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Original Article

Experimental Study of Fast and Ultrafast T2-Weighted Imaging Sequences Using AMI-25 Superparamagnetic Iron Oxide (SPIO)

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The objective of this study was to evaluate fast and ultrafast T2-weighted images (T2WI), including echo planar imaging (EPI), using an AMI-25 agar phantom. Image quality for conventional spin echo (CSE) and turbo spin echo (TSE) was almost equivalent. In high-resolution TSE, image quality was highest due to the use of a 512 × 256 matrix. Half-Fourier single-shot turbo SE (HASTE) was associated with blurring of images, and turbo-gradient SE (TGSE) showed a deterioration of image quality. EPI also suffered from poor image quality because this method is very sensitive to magnetic field inhomogeneity. CSE showed good signal-to-noise ratio (S/N) and contrast ratio (CR), but also required the longest imaging times. Among the TSE sequences, TSE with a short echo train length (ETL) was superior in terms of S/N. The CR of EPI and fast low angle shot (FLASH) images were improved in proportion to the effective echo time (TE). At present, TSE is inferior to CSE in terms of S/N and CR. However, taking into consideration scanning time, TSE with a short ETL is thought to be suitable for routine examinations. Effective TE is an important factor in gradient echo (GRE) examinations.

Key words: MRI, SPIO (superparamagnetic iron oxide), liver phantom, various T2WI (T2-weighted images)

Due to recent advances in MRI hardware, many new sequences, including echo planar imaging (EPI) [1-4], have become available. In particular, a variety of imaging sequences have been developed for obtaining T2WI, which have high contrast resolution and are superior in the detection of lesions, but which suffer from a long scan time and greater susceptibility to artifacts. It is therefore often difficult to select the optimal imaging method in the context of clinical practice.

AMI-25 is a form of superparamagnetic iron oxide (SPIO) that has been reported to be useful as a negative contrast agent in MRI studies of liver tumors [5-15]. We previously investigated the fast and ultrafast T2WI of various solutions. One of the limitations of this technique may be that the proton coupling characteristics differ between solid tumors or parenchymal organs and the aqueous solutions that are used to model each component [16]. In imaging the human body, free water, which affects signal intensity, causes a crossed relaxation with large molecules, resulting in magnetization transfer [17]. This is thought to affect the contrast between tumors and surrounding normal parenchyma. Therefore, in order to evaluate the negative contrast effect of SPIO in the liver, it is necessary to determine the optimum imaging method using a phantom that contains protein and is closely matched to the characteristics of normal liver parenchyma.

Several papers have compared various imaging techniques using SPIO for the evaluation of liver tumors [5-15]. However, very few basic studies have investigated the signal intensity and contrast of this negative contrast agent when it is used in fast and ultrafast T2WI. In this paper, we describe special agar liver phantoms containing

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SPIO at various concentrations that we have designed for use in our studies, and also discuss the optimum methods for employing this contrast agent in the fast and ultrafast T2WI of liver tumors. In this study, the most effective sequence could be selected from a large number of sequences and a reduction in scan time could be expected.

Materials and Methods

1. MR Imaging

MR imaging was performed using a 1.5-T superconductive system (Magnetom Vision, Siemens, Erlangen, Germany) with a gradient switching capability of 25 mT/m in a rise time of 300 μsec, a slew rate of 83 T/m/s, and single-shot EPI capabilities. The body coils were used as the receiving coils. The phantom was filled with nickel chloride solution (5 mmol/L) in order to adjust the impedance. A plastic container was placed in the center of the phantom, and the phantom was then positioned at the center of the magnetic field. The magnetic field uniformity of this MRI system is 5 ppm within a 50 cm spherical volume, with shimming allowing the body coil to attain a uniformity of 0.5 ppm at the center of the magnetic field.

Table 1 shows the objectives and features of the imaging sequences and methods we employed. With regard to pulse parameters (inversion time [TI], repetition time [TR], echo time [TE], flip angle [FA], echo train length [ETL], number excitation [NEX]), matrix, field of view (FOV), and number of slices, standard values for body parts were used. Therefore, the scan time was equal to that in routine clinical examination. Other scan parameters were specified as follows: FOV = 330 mm, 3:4 rectangle (335 mm for EPI, non-rectangular FOV), slice thickness = 7 mm, distance factor = 0.25, and number of slices = 17. No presaturation pulse was used. Only fat saturation sequences can be used in EPI sequences. In other sequences, a fat saturation sequence is normally used as required. However in our studies, fat saturation was not employed.

2. Contrast Medium (Negative Contrast Agent, AMI-25)

Superparamagnetic iron oxide (SPIO; AMI-25, Eiken Kagaku, Tokyo, Japan) [8, 18-21] was used. SPIO is composed of a magnetically active core of iron oxide surrounded by dextran. The particle sizes in SPIO range from 35 nm to 227 nm. Based on animal studies, SPIO is taken up mostly by the Kupffer cells in the liver and by bone marrow cells. It is not eliminated by the kidney, but is metabolized by a process similar to that for iron metabolism. Thirty minutes after administration, 70 % of the injected dose remains in the body (outside of the blood vessels), and is diluted by a factor of several thousand in the liver.

3. Preparation of Phantoms

The solvent should be a solid with the same T1 and T2 values as those of the liver so as to accurately reflect the uptake of contrast agent by the liver to enhance imaging. T2WI is discussed here, but the T1 value also affects image contrast. We prepared phantoms with T1 and T2 values as close as possible to those of the liver by mixing agarose with $CuSO_4$.

The materials used were agarose (Type 1, Agarose (Sigma Chemical Corp. Type 1, #A-6013, St. Louis,

Table 1 The objectives and features of the imaging sequences

Sequence	Parameter: (TI)/TR/TE/ETL/NEX	Feature	Time
CSE	2000/90/1/2	Conventional T2WI	8 min 7 sec/17 slices
TSE1	4900/138/29/1	Breath holding	25 sec/17 slices
TSE2	3500/99/11/2	High resolution	2 min 24 sec/17 slices
HASTE	Infinite/59/72/1	Subsec: motion freezing	25 sec/17 slices
TGSE1	3600/108/33/1	Breath holding	32 sec/17 slices
TGSE2	6000/115/69/1	High resolution	1 min 6 sec/17 slices
EPI1	Infinite/67/128/1	Subsec: SE contrast	3.19 sec/17 slices
EPI2	Infinite/22/128/1	Subsec: GRE contrast	2.19 sec/17 slices
EPI3	(150)/infinite/67/128/1	Subsec: SE IR contrast, fat sat; short TI	5.82 sec/17 slices
FLASH	FLASH 2D: 600/15 (FA = 15)/1	GRE contrast	1 min 57 sec/17 slices

FOV = 330 mm with 3/4 rectangular (EPI; 335 mm, no rectangular FOV), Slice thickness = 7 mm, Distant factor = 0.25, No. of slices = 17

MO, USA.), copper sulfate ($CuSO_4$), and Delux Model Phantom (Siemens, Erlangen, Germany). Agarose (3 g) was dissolved in pure water (120 mL) with heating in order to ensure complete uniformity [21]. AMI-25 was diluted with pure water by factors of 300, 400, 600, and 1,000, and copper sulfate (0.3 mmol) was dissolved in aliquots (30 mL) of these solutions. The components were then heated and thoroughly mixed. At this time, the concentrations of AMI-25 were 0.067%, 0.050%, 0.033 %, 0.020% and 0% (Table 2). The preparations were then mixed thoroughly, gently transferred to 150 cc plastic containers, and allowed to set overnight in a refrigerator.

The T1 and T2 values of the agar samples were measured, and the relationship between AMI-25 concentration (%) and the relaxation time was determined. The T1 and T2 values of each sample were measured for reference in evaluating the contrast of each image. This was based on the method described by Kitagawa [22]. For the measurement of T1 values, the TE was fixed at 20 ms in the spin echo (SE) method, and the TR was varied in the range of 40-20,000 ms. For T2 values, a multi-echo sequence for measuring T2 values (16 echoes, TE = 22.5-360 every 22.5 ms) was used. The T1 and T2 values were then calculated using the least-squares method from the theoretical formula for SE imaging.

Signal intensity was measured by setting a region of interest (ROI) in each agar sample. After it was confirmed that the components within the ROI were confirmed to be uniform, the largest possible ROI (12.56 cm^2) was set. Since the position of the phantom was not changed in each series with equivalent imaging conditions, the same size could be set for all samples.

With regard to the relationship between AMI-25 concentration and the relaxation time, graphs were plotted with the concentration (%) of SPIO on the horizontal axis and 1/T1 or 1/T2 on the vertical axis in order to evaluate the samples. The data points on these graphs lay on straight lines, confirming that the samples were diluted uniformly (Fig. 1).

4. Analysis

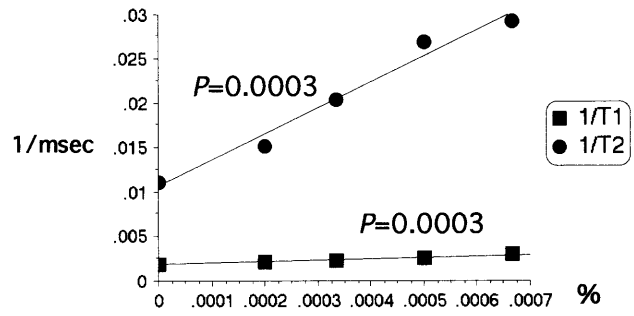
For each sequence, a) the signal-to-noise ratio (S/N), b) the contrast ratio (CR) and d) visual evaluation were obtained. Then, c) changes in S/N and CR for various TE values in gradient echo (GRE) sequences were determined.

a) S/N for each sequence

This was defined as follows: S/N = signal intensity of each component/standard deviation of the background.

b) CR for each sequence

This was defined as follows: CR = signal S/N of component "a"/S/N of component "b". The conventional contrast-to-noise ratio (C/N) is the S/N of component "a"-the S/N of component "b". Therefore, when the signal becomes larger, the difference increases as the C/N increases. This does not always match the C/N observed visually [16]. This is why we defined the CR as a new evaluation method. Since evaluation before/after



AMI-25	T1 value	T2 value
agar1 0.0666%	336	34
agar2 0.0500%	379	37
agar3 0.0333%	435	48
agar4 0.0200%	463	65
agar5 0.0000%	518	89

Fig. 1 The correlation between 1/T1 or 1/T2 and the concentration of SPIO. A strong correlation is seen between 1/T1 or 1/T2 and the concentration of SPIO.

Table 2 The contents of the phantom

Sequence	CuSO4	Agarose	AMI-25	Concentration (%)
Agar 1	0.3 mmol/l	3%	1500 times with pure water	0.067
Agar 2	0.3 mmol/l	3%	2000 times with pure water	0.05
Agar 3	0.3 mmol/l	3%	3000 times with pure water	0.033
Agar 4	0.3 mmol/l	3%	5000 times with pure water	0.02
Agar 5	0.3 mmol/l	3%	Pure water	0

imaging was to be conducted in clinical studies, the CR values between Agar 5 and Agar 1 to Agar 4 were determined.

c) Changes in S/N and CR for various effective TE values in EPI and FLASH

With regard to routine SE studies, imaging parameters tend to be relatively constant from institution to institution, while the imaging parameters used in GRE sequences tend to show a wider range of variation. It was expected that AMI-25, in particular, would show marked changes in contrast according to changes in TE values. Therefore, in our studies, we obtained S/N and CR values for a range of TE values in fast low angle shot (FLASH) and EPI 2 sequences.

d) Visual evaluation

Sharpness, margins, and susceptibility artifacts were evaluated in 4 steps. Sharpness was evaluated in terms of the degree of clarity, while margins were evaluated in terms of the degree of irregularity, with poor = 1, moderate = 2, good = 3, and excellent = 4. Susceptibility artifacts were classified as severe = 1, moderate = 2, mild = 3, and absent = 4. The final results were based on the consensus of 2 radiologists.

Results

a) Signal-to-noise ratio (S/N)

Fig. 2 shows the S/N in each sequence for agar samples containing various AMI-25 concentrations. When the S/N was evaluated for Agar 5, with T1 and T2 values similar to those of the liver, conventional spin echo (CSE) was found to have the highest value of about 110, followed by turbo-gradient SE (TGSE 1), FLASH, and turbo SE (TSE 2), which showed S/N values of about 40–60. In other sequences, S/N was rather poor, at 30 or less.

b) Contrast ratio (CR)

Fig. 3 shows the CR values for AMI-25 at various concentrations. Compared with other sequences, half-Fourier single-shot turbo SE (HASTE), EPI 2, and FLASH sequences were found to have poor CR values, particularly at high concentrations. The other sequences did not show large differences in CR values. Theoretically, the GRE sequences (FLASH and EPI) are very sensitive to magnetic field inhomogeneities [1-3], and were initially expected to show the largest signal drop with negative contrast agents based on magnetic field inhomogeneity. We thought that the short effective TE was related to the CR, and investigated the effects of varying the effective TE.

c) Relationships between S/N, CR, and effective TE for each GRE sequence

Fig. 4 shows the relationships between effective TE, S/N, and CR for EPI 2 (a and b) and FLASH (c and d) sequences. When the effective TE is increased, the S/N falls, but the CR is improved in the GRE sequence.

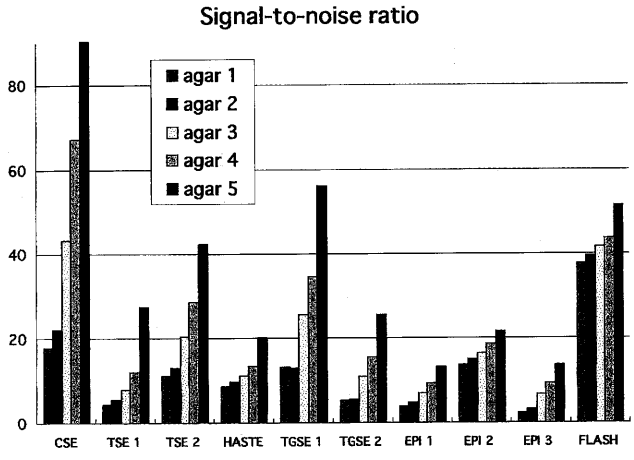


Fig. 2 Signal-to-noise ratio.
CSE showed the highest value of about 110, followed by TGSE 1, FLASH and TSE 2 which showed S/N values of about 40–60. In other sequences, S/N was rather poor, at 30 or less.

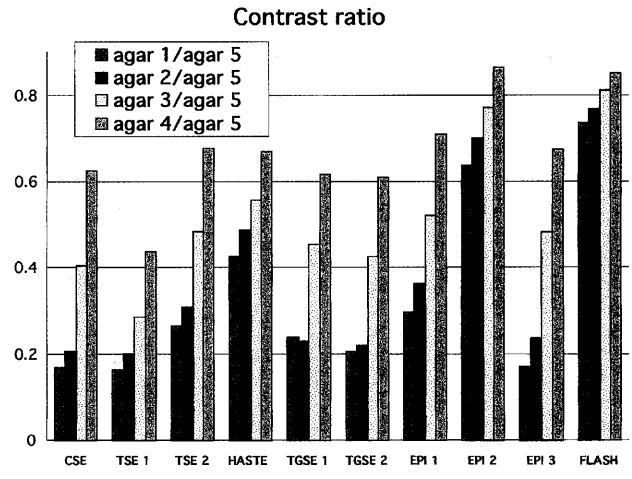


Fig. 3 Contrast ratio.
HASTE, EPI 2, and FLASH sequences showed poor CR values, particularly at high concentrations. The other sequences did not show large differences in CR values.

When a GRE sequence is used, the effective TE has a greater effect on the CR. Therefore, great care is required when setting the TE. When a negative contrast agent is used, a sequence with a longer TE would be expected to be useful.

d) Visual evaluation

Table 3 shows the results of image evaluation for each sequence. Total scores for CSE, TSE 1 and TSE 2 were high (Figs. 5a-c). Blurring artifacts were recognized in HASTE (Fig. 5d), and truncation artifacts were recognized in TGSE (Figs. 5e, f). Image distortion was

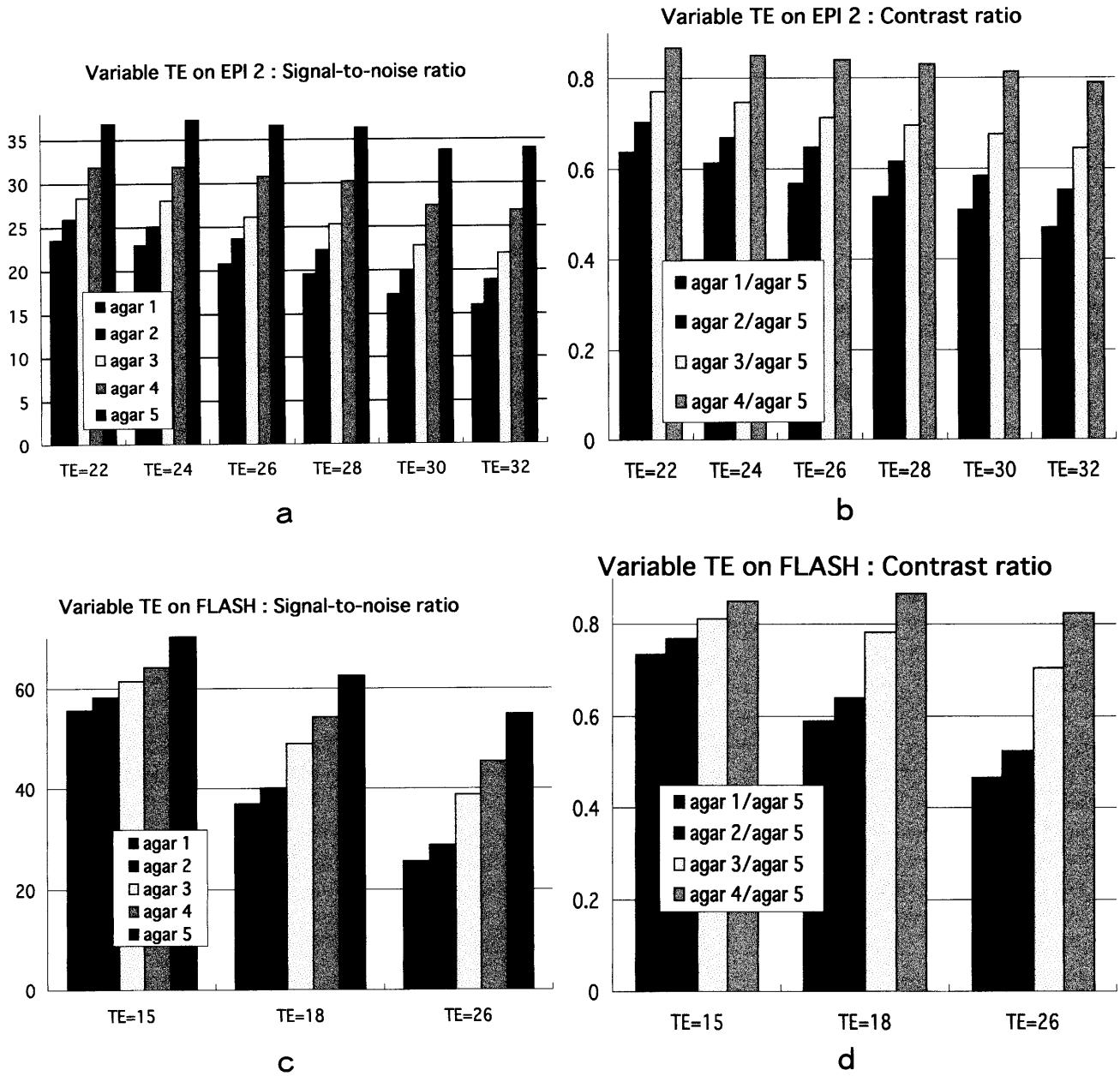


Fig. 4 Relationships between S/N, CR, and effective TE for each GRE sequence.
a, variable TE on EPI 2: Signal-to-noise ratio; b, variable TE on EPI 2: Contrast ratio; c, variable TE on FLASH: Signal-to-noise ratio; d, variable TE on FLASH: Contrast ratio. As the effective TE is increased, the S/N falls, but the CR is improved in GRE sequence.

Table 3 Visual evaluation

Sequence	Sharpness	Margin	Susceptibility artifact	Total
CSE	3	4	4	11
TSE1	3	4	4	11
TSE2	4	4	4	12
HASTE	2	2	4	8
TGSE1	2	2	3	7
TGSE2	2	3	3	8
EPI1	1	1	1	3
EPI2	1	1	1	3
EPI3	1	1	1	3
FLASH	3	3	3	9

CSE, TSE1 and TSE2 showed high scores. HASTE, TGSE1, TGSE2 and FLASH showed middle scores. EPI1, EPI2 and EPI3 showed low scores.

observed in EPI, and susceptibility artifacts and N/2 artifacts were also recognized (Figs. 5g-i). The visual contrast of FLASH was poor (Fig. 5j).

Discussion

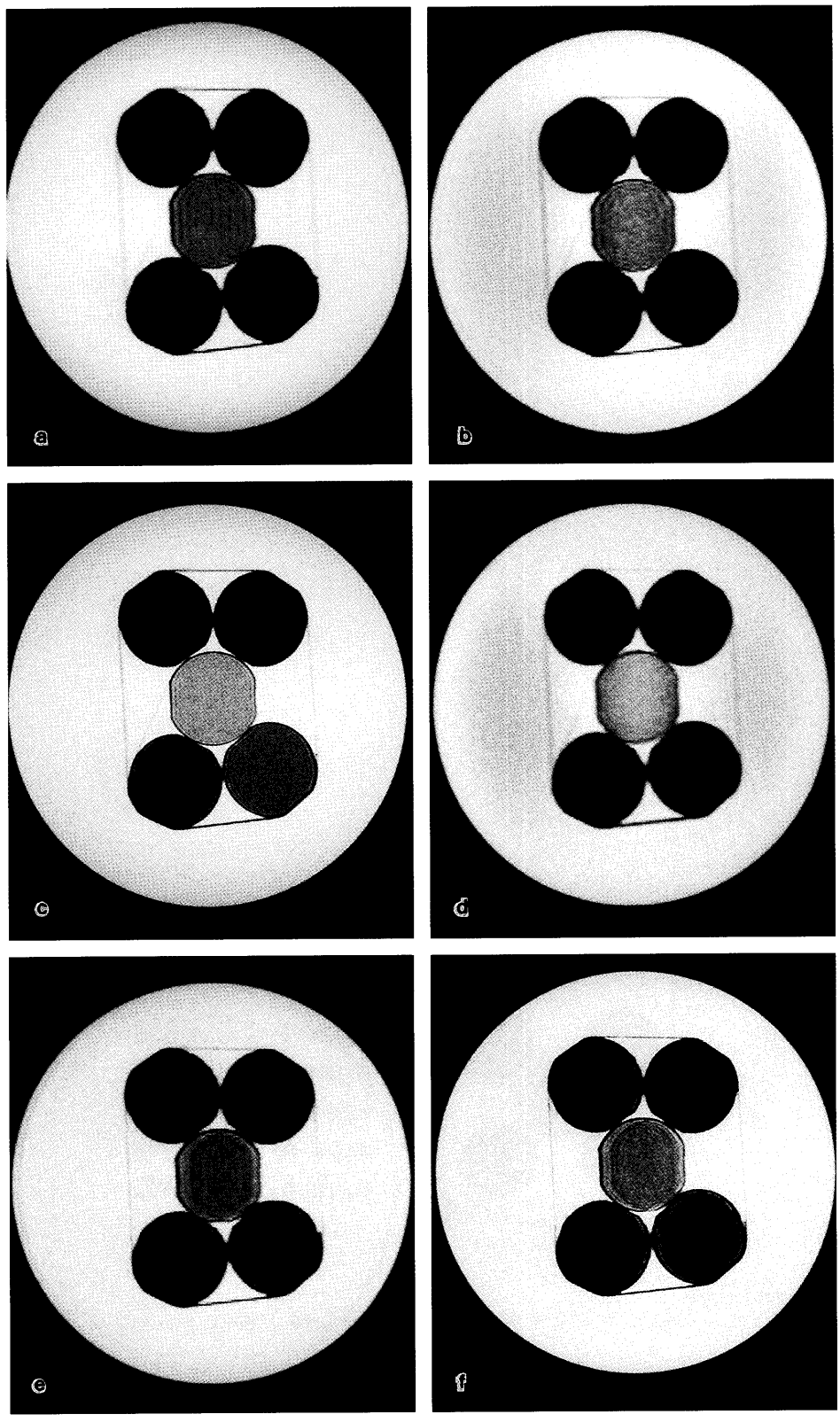
Thanks to the development of new hardware and software, various fast imaging techniques can now be employed in the clinical setting, with the EPI method used to acquire images in only tens to hundreds of milliseconds. In the GRE imaging methods (FLASH, *etc.*) [1-4] that were developed in the earlier stages of fast imaging, the TR was reduced and higher speeds were achieved by reducing the encoding number in the phase direction. Later, methods for acquiring more than one echo (with different phase encodings) following a single excitation pulse were applied clinically, and such methods have become the mainstream in fast imaging today. Based on the technique used to acquire signals, these can be broadly classified into the SE method, the GRE method, and methods that combine the two.

Of the methods mentioned above, the first to be clinically employed was the TSE method [2-4] using more than one 180° pulse to acquire signals. In this method, fat is depicted with higher signal intensity than in the CSE method. TSE is more strongly affected by magnetization transfer contrast (MTC) effects [1, 17] because 180° pulses are applied repeatedly, and is less likely to be affected by susceptibility effects. Using this sequence, it is possible to obtain T2WI during a single breath-hold even if the TR is extended to about 5,000 ms (TSE 1 in our studies), and images with strong T2 contrast that are free of respiratory motion artifacts can be obtained. It is also possible to enhance the spatial resolution in half the time or less of CSE (TSE 2 in our studies). With regard to the usefulness of TSE (at its current level of development) for the evaluation of liver tumors, contrast between the tumor and liver parenchyma is relatively poor compared with CSE [9, 12]. The negative contrast agent described in this report may be one way to overcome this problem.

According to the results of the present study, S/N falls significantly as the AMI-25 concentration is increased in CSE, TSE 1, and TSE 2. This means that the technique is a clinically useful imaging method when contrast agent is employed. TSE 2 was found to be superior to TSE 1 in terms of S/N. We feel that this is because TSE 1 in which more than one 180° pulse is used, is more susceptible to MTC effects than TSE 2, for images scanned during breath-holding. Theoretically, the S/N should be improved in sequences in which the ETL is reduced by extending the TR and TE. This would be a sequence similar to CSE. In this experiment, CSE was superior to TSE in terms of both S/N and CR, as predicted from theory. In TSE, however, the effectiveness of negative contrast imaging was clearly recognized, and contrast between the tumor and liver parenchyma was improved. This means that it is possible to employ a shorter scan time than that required in CSE, helping to minimize the effects of respiratory motion. This is expected to lead to significant advances in the clinical evaluation of liver tumors.

Among the TSE methods, the HASTE method [1-4] acquires all signals following a single excitation pulse by employing the half-Fourier method. HASTE, which has features similar to those of TSE, is a single-shot method with an infinite TR, and can achieve strong T2 contrast. Since one slice can be obtained in 1 s or less, clear images can be obtained even if breath-holding is not possible. This could be useful in a wide range of applications. In our experiments, the S/N for SPIO was low at low concentrations, but high at high concentrations, and the CR values were also quite poor. We feel that this was due to the longer ETL and stronger MTC effects. Therefore, HASTE should be the imaging method of choice when breath-holding is not possible. However, it is also important to note that this method shows weak enhancement effects when a negative contrast agent is used.

The TGSE sequence is similar to the TSE sequence,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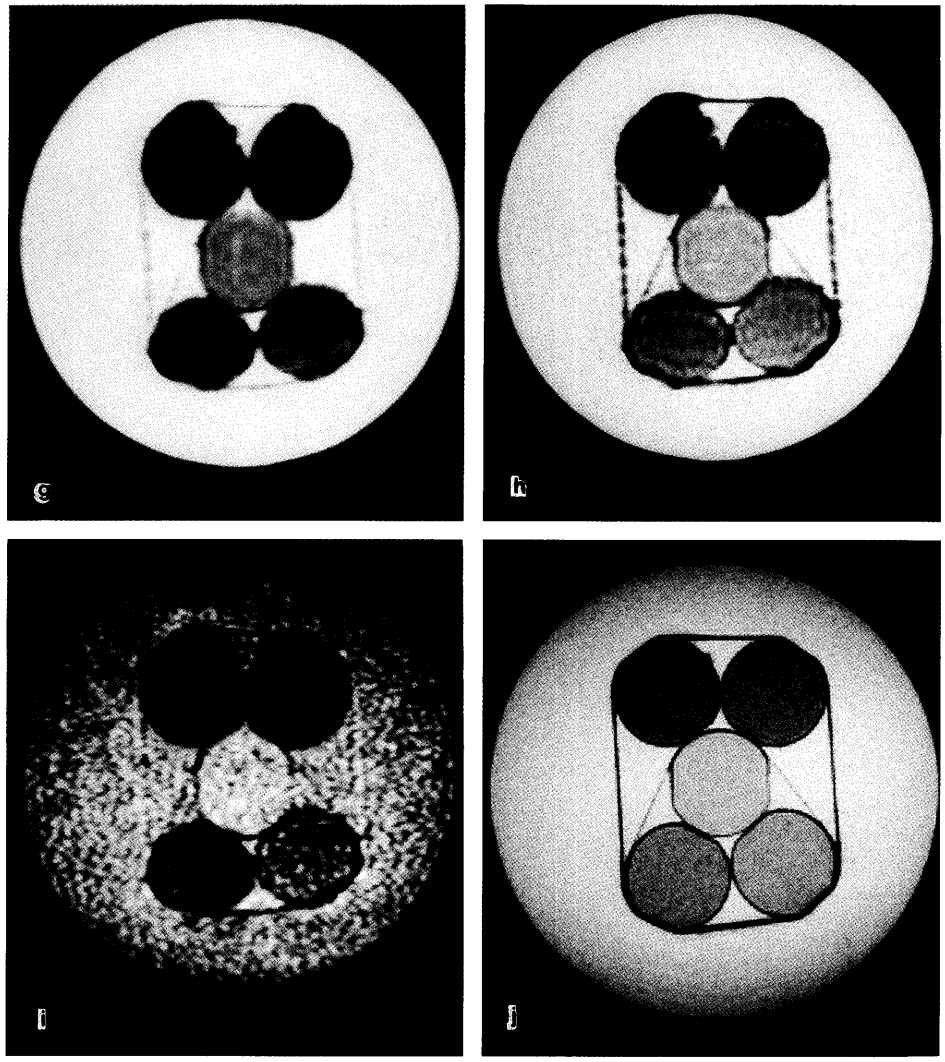

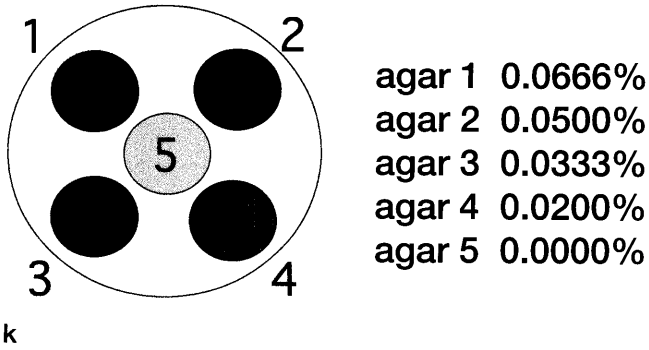

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Fig. 5 Various T2-weighted images.
a, CSE; b, TSE 1; c, TSE 2; d, HASTE; e, TGSE 1; f, TGSE 2; g, EPI 1; h, EPI 2; i, EPI 3; j, FLASH; k, the schema of the phantom.

but gradient echoes are placed at both ends of the spin echoes for signal acquisition, a technique that is referred to as gradient and SE (GRASE) [2, 3]. Since the number of 180° pulses is smaller in this method than in TSE, the imaging characteristics such as strong fat signals, MTC effects, and weak susceptibility effects of TSE are offset, permitting images closer to those acquired by CSE to be obtained. The ETL, however, can be increased so that it is equal to or greater than that in TSE. In this way, images acquired during breath-holding (TGSE 1 in our study) and high-resolution images (TGSE 2 in our study) can be obtained. The disadvantage of this method is the fact that it is more strongly affected by adjustment of eddy currents or the gradient magnetic field. In these experiments, TGSE showed relatively lower S/N and CR values than CSE, but these values were comparable to those observed for TSE. With regard to visual evaluation, deterioration in image quality due to truncation artifacts was recognized. Based on the results of these experiments, we conclude that it is impossible to acquire more information than that acquired by TSE.

The FLASH and EPI sequences [1-4] employ a sequence used in the GRE method, and this sequence is theoretically sensitive to magnetic field inhomogeneities. It was initially expected to provide better CR values. The FLASH method (TR/TE/FA = 600, 30, 15) used in the present study had the lowest CR values of all the methods evaluated.

EPI [1-3] is a method for acquiring echoes by rapidly switching the scanning gradient magnetic fields. In the single-shot method, in which all of the echo trains are obtained using a single excitation, scanning can be completed in 50-100 ms. This is the fastest scanning technique currently available. Motion artifacts are suppressed, and freeze-motion images can be obtained. It can be classified into 2 types: the free induction decay (FID) type (EPI 2 in our studies), in which signals are acquired after a radiofrequency (RF) pulse, and the SE type (EPI 1 and 3 in our studies), in which signals are acquired after a 90° pulse and a 180° pulse. Basically, however, this is a GRE method in which echoes are acquired by switching the gradient magnetic fields, and is therefore very sensitive to magnetic field inhomogeneities. In order to obtain high-quality images, an extremely uniform magnetic field is required. In our system, magnetic field uniformity is 0.5 ppm at the center of the magnetic field. Images were slightly distorted, even though they were obtained at the center of the magnet. Since marked chemical shift artifacts are seen in the phase direction, fat saturation by chemical shift selection (CHESS) is essential. However, if the magnetic field is inhomogeneous, this may be insufficient. Therefore, the short TI inversion recovery (STIR) method is often used in combination (EPI 3 in our studies). EPI produces relatively poor spatial resolution, and is associated with unique artifacts such as N/2 artifacts, susceptibility artifacts, and T2* filter effects [1-3]. As demonstrated in the present study, EPI 1 and 3 can achieve contrasts equal to that of other sequences, and the scan time is 17 slices within a few seconds. If a negative contrast agent is administered, strong contrast effects are obtained. We feel that these advantages are more than sufficient to recommend this method as an adjunct in clinical diagnosis. With regard to EPI, on the other hand, multi-shot (segmented EPI) has also been proposed, but this method requires a scan time of several seconds, although the performance of the system is not severely taxed. Therefore, ultrafast sequences, which are unique to EPI, cannot be employed.

In the present study, CR values of the FLASH and EPI 2 sequences were poor. In particular, one of the most effective ways to reduce the artifacts unique to EPI is to shorten the effective TE, which is actually shortened in routine EPI studies. We thought that the short effective TE was related to the CR, and investigated the effects of varying the effective TE. As the TE is extended, the S/N falls in accordance with the T2* relaxation, but the CR is improved. In addition, when a GRE sequence is used, the effective TE has a greater effect on the CR. Therefore, great care is required when setting the TE. When a negative contrast agent is used, a sequence with a longer TE would be expected to be useful. Based on our results, EPI of the SE type (EPI 1 and 3 in our study) was thought to be optimal from the viewpoint of image quality and CR.

Based on the results of the studies described above, we conclude that TSE, although slightly inferior to CSE in terms of S/N and CR values, should be the imaging method of choice for routine examination of the liver if the scan time is taken into account. HASTE should be used when breath-holding is not possible, and EPI should be regarded as a useful adjunctive imaging method for obtaining additional information in order to increase the contrast effect when a negative contrast agent is administered.

One limitation of the studies that have been carried out to date is that the S/N value alone is not sufficient for

overall evaluation. Another limitation of these studies is that agar phantoms are homogeneously mixed with SPIO particles, which differs from the conditions in the liver. SPIO particles accumulate in liver Kupffer cells, resulting not only in a heterogeneous distribution of particles but also in a change in their effective size from the nanometer to the micrometer range. Unlike the smaller particles in the phantom, the T2 values and T2 contrast of SPIO-containing liver tissue becomes very dependent on the TE. In addition, due to the differential magnetic susceptibilities between SPIO-containing Kupffer cells and hepatic parenchyma, the signal of the liver is lower than that of our phantoms [23].

In the present study, negative enhancement could be adequately evaluated in TSE, so contrast between tumors and normal liver parenchyma in *in vivo* studies should be improved. At this time, we conclude that TSE should be used for routine scanning, based on scan time, even though the S/N and CR values are slightly inferior to those that can be achieved by CSE. In addition, HASTE and EPI should be used as required.

Further studies are needed in order to confirm that our results are applicable to clinical examinations in which SPIO is employed.

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