—**Original**—

Sequential Gadolinium-Enhanced Magnetic Resonance Angiography of the Aortoiliac and the Femoropopliteal Arteries with Repetitive Administration of Low-Dose Contrast Agent

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Abstract

To obtain a wide-range contrast MR angiography in a single examination, we performed two sequential administrations of low-dose (0.08 mmol/kg) gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) with three dimensional inversion recovery prepared fast spoiled gradient recalled acquisition in the steady-state (3D IR-fast SPGR) sequence.

Signal characteristics of the sequence were estimated by computed simulations and an in vitro study. A clinical study of 19 examinations was done with sequential MR angiography of the aortoiliac and femoropopliteal arteries.

Great signal differences were observed between the high and low Gd concentrations. Higher Gd concentrations generated significantly stronger signals. Greater signals were produced at TIs of longer than 150 msec than at shorter than 100 msec.

In the clinical study, the arteries were visualized with sufficient signals even with a small amount of contrast agent. Contrast-to-noise ratios between the arteries and surrounding skeletal muscles or fat tissues ranged from 10.5 ± 9.6 to 4.7 ± 2.2 and 6.6 ± 2.8 to -3.1 ± 11.2, respectively. No venous enhancement was found with diluted contrast agent on the second MR angiography.

Two consecutive contrast MR angiographies can be obtained with repetitive administration of low-dose contrast agent. (J Nippon Med Sch 2000; 67: 421—428)

Key words: magnetic resonance angiography (MRA), contrast enhance, gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), distal arteries

Introduction

Gadolinium-enhanced MR angiography has been improved over the past several years and is widely used for evaluation of arterial diseases[1-11]. Arterial signals are developed with a high concentration paramagnetic contrast agent by rapid recovery of longitudinal magnetization of protons in blood. Usually, arteriosclerotic vascular disorders spread over a long segment, and additional MR angiography is often necessary to cover a large anatomical region. However, when a contrast agent is administered, vascular enhancement remains a long time, and it superimposes on a second contrast MR angiography. To avoid this problem, we applied a new acquisition technique that consists of a 3D IR-fast SPGR (three-dimensional inversion recovery prepared fast spoiled gradient re-

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called acquisition in the steady-state) sequence and repetitive administration of low-dose contrast agent for sequential contrast MR angiography. Signal characteristics of the sequence were estimated by computed simulations and in vitro phantom experiments, and the clinical feasibility of the technique was evaluated.

Materials and Methods

(1) *Computational simulations*

A 3D IR-fast SPGR sequence consists of inversion preparation pulses followed by fast SPGR acquisitions[12]. Slice-encoding SPGR acquisitions are performed in a centric order as an inner cycle, and phase-encoding steps, including IR pulse and SPGR acquisitions, are performed in a sequential order as an outer cycle. When integer numbers (m, n) are defined as phase-encoding and slice-encoding numbers, respectively, the longitudinal magnetization M_z is represented as

$$M_{z(m,n)} = 1 - (1 - M_{z(m,n-1)}\mathrm{Cos}\alpha)\ \mathrm{Exp}\ (-\mathrm{TR}/\mathrm{T1})$$

(TR: repetition time) during a slice encoding cycle.

After the slice-encoding gradient, n, is distributed incrementally from 1 to 32 in a SPGR acquisition cycle, an inversion pulse is applied, and the longitudinal magnetization occurs during inversion time (TI).

In the phase-encoding cycle, Mz is calculated as

$$M_{z(m,1)} = 1 - [1 - (-1)\ M_{z(m-1,32)}]\ \mathrm{Exp}\ (-\mathrm{TI}/\mathrm{T1}),$$

$$M_{Z(0,0)} = 1.$$

Phase-encoding gradient, m, is distributed incrementally from 1 to 48, a half of the total phase encoding steps at which the image contrast is mainly decided.

Transverse signal intensity (SI) immediately after application of radiofrequency pulse is calculated as

$$SI = M_{Z(48,1)}\sin\alpha.$$

The parameters were: repetition time, 11 msec; phase-encoding number, 256; slice-encoding number, 32; α, flip angle. T2* was not considered because the echo time (TE) used in this study was very short. These equations were translated into computer programs and signal intensity curves against T1 value were plotted at various flip angles and inversion times.

(2) *In vitro study*

MR signal intensity was measured over a wide range of concentrations of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) solutions (0, 0.125, 0.25, 0.5, 1.0, 2.0, and 4.0 mmol/L). Phantom columns with 80×55 mm bottles containing each solution were placed vertically in a 1.5 T MR scanner (Signa Advantage; GE Medical Systems, Milwaukee, WI, USA), and coronal images were taken with the body coil. A 3D IR-fast SPGR sequence was used with the following parameters: TR, 11 msec; TE, 1.9 msec; matrix size, 256×128; field of view (FOV), 40×30 cm; slab thickness, 84 mm; and partition number, 32. Inversion time was varied from 50 to 200 msec in 50 msec increments, and flip angle was changed from 20° to 60° in 10° intervals. Five scans were performed for all parameters, and signal intensities of the solutions were measured. Signal-to-noise ratios (SNRs) were calculated as the signal intensity of each solution divided by standard deviation (SD) of the background noise. Twenty additional scans were performed with the same parameters as the clinical studies (TI of 150 msec, flip angle of 40°). Contrast-to-noise ratio (CNR) between high (2 mmol/L) and low (0.5 mmol/L) concentrations, which corresponded with arterial and venous Gd concentrations in the clinical study, was calculated as follows:

$$\mathrm{CNR} = \{SI(2\ \mathrm{mmol}/l) - SI(0.5\ \mathrm{mmol}/l)\}/SD\ (\mathrm{background})$$

(3) *Statistical analysis*

In all statistical analyses, significant levels α were set at 0.05. SNRs of seven concentrations were evaluated with a one-way analysis of variance (ANOVA) with Bonferroni post hoc tests. A two-way ANOVA at five flip angles and four inversion times was performed with Bonferroni post hoc tests.

(4) *Clinical study*

Nineteen gadolinium-enhanced MR angiography examinations were done in 17 patients (14 men and 3 women, ages 33 to 81 years, mean 63.2 years). Body weight of the patients ranged from 50 to 85 kg (mean 62.6 kg). Thirteen patients were suspected to have arterial occlusive disease, and four patients had undergone grafting.

All images were acquired with a body coil on a 1.5 T scanner system (Signa Advantage; GE Medical Sys-

tems). Gadolinium-enhanced contrast MR angiography of the aortoiliac arteries was taken with a 3D IR-fast SPGR sequence in the coronal plane. Acquisition parameters were as follows: TR/TE, 11/1.9 msec; flip angle, 40°; TI, 150 msec; bandwidth, 32 kHz; matrix size, 256×128; and signal average, 1. These parameters were determined with a reference to the results of computational simulations and in vitro study. FOV and slab thickness were fitted to each patient. Thirteen examinations were taken with 32 partitions, and 6 examinations were taken with 16 partitions. Acquisition time was 32 sec in 16 partitions and 63 sec in 32 partitions. 10 m*l* (5 mmol) Gd-DTPA diluted in 50 m*l* saline was administered manually through a 22-gauge catheter placed in the antecubital vein. The mean dose of contrast agent was 0.08 mmol/kg. Contrast infusion was started at 25 seconds before the start of data acquisition and was finished at 25 seconds before the end of data acquisition.

Immediately after the aortoiliac MR angiography, 3D IR-fast SPGR contrast MR angiography of the femoropopliteal to calf arteries was obtained with an additional 10 m*l* of contrast agent. The imaging parameters and technique for infusion of contrast agent were the same as those for the aortoiliac MR angiography, except that contrast infusion started at 35 seconds before data acquisition, and continued until 35 seconds before the end of data acquisition.

All MR angiographic images were reconstructed into maximum intensity projection (MIP) images at multiple angles. Signal intensities of the arteries, surrounding skeletal muscle, and the fat tissue were measured. Contrast-to-noise ratio between the arteries and skeletal muscle (CNR*A/M) or fat tissue (CNR*A/F) were calculated as follows:

$$CNR^*A/M = \{SI(\text{artery}) - SI(\text{muscle})\} / SD(\text{artery}),$$

$$CNR^*A/F = \{SI(\text{artery}) - SI(\text{fat})\} / SD(\text{artery}).$$

We did not use the SD of the background noise because in some cases only a small area represented the background, and we were unable to set a region of interest (ROI) on it, but instead use the SD of the arterial signal[5]. Venous enhancement was estimated visually on the second contrast MR angiography. Comparison with conventional contrast angiography was available for 7 cases.

Results

1. Computational simulations

The signal intensity curves plotted against T1 values for four inversion times at a flip angle of 40° are displayed in **Fig. 1**. High signal intensities were generated within the short T1 range, and the signal decreased with longer T1 values. Longer inversion times corresponded to higher signal intensities.

2. In vitro study

Median SNR values of the Gd-DTPA solutions in five measurements are presented in **Figs. 2** and **3**. Great signal differences were observed between the high and low Gd concentrations. CNR between 2 mmol/L and 0.5 mmol/L was 144.7±9.9.

3. Statistical analysis

In all seven concentrations, higher concentrations generated statistically significant higher signals with Bonferroni post hoc tests. Comparison with flip angles, there were no significant differences except between 20° and 60°. Concerning about inversion times (TIs), significantly greater signals were produced at TIs of longer than 150 msec than at shorter than 100 msec.

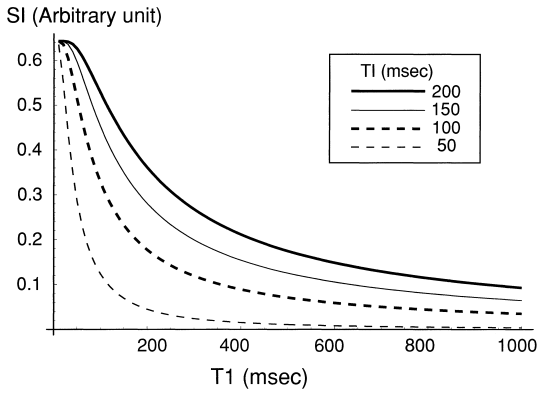

Fig. 1 Computed simulation of signal intensity plotted against T1 value for 3D IR-fast SPGR sequences at a flip angle of 40°. Inversion time varied from 50 to 200 msec in 50 msec increments. High signal intensities are generated within a short T1 range, and the signal intensity rapidly decreases with longer T1s. Longer inversion times corresponds to higher signal intensities.

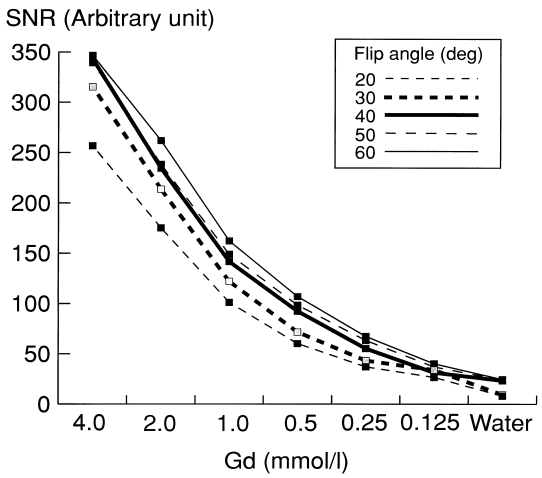

Fig. 2 SNR vs Gd-DTPA concentration in a 3D IR-fast SPGR sequence with an inversion time of 150 msec in the phantom study. Graphs depict the median values of five measurements. Flip angle varied from 20° to 60° in 10° increments. High signal intensities are produced at high Gd concentration solutions, and the signal intensity rapidly decreases with lower concentrations. Signals are weak at concentrations below 0.25 mmol/L.

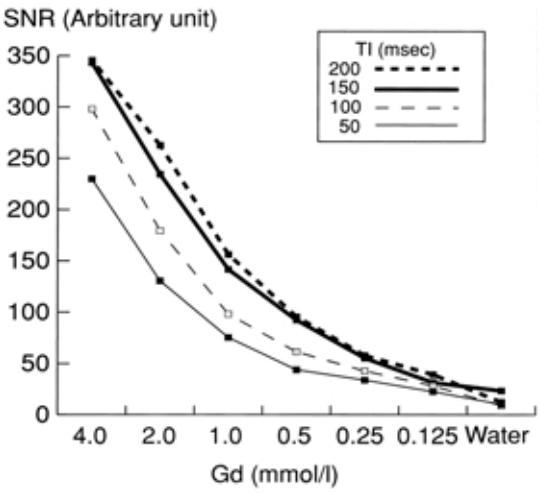

Fig. 3 SNR vs Gd-DTPA concentration in a 3D IR-fast SPGR sequence at a flip angle of 40° in the phantom study. Graphs depict the median values of five measurements. Inversion time varied from 50 to 200 msec in 50 msec increments. High signal intensities are produced at high Gd concentrations, and the signal intensity rapidly decreases with lower concentrations. Signals are weak at concentrations below 0.25 mmol/L.

4. Clinical study

All patients tolerated the examinations without any complications. In all cases, sufficient arterial signals were observed. **Figs. 4–6** show sequential-contrast MR angiograms of the aortoiliac and femoropopliteal arteries with repetitive administrations of 10 m*l* Gd-DTPA. CNRs*A/M and CNRs*A/F measurement values are presented in **Table 1**. CNRs*A/M were sufficient in all segments. Although CNRs*A/F of some calf arteries were indicated negative values, these arteries were well discriminated because they were spatially separated from the subcutaneous fat. With respect to venous enhancement, the saphenous and popliteal veins were observed in two cases on the second contrast MR angiographic images. These venous signals were considered not from the first injection, but from early venous return, because no other venous signals were noted in these cases. In the other cases, no venous signals were observed on the second MR images.

In 5 occluded and 12 stenotic segments shown by the conventional angiography, MR imaging correctly depicted 4 occlusions and 9 focal stenoses. Two occluded segments, one focal stenosis, and two diffuse stenotic segments interpreted with the MR angiography were overdiagnosed. Thirty-one normal segments, including 3 patent grafts, were depicted accurately with the MR images.

Discussion

For examination of vascular disorders, imaging of a large anatomical area is required to evaluate long segment arteries. Because imaging volume in a single acquisition is limited to the FOV, additional imaging is often necessary to cover other regions. However, once a contrast agent is administered, it remains in the intravascular and interstitial spaces until it is eliminated via the kidney[13]. In some descriptions, Gd chelates of 0.2 mmol/kg or more than 40 m*l* were required in 3 D contrast MR angiography[1–5,7,8,11]. Venous enhancement is apparent in Gd-enhanced MR angiography within several minutes of infusion of 0.2 mmol/kg Gd-DTPA[3]. Therefore, venous signals would superimpose on the second image with a usual Gd dose of MR angiography. A pixel-by-pixel subtraction technique to eliminate venous signal on both two dimensional[14,15] and three dimensional[16,17] imaging sequences has been

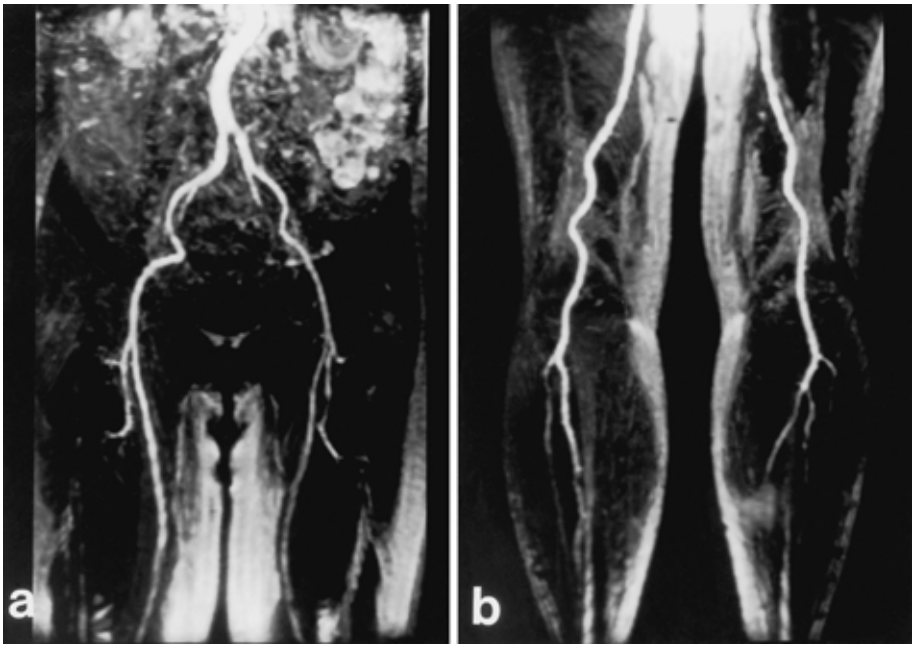

Fig. 4 Typical images of sequential Gd-enhanced MR angiography. (a) The initial contrast MR angiogram with 10 m*l* Gd-DTPA clearly shows the arteries from the lower portion of the abdominal aorta to the proximal femoral arteries. (b) Sequential MR angiogram taken immediately after (a) with administration of an additional 10 m*l* of contrast agent clearly shows the distal femoral arteries, the popliteal arteries, and the proximal calf arteries. Venous enhancement is not visible on the second MR angiogram.

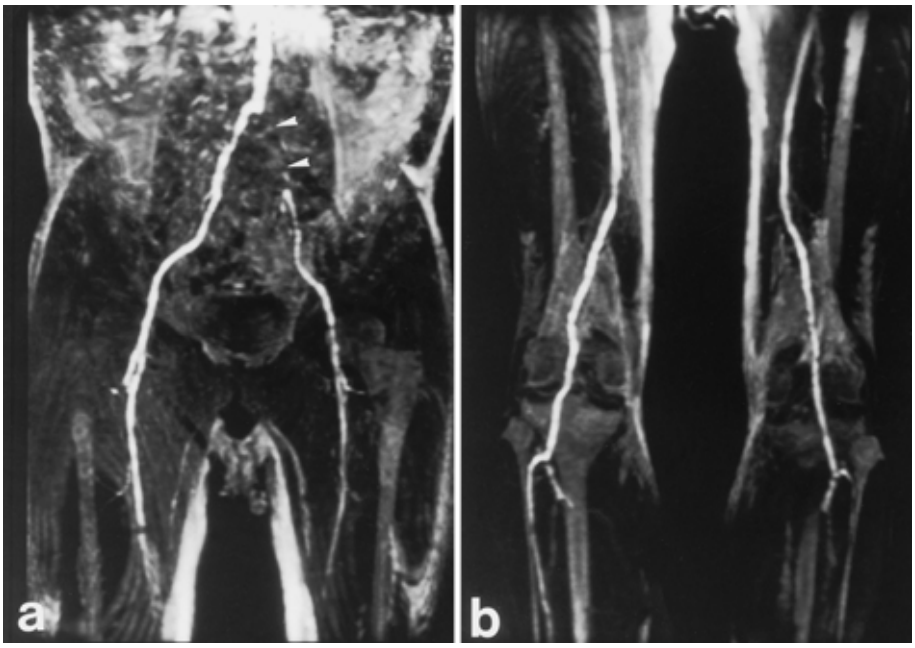

Fig. 5 A case of peripheral arterial occlusion. (a) The initial contrast MR angiogram with 10 m*l* Gd-DTPA reveals occlusion of the left common iliac artery (arrowheads). The distal arteries appear as weak signals. (b) Sequential contrast MR angiogram with an additional 10 m*l* of contrast agent shows the femoropopliteal arteries. The calf arteries are not clearly visible and are considered to have diffuse stenotic changes.

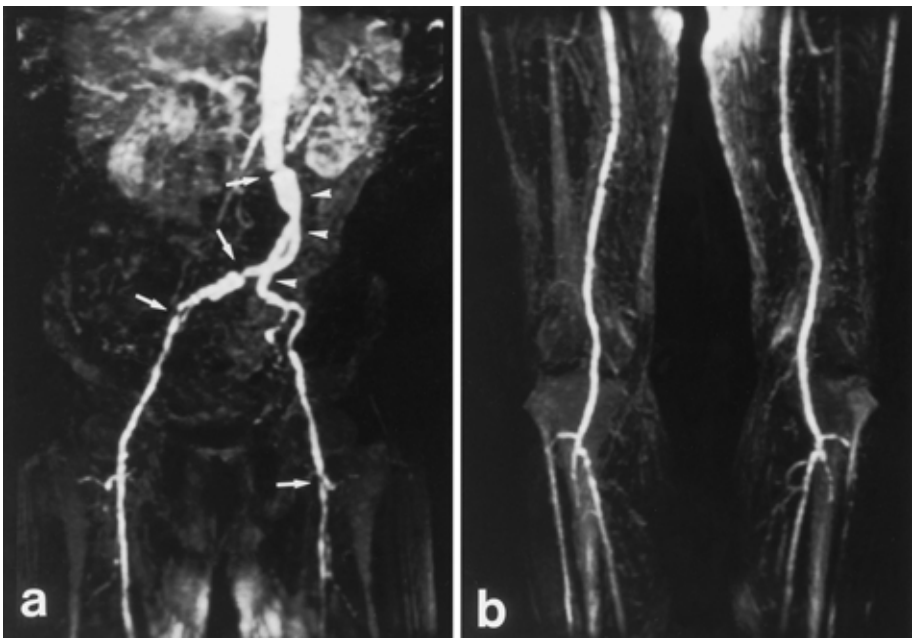

Fig. 6 A case of post aortoiliac graft implantation for treatment of abdominal aortic aneurysm. (a) The initial contrast MR angiogram with 10 m*l* Gd-DTPA shows the artificial graft vessels (arrowheads). Stenoses (arrows) are indicated at the anastomoses, right external iliac artery, and proximal portion of the left superficial femoral artery. These findings were confirmed by conventional angiography. (b) Sequential MR angiogram with an additional 10 m*l* of contrast agent immediately after the aortoiliac MR angiography clearly shows the distal femoral arteries, popliteal arteries, and proximal calf arteries without any venous enhancement.

Table 1 Contrast-to-noise ratios between arteries and surrounding skeletal muscles (CNR*A/M) or fat tissues (CNR*A/F)

	CNR*A/M	CNR*A/F
Abdominal aorta[a)]	6.6±2.8	6.6±3.3
Rt. iliac a.[a)]	4.7±2.2	5.2±2.2
Rt. femoral a.	10.5±9.6	5.5±5.3
Rt. popliteal a.	6.7±5.3	2.3±3.1
Rt. calf a.	9.7±15.8	−3.1±11.2
Lt. iliac a.[a)]	7.2±2.9	5.3±2.0
Lt. femoral a.	9.4±7.5	5.6±5.9
Lt. popliteal a.	8.3±4.8	4.5±4.2
Lt. calf a.	5.5±4.0	−0.1±3.3

[a)] including grafts.
Numbers are mean values±standard deviations.

proposed. However, this method is limited by misregistration artifacts as well as the time consumed by two acquisitions and postprocessing. With these backgrounds, we developed the sequential low dose Gd-enhanced MR angiography technique to suppress the venous signal in the second MR angiography.

An IR-fast SPGR sequence generates a heavily T1-weighted contrast with a short acquisition time[12, 18, 19]. Our computed simulations and in vitro experiments correspond with this property, which shows very high signal within a high Gd concentration range and weak signal within a low concentration range. These characteristics yield sufficient contrast between the arteries and background tissues even with a small amount of contrast agent compared with widely used techniques. In our clinical study, when 5 mmol Gd-DTPA was infused over 32 or 63 seconds, the arterial Gd concentration is estimated at approximately 1 or 2 mmol/L when cardiac output is 5 L/min if recirculation is not considered. Gd- DTPA of 1 or 2 mmol/L correspond to T 1 values of 188 or 102 msec, respectively, as calculated by

$$1/T1\ (CE) = 1/T1\ (blood) + R\ [Gd] \quad <1>;$$

where blood T1 is 1200 msec, relaxivity (R) is 4.5 L/mmol・sec, and [Gd] represents the concentration of Gd contrast agent (mmol/L)[3]. Thus, the contrast between the arteries (T1=102 to 188 msec) and surrounding skeletal muscles (T1=850 msec[20]) should be sufficient even with 10 m*l* (5 mmol) of contrast agent. We could not obtain a satisfactory contrast between the arteries and fat tissues (T1=270 msec) especially

in peripheral regions, but this is not a clinically significant problem because the arteries and fat tissues are spatially separated and therefore easily distinguished.

No obvious venous enhancement was found in the second MR angiography. Ten milliliters of Gd-DTPA administered to a 63 kg subject, the mean value in our clinical study, represents a dose of 0.08 mmol/kg. It is reported that when 0.1 mmol/kg Gd-DTPA is administered to healthy volunteers, 0.7 mmol/L contrast agent is detected in the venous plasma after 3 minutes[21]. In our patients, 0.08 mmol/Kg Gd-DTPA was injected, and no more than 0.7 mmol/L of contrast agent remained in the venous blood plasma at the second imaging. Because Gd-DTPA does not cross the membranes of blood cells[13], the blood T1 value is determined by the weighted average of the intracellular and plasma fractions when there is rapid water exchange across the cell membranes[22]. A Gd-DTPA concentration of 0.7 mmol/L in plasma is equivalent to 0.42 mmol/L in blood when hematocrit is 40%, and venous T1 value would be approximately 370 msec as calculated in equation <1>[3]. The diluted contrast agent with a T1 value of 370 msec has already lost its ability to generate a strong signal in the venous system. Thus, a small amount of contrast agent for the first imaging would suppress venous enhancement on the second MR angiography; subtraction or other postprocessing would not be necessary.

We used 10 m*l* of Gd-DTPA in each MR angiography. However, Earls et al.[23] reported that 15 m*l* of Gd-DTPA did not prevent second MR angiography after 15 minutes. On the other hand, 0.1 or 0.2 mmol/kg of Gd-DTPA yielded clear MR venography[24]. These discrepancies may be caused by differences in the pulse sequence, parameters, and the data acquisition timing. Further investigations are needed to determine the optimal dose of contrast agent and the interval between the two acquisitions.

Although our data was limited to a small number, this technique correlated well with the conventional angiography. Misdiagnosis would be mainly caused by limited spatial resolution. In conclusion, a 3D IR-fast SPGR sequence with repeated administration of low-dose contrast agent is able to obtain sequential MR angiography, and this technique is clinically feasible to evaluate long segments of arteries in a single examination.

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