Report on Experiments and Clinical Cases

T1-weighted Magnetic Resonance Imaging Sequence Appropriate for the Evaluation of the Longitudinal Relaxation Effect of Superparamagnetic Iron Oxide: a Phantom Study

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Abstract

The goal of this study was to determine a T1-weighted magnetic resonance (MR) imaging sequence appropriate for evaluating the longitudinal relaxation effect of superparamagnetic iron oxide (ferumoxides) in a phantom study. An agarose phantom that included various concentrations of ferumoxides (0～0.5 mmol/*l* in 0.05 mmol/*l* increments) was examined for six types of T1-weighted imaging sequences using a 1.5-T MR unit. Three-dimensional (3D) fast spoiled gradient-echo (SPGR) imaging with a short echo time showed a strong linear correlation between the concentration of ferumoxides and the enhancement ratio. Two-dimensional (2D) fast SPGR imaging showed a high signal-to-noise ratio of the phantom even at low ferumoxides concentrations. These results suggest that 3D fast SPGR imaging is an appropriate technique for the evaluation of the longitudinal relaxation effect of ferumoxides, and that 2D fast SPGR imaging can be useful for evaluating the longitudinal relaxation effect at lower ferumoxides concentrations. (J Nippon Med Sch 2002; 69: 571–576)

Key words: longitudinal relaxation effect, magnetic resonance imaging, superparamagnetic iron oxide, ferumoxides, phantom study

Introduction

Superparamagnetic iron oxide (SPIO) is a tissue-specific contrast agent used in magnetic resonance (MR) imaging[1,2]. It is specifically absorbed into the reticuloendothelial system (RES) in the liver and spleen, resulting in the markedly short longitudinal and transverse relaxation times of these organs[1,2]. By reducing the signal intensity of the normal liver parenchyma, metastatic liver tumors can be clearly depicted as high intense lesions in T2-weighted MR images[3]. Because fibrous nodular hyperplasia, which includes the RES, exhibits a decreased signal intensity following the administration of SPIO, the diagnosis of this tumor can be made by comparing pre- and postcontrast T2-weighted MR images[4]. Recently, T1-weighted MR imaging has been performed after an SPIO injection to characterize focal liver lesions[5–9]. SPIO-enhanced T1-weighted imaging depicts hemangioma as a homogeneously enhanced lesion, as does gadolinium-enhanced T1-weighted imaging[7,9]. Previous reports have showed that malignant liver tumors such as metastatic liver tumors and hepatocellular carcinoma demonstrate ring-like enhancement in SPIO-enhanced T1-weighted imaging[7,8]. Therefore, by adding T1-weighted imaging, the clinical efficacy of SPIO-enhanced MR imaging for the detection of focal liver lesions as well as the characterization of these lesions may be

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improved[5-9].

However, no T1-weighted MR imaging method suitable for the evaluation of the longitudinal relaxation effect of SPIO has been confirmed, because this agent has short longitudinal and transverse relaxation time effects and previous reports have applied a wide variety of T1-weighted MR imaging sequences[5-11]. Tanimoto et al. have evaluated the dependency of the signal on the concentration of SPIO in an agarose phantom in T1-weighted spin-echo (SE) imaging[10,11]. However, the recently developed fast spoiled gradient-echo (fast SPGR) imaging technique has not been used.

The purpose of this study was to determine a T1-weighted MR imaging sequence appropriate for the evaluation of the longitudinal relaxation effect of SPIO in an agarose phantom with various concentrations of SPIO.

Materials and Methods

Contrast agent and Phantom

The contrast agent used in this study was a commercially available SPIO: ferumoxides (Feridex, Tanabe Seiyaku and Eiken Kagaku, Japan). Ferumoxides consists of SPIO crystals coated with high-molecular-weight dextran. The iron particle cores are approximately 4 nm in diameter and the SPIO particle diameter ranges from 70 to 140 nm. Relaxivity measurements yield an R1 value of approximately 24 *l*/mmol/s and an R2 value of approximately 85 *l*/mmol/s (at 40℃ and 20 MHz, reported by Eiken Kagaku). Based on the previous report, we fabricated agarose phantom columns using agarose solvent with a T1 value of 3.15 ms and a T2 value of 83.31 ms with ferumoxides in the concentration of 0～0.5 mmol/*l* in 0.05 mmol/*l* increments[10,11]. Thus, the agarose phantom used in this study consisited of 11 columns (**Fig. 1A**).

MR imaging examination

MR imaging was performed using a 1.5-T MR unit (Signa LX, GE Medical Systems, Wis, USA) with a maximum gradient strength of 23 mT/m and a slew rate of 120 mT/m/ms. The head coil was used for RF transmission and signal reception and the agarose phantom was carefully placed in the center of the coil.

The MR imaging sequences used in this study are summarized in **Table 1**. Because of the potentially marked short transverse relaxation effect of ferumoxides, the T2-weighted fast SE and T2*-weighted gradient-echo imagings were measured first to validate the phantom. Then, six types of T1-weighted MR imaging sequences were performed: (i) SE imaging, (ii) two-dimensional (2D) fast SPGR with opposed-phase and (iii) in-phase echo time (TE), (iv) 2D fast SPGR with double TE, and (v) three-dimensional (3D) fast SPGR with, and (vi) without fat-suppression. These T1-weighted MR imaging sequences are routinely used in many institutions[3,5,6,8,12]. Imaging parameters such as the field-of-view (28 cm), imaging matrix (256×256), section thickness (5 mm), and signal averaging (four) were kept the same for all sequences except that one signal averaging was used in the case of the 2D fast SPGR with double TE because of the software limitations.

Imaging Analysis

A region-of-interest (ROI) was placed in the center of each column for each imaging sequence, and the ROI signal was estimated. A second ROI was then located in the background outside the column and the standard deviation (SD) of the background signal was estimated. The signal-to-noise ratio (SNR) of each column was calculated as the signal from each column divided by the SD of the background signal. The enhancement ratio (ER) of each column was defined as (the SNR of each column—the SNR of pure agarose solvent (i.e. ferumoxides at a concentration of 0 mmol/*l*)) divided by the SNR of pure agarose solvent. The changes in the SNR and ER values associated with the concentration of ferumoxides were investigated for all the MR imaging sequences, and when a linear relation between the concentration of ferumoxides and the SNR or ER values was found, it was evaluated using correlation analysis.

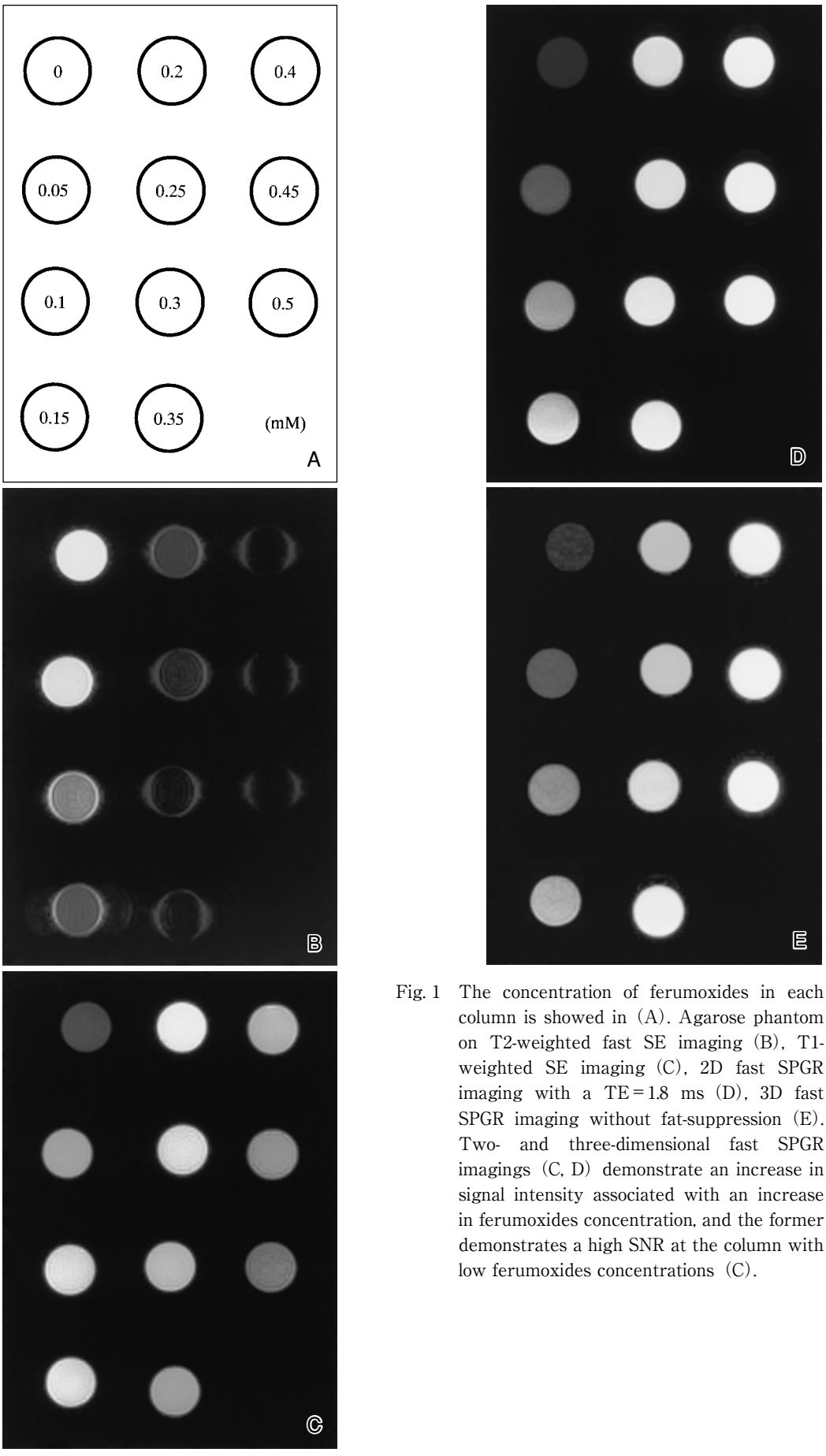

Fig. 1 The concentration of ferumoxides in each column is showed in (A). Agarose phantom on T2-weighted fast SE imaging (B), T1-weighted SE imaging (C), 2D fast SPGR imaging with a TE = 1.8 ms (D), 3D fast SPGR imaging without fat-suppression (E). Two- and three-dimensional fast SPGR imagings (C, D) demonstrate an increase in signal intensity associated with an increase in ferumoxides concentration, and the former demonstrates a high SNR at the column with low ferumoxides concentrations (C).

Table 1 Imaging parameters of MR imaging sequences used in this study

imaging sequences	TR	TE	FA	RBW
T2-weighted fast SE	6,000	99.4	90	31.25
T1-weighted SE	500	20	90	15.6
GRASS	180	30	30	31.25
2D fast SPGR with opposed-phase	195	1.8	90	31.25
2D fast SPGR with in-phase	195	4.2	90	31.25
2D fast SPGR with double TE	195	2.4, 4.7	90	62.5
3D fast SPGR with or without fat-suppression	4.3	1.2	20	62.5

TR: repetition time, TE: echo time, FA: flip angle, RBW: receiver bandwidth

Table 2 Signal-to-noise ratio and enhancement ratio of each MR imaging sequence

ferumoxides (mmol/*l*)		0	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	slope
T2-weighted fast SE	SNR	183.2	148.4	80.5	45.3	27.1	16.6	8.7	6.7	4	3.3	2.7	
	ER		− 0.18	− 0.56	− 0.75	− 0.85	− 0.9	− 0.95	− 0.96	− 0.97	− 0.98	− 0.98	
T1-weighted SE	SNR	170.1	339.5	423.1	422.5	452.4	437.8	406.5	336.7	361.3	308.4	287.7	
	ER		0.99	1.48	1.48	1.66	1.57	1.39	0.97	1.12	0.81	0.69	
GRASS	SNR	78.4	163.7	145	35.6	93.5	114	38.5	33	56	52.2	43.7	
	ER		1.09	0.85	− 0.54	0.19	0.45	− 0.5	− 0.57	− 0.28	− 0.33	− 0.44	
2D fast SPGR	SNR	91.8	183	262.5	314.5	343.1	377.8	411.5	418.3	444.8	459.1	477.1	701
with opposed-phase	ER		0.99	1.85	2.42	2.73	3.11	3.48	3.55	3.84	4	4.19	7.63
2D fast SPGR	SNR	106.3	208.6	294.8	347	375.2	404.3	434.6	434	451.4	461.4	472.5	646
with in-phase	ER		0.96	1.75	2.27	2.53	2.81	3.09	3.09	3.25	3.34	3.45	6.08
2D fast SPGR with double	SNR	11.5	23.4	34.1	41.8	42.8	47.6	53	54.3	54.4	57	60	86
TE (TE = 2.4)	ER		1.02	1.94	2.61	2.69	3.1	3.57	3.69	3.7	3.92	4.18	7.42
2D fast SPGR with double	SNR	16.6	30.9	40.9	45.1	58	58.9	59.7	55.7	69	66	63.5	87.7
TE (TE = 4.7)	ER		0.85	1.45	1.7	2.47	2.53	2.57	2.34	3.13	2.97	2.81	5.26
3D fast SPGR	SNR	24.5	57.5	92.8	117.5	136.7	162	190	201	210.7	232.1	251.9	438.1
with fat-suppression	ER		1.33	2.77	3.77	4.56	5.59	6.72	7.17	7.57	8.44	9.25	17.83
3D fast SPGR	SNR	17.1	42.8	73.8	99	109.6	134.1	162.4	183.1	182.1	204.9	226.2	407.2
without fat-suppression	ER		1.5	3.31	4.78	5.4	6.83	8.49	9.7	9.63	10.9	12.2	23.78

SNR: signal-to-noise ratio, ER: enhancement ratio, Slope: slope of the linear correlation between the ferumoxides concentration and SNR or ER using correlation analysis. Three-dimensional fast SPGR imaging demonstrates the good linear correlation between the ferumoxides concentration and enhancement ratio.

Results

The SNR and ER values of each column of the MR imaging sequence are summarized in **Table 2**. As expected, the T2-weighted fast SE (**Figs. 1B, 2**) and the T2*-weighted gradient-echo imagings demonstrated an apparent decrease in their SNR and ER values at high ferumoxides concentrations.

Three-dimensional fast SPGR imaging, especially without fat-suppresion, showed a strong correlation between the concentration of ferumoxides and the SNR or ER value (Figs. 1, 2B, $p < 0.0001$ and $r = 0.992$ for both the SNR and ER values, and the slope = 407.2 and 23.8 for the SNR and ER values, respectively). Two-dimensional fast SPGR imaging at a receiver bandwidth (RBW) of 31.25 kHz also showed a good linear correlation between the concentration of ferumoxides and the SNR or ER values ($p < 0.0001$ and $r > 0.90$ for both the SNR and ER values). Although the slope of the linearity between the concentration of ferumoxides and the ER value was lower for the 2D fast SPGR imaging than for the 3D fast SPGR imaging (**Fig. 2**), the 2D fast SPGR imaging demonstrated a high SNR value at the column with low ferumoxides concentration (**Fig. 1D**). T1-weighted SE imaging showed a decrease in the SNR value when the ferumoxides concentration was higher than 0.3 mmol/*l* (**Figs. 1C, 2**).

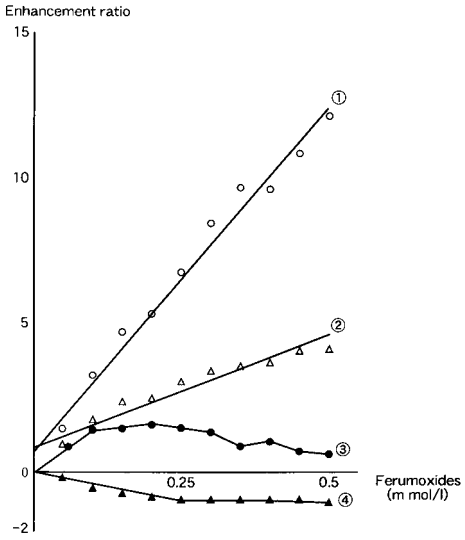

Fig. 2 Correlation between the ferumoxides concentration and the enhancement ratio ① 3D fast SPGR imaging without fat-suppression, ② 2D fast SPGR imaging with a TE = 1.8 ms, ③ T1-weighted SE imaging, ④ T2-weighted fast SE imaging T2-weighted fast SE imaging shows a negative correlation between the ferumoxides and the concentration enhancement ratio. T1-weighted SE imaging shows a decrease in the enhancement ratio at the ferumoxides concentration higher than 0.3 mmol/*l*. Two- and three-dimensional fast SPGR imagings demonstrate the good linear correlation between the ferumoxides concentration and the enhancement ratio ($p < 0.0001$ and $r > 0.95$) and the slope of the linearity is larger for 3D fast SPGR imaging than for 2D fast SPGR imaging (23.8 vs 7.63).

Discussion

This phantom study demonstrated a signal decrease associated with the susceptibility and short transverse relaxation effect of ferumoxides in T2-weighted fast SE, T2*-weighted gradient-echo and T1-weighted SE imaging techniques[1,2,10,11]. It has also shown a strong linear correlation between the concentration of ferumoxides and the SNR or ER value using 3D fast SPGR imaging, and a high SNR value of each column using 2D fast SPGR imaging.

The good linear correlation between the concentration of ferumoxides and the SNR or ER value in 3D fast SPGR imaging can be attributed to the very short TE of this sequence, which might reduce the susceptibility and short transverse relaxation effect of the ferumoxides[12]. The short repetition time (TR) of this imaging sequence might contribute to a suppression of the agarose solvent signal and result in an improved visualization of the longitudinal effect of ferumoxides. Therefore, 3D fast SPGR imaging might prove to be of great value for monitoring the longitudinal relaxation effect and concentration of ferumoxides. On the other hand, the SNR value of the agarose phantom, especially at low ferumoxides concentrations, was high using the 2D fast SPGR imaging. This is probably because the TR is longer than 150 ms, and this leads to a recovery in magnetization. In addition, 2D fast SPGR imaging with the RBW of 31.25 kHz yields a higher SNR value than 3D fast SPGR with the high RBW of 62.5 kHz. Therefore, the 2D fast SPGR imaging might be useful for the depiction of subtle contrast enhancement of ferumoxides at low concentrations.

We have to address one limitation of this study. We did not investigate the relaxation effect of ferumoxides at concentrations higher than 0.5 mmol/*l*. However, when using a normal clinical dose of ferumoxides (0.01 mmol/kg), the concentration of ferumoxides in the circulating blood is approximately 0.12 mmol/*l* (e.g. 60 kg in 5 L of blood), and this concentration is much lower than the highest ferumoxides concentration investigated in this study. Therefore, our results were suitable for clinical consideration regarding the relation between the T1-weighted MR imaging sequence and the concentration of ferumoxides.

In conclusion, 3D fast SPGR imaging with a short TE is appropriate for the evaluation of the longitudinal relaxation effect of ferumoxides, and 2D fast SPGR imaging can be useful for elucidating this effect at lower ferumoxides concentrations.

Clinical implication

When SPIO is used in a dynamic study to evaluate the vascularity of focal liver lesions, 3D fast SPGR imaging should be applied as this sequence may show a good linear correlation between the concentration of ferumoxides and the ER value. The fat-suppression technique should be used in clinical situations, because this technique improves the

dynamic range of the imaging[12]. Two-dimensional fast SPGR imaging with a TE = 1.8 ms can be used as an alternative method to 3D fast SPGR imaging when the subtle enhancement of focal liver lesions needs to be depicted for characterization in the equilibrium phase of ferumoxides-enhanced T1-weighted MR imaging. The 2D fast SPGR imaging with a TE = 4.2 ms is also recommended to avoid the paradoxical suppression of fat-containing liver lesions (e.g. well-differentiated hepatocellular carcinoma and liposarcoma)[13].

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