Fluorine-19 Fast Recovery Fast Spin Echo Imaging for Mapping 5-Fluorouracil

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We investigated the effects of fast recovery (FR) to increase the sensitivity of fluorine-19 (19F) fast spin echo (FSE) in mapping 5-fluorouracil (5-FU) and its metabolites. We added an additional 90° pulse (which flips back longitudinal magnetization at the end of the sequence) to the chemical shift selective 19F FSE pulse sequence. In 5-FU solution, FR remarkably improved the signal-to-noise (S/N) ratio of 19F 5-FU images, having higher effects with shorter repetition time and smaller echo train numbers. In animal studies, FR produced a conspicuous increase in 19F signals in the urinary bladder. FR effects for 19F signals in the liver were smaller than those in other organs but still substantial. Utilization of FR in 19F FSE images promises more sensitive observation of 19F metabolite maps of 5-FU and other 19F-containing compounds that have relatively long relaxation times.

Keywords: 19F imaging, 5-FU, fast recovery, fast spin echo

Introduction

Nuclear magnetic resonance (NMR) signals from some fluorine-19 (19F)-containing compounds have relatively long T1 and T2. Because long T2 is advantageous, spin echo rapid acquisition with relaxation enhancement (RARE) sequence,1 called fast spin echo (FSE) or turbo spin echo (TSE), has been used to map 19F-containing compounds, such as 5-fluorouracil (5-FU) and its metabolites,2 fluorinated hexoses,3 perfluorocarbon4 and probes for β-amyloloids in the brains of a mouse model of Alzheimer’s disease.5 However, long T1 does not allow short repetition time (TR) and so requires a long time for data acquisition. Fast recovery (FR) FSE has been used to increase the 1H signal intensity of fluids having long T1 with short TR in clinical MR images of joints6 and the inner ear7,8 or in MR cholangiopancreatography.1 To our knowledge, FR has not been applied to 19F chemical shift selective imaging. This technique might be advantageous for collecting 2-dimensional maps of such 19F compounds with higher signal-to-noise (S/N) ratio with shorter acquisition time. We investigated the effects of FR on 19F FSE images of 5-FU.

Materials and Methods

We used a 7.0T horizontal-bore NMR system (Unity Inova, Varian, Palo Alto, CA) and added to the FSE pulse sequence an optional FR with additional 90° pulse, which flips back the longitudinal magnetization at the end of the sequence. The center frequency was adjusted to the chemical shift of the 19F signal of 5-FU, and Gaussian-shaped 90° and 180° pulses were used to select the frequency of excitation. As a phantom study, an ampoule of 5-FU for injection (250 mg/5 mL, Kyowa Hakko, Tokyo, Japan) was used as a test sample. A home-built solenoid-type volume coil measuring 3 cm in diameter and tuned for both 1H and 19F (300 and 282 MHz) was used to collect data. T1 of 19F signal of 5-FU was obtained using inversion recovery with various inversion times and T2 was obtained using spin echo with various echo times. 19F FSE images of 5-FU were basically acquired with 2 ms Gaussian-shaped pulses; 30×30 mm² field of view (FOV) in the horizontal plane; 128×64 matrices; 2 s TR; 32 echo trains with 10 ms echo space in the centric order; and 8 averages with 2 dummy scans. Slice-selective gradients were not applied for metabolite-specific mapping. FR effects were examined using various repetition times, echo trains,
Male Wistar rats were used for preliminary animal study; experimental protocols and procedures were reviewed and approved by the Laboratory Animal Care and Use Committee at Shiga University of Medical Science. Each rat was anesthetized with 1.5% to 1.8% isoflurane administered in combination with 50% O₂ through a face mask. The femoral vein was cannulated with a polyethylene tube for the infusion of 5-FU. A 1H and 19F dual-tuned volume coil, 18 cm long and 6.5 cm in diameter (Varian, Palo Alto, CA), was used for data collection. Initially, multi-slice 1H spin echo images were acquired with 500 ms TR, 15 ms echo time (TE) and 140 × 70 mm² FOV in the coronal plane. Next, the center frequency was adjusted to the 19F signal of the 5-FU. Thereafter, 150 mg/kg 5-FU was intravenously infused for 30 min. 19F FSE images were acquired with 2 ms Gaussian pulses, 140 × 70 mm² FOV in the coronal plane without slice selection, 64 × 16 matrices, 1 s TR, 16 echo trains with 6.5 ms echo space in the centric order, and 256 averages. As in multi-slice data acquisition, 4 chemical shifts were selected and interleaved within the 1 s TR: +80 ppm for isoflurane; +5 ppm for fluorinated nucleosides and nucleotides (Fnuc); 0 ppm for 5-FU; and −19 ppm for α-fluoro-β-alanine (FBAL). Acquisition time was 4.3 min for one dataset with 4 chemical shift selective images. Datasets with and without FR were alternately and repeatedly acquired for 4 hours from the beginning of 5-FU infusion. Seven raw datasets with and without FR, which were acquired every hour, were separately summed up and processed into images with 128 × 64 matrices by zero-filling. During the data acquisition, rectal temperature was monitored with a fluoroptic thermometer (Model 3100, Luxtron, Santa Clara, CA) and maintained at 37 to 38°C by blowing warm air with a drier for bedclothes.

Results

The T₁ of the 19F signal of the 5-FU solution was 2300 ms, and T₂ was 480 ms. The effects of FR on 19F FSE images were examined with 32 echo trains and various TRs. The top row of Fig. 1 shows 19F FSE images of a 5-FU solution acquired with TRs of 0.5 s, 1 s, 2 s and 4 s without FR. Longer TRs were required to obtain clear 5-FU images. The lower row shows corresponding images using FR that demonstrate clearly improved results. The percent increases induced by FR were larger with shorter TRs, but the beneficial effects of FR were seen even in the images with 4 s TR. We compared the images with the same total acquisition times of 16 s (32 averages with 0.5 s TR; 16 averages with 1 s TR; 8 averages with 2 s TR; and 4 averages with 4 s TR). Without FR, the S/N ratio was the highest in the image with 4 s TR (38.6), and with FR, in that with 2 s TR (48.4).

Next, the effects of FR with 2 s TR and various echo train numbers were examined. 19F FSE images acquired with 64, 32, 16 and 8 echo trains without the FR option are shown in the upper row in Fig. 2. The images with small numbers of echo train were

![Fig. 1](image-url)

**Fig. 1.** Fluorine-19 fast recovery (FR) fast spin echo images of a 5-fluorouracil solution acquired with 0.5 s (a); 1 s (b); 2 s (c); and 4 s (d) repetition times. The upper row shows images without FR, and the lower row shows those with FR. Other acquisition parameters are described in the text. All images are shown with the same scale factor. The values in the images are the signal to noise ratios of individual ones.
clear, but similar S/N ratios were obtained with 16 and 8 echo trains. Corresponding images with the FR option in the lower row show clearly improved results. The percent increases were larger with small numbers of echo trains, but the beneficial effects of FR were seen even in the images with 64 echo trains.

To apply FR-FSE for $^{19}$F chemical shift selective images of 5-FU and its metabolites, we examined the effects of frequency offsets and pulse widths. To acquire the images in Fig. 3, we used Gaussian-shaped pulses for 1 ms (A); 2 ms (B); and 3 ms (C). The selectivity of the frequency was better with longer pulse widths. At a frequency of 5-FU signal (0 ppm), FR increased the S/N ratios by 43–62%. With a 1-ms pulse width at +2 ppm frequency offset, FR increased the S/N ratio only by 28%. With all the other acquisition conditions (2 ms and 3 ms at +2 ppm, and all at +5 ppm), FR showed no effects on the S/N ratios ($-5\% \sim +7\%$).

In an animal study, isoflurane images at +80 ppm showed substantial accumulation of isoflurane in fat tissues, but Fnuc images at +5 ppm showed no significant signals (data not shown). Figure 4 shows that at 0 ppm, 5-FU images only visualized the urinary bladder, but at at −19 ppm, FBAL images also showed the liver and kidneys slightly. The signals in the urinary bladder clearly increased with FR. In addition, the contours of the kidneys and liver were clearer with FR. The S/N ratios were measured using the summed-up images at 0 to 4 hours. The results (S/N with FR/without FR/% increase) of 5-FU in the bladder were 100.5/37.9/+165%, and those of FBAL were: in the bladder (26.2/13.3/+98%); in the r-kidney (10.5/6.3/+67%); and in the liver (8.4/6.6/+27%). Substantial effects of FR were detected in FBAL signals of the liver, but were smaller than in the other organs.

**Discussion**

The sensitivity of $^{19}$F NMR signals is relatively high compared to the sensitivity of various nuclei other than $^1$H. However, the amounts of $^{19}$F-containing compounds are generally small in living tissues. Therefore, improved $^{19}$F NMR signal acquisition techniques are required for in vivo $^{19}$F metabolite mapping. To investigate the distribution of 5-FU and its metabolites, conventional chemical shift imaging has been utilized, but spatial resolution is relatively low.$^{10,11}$ For fast acquisition of $^{19}$F metabolite maps of 5-FU, chemical shift selective FLASH$^{12,13}$ or FSE$^2$ has also been reported. As shown, the $T_1$ of the $^{19}$F signal of 5-FU solution used was 2300 ms. Short TR reduces acquisition time but is not suitable to detect NMR signals having such a long $T_1$. We investigated the characteristics of $^{19}$F FR-FSE using 5-FU solutions to explore rapid acquisition of $^{19}$F metabolite maps.

Short TR caused higher signal loss of 5-FU. FR clearly increased the 5-FU signals, and its relative effects were higher with shorter TR (Fig. 1). Using FR, however, the best S/N ratio was obtained with 2-s TR, comparing the images with the same total acquisition time of 32 s. This indicates that excess saturation in the longitudinal magnetization of $^{19}$F...
Fig. 3. Fluorine-19 fast recovery (FR) fast spin echo images of a 5-fluorouracil (5-FU) solution acquired with 1 ms (a); 2 ms (b); and 3 ms (c) Gaussian-shaped pulses. The center frequency was set at 0 ppm (left column); +2 ppm (middle column); and +5 ppm (right column) from the chemical shift of the 5-FU signal. The upper row shows images without FR, and the lower row shows those with FR. Other acquisition parameters are described in the text. All images are shown with the same scale factor. The values in the images are the signal to noise ratios of individual ones.

nuclei with shorter TR was overcome by the FR pulse, but its effects were not perfect. Some relaxation period is still required, even with FR. The relative effects of FR were stronger with smaller echo train numbers. Transverse as well as longitudinal magnetization seems to affect FR, and its dispersion might decrease the effects of FR. Because we have intended to use this technique for the chemical shift selective mapping of 5-FU and its metabolites, the selectivity of frequency was important. As shown in Fig. 3, FR increased the signals at on-resonance frequency but showed no effects on those at off-resonance frequencies. As a result, FR increased the selectivity of chemical shifts by increasing the signals close to the center frequency. Using 2-ms Gaussian-shaped pulses, almost no signals were observed with +5 ppm offset. Therefore, this technique can be used in practice to observe 5-FU, FBAL, and Fnuc images separately.

Based on these findings, a preliminary animal study was initiated with normal rats. Acquisition parameters were basically those reported by Kuribayashi’s group. Isoflurane, a fluorine-containing compound, was used for general anesthesia, and prominent signals of isoflurane were observed in the images at +80 ppm from 5-FU. However, isoflurane did not interfere with Fnuc (+5 ppm); 5-FU (0 ppm); or FBAL (−19 ppm) images. Because we used normal rats, we observed no Fnuc signals at +5 ppm, indicating no signal bleeding from the isoflurane. As Fig. 4 shows, FR remarkably increased the 5-FU and FBAL signals in the urinary bladder, producing intensities with FR at least double those without FR. The effects of FR on the FBAL signals in the liver were substantial (+27% in S/N) but smaller than those in other organs. This seems to have been caused by the shorter T1 of FBAL in living tissues than those in solution. The results of FBAL in the kidney were intermediate (+67% in S/N). The signals derived from the parenchyma and urine in the calyx might be mixed. We recognize that the sensitivities of our 19F images are not as good as those previously reported. As Brix and colleagues reported, high signal in the bladder disturbs the detection of low signals in other organs, and they remove urine with a catheter. We therefore infused a smaller dose of 5-FU continuously for 30 min in the magnet. Nevertheless, prominent signals of both 5-FU and FBAL were detected in the urinary bladder, and FR showed striking effects on them. It is reported that the T1 of 5-FU and FBAL in living tissues is 380 ms ± 1.7 s and 760 ms ± 1.6 s, indicating its distribution over a wide range. We need to optimize acquisition parameters, administration protocols of 5-FU, animal preparations, and RF probes for signal detection to improve image quality.
Conclusion

Use of FR to obtain $^{19}$F FSE images of 5-FU resulted in higher S/N ratios under various acquisition conditions. In preliminary animal studies, FR remarkably increased 5-FU and FBAL signals in the urinary bladder of rats. The effects of FR on FBAL signal in liver and kidney were not as markedly increased but were still substantial. $^{19}$F FR-FSE may be a promising option for the sensitive observation of in vivo $^{19}$F metabolite maps of 5-FU and other $^{19}$F-containing compounds with relatively long relaxation times.

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References


