tuned surface coil. Before correction, the ^{19}F image (a) and $^{19}\text{F}/^1\text{H}$ overlay image (b) illustrate the inhomogeneous RF field produced by the surface coil. ^1H B₁-field was mapped with actual flip angle imaging (% actual/requested FA) (c), and input into balanced GRE signal model to create correction ratio (d), which was used to correct ^{19}F and ^1H signal intensities. The corrected ^{19}F image (e) and $^{19}\text{F}/^1\text{H}$ overlay image (f) demonstrate the image-based compensation technique.