Yonsei Medical Journal
Vol. 40, No. 5, pp. 413-419, 1999

Comparison of Gadomer-17 and Gd-DTPA in Image Quality of Contrast-Enhanced MR Angiographies Using Flow Phantom Model

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Abstract

The purpose of this study was to compare the image quality of 3D-TOF MR angiography (MRA) using Gadomer-17 with that using Gd-DTPA in a flow phantom model, and to present preliminary data about the proper dose concentration of Gadomer-17. In the visual analysis of vessel conspicuity, we compared the quality of pre- and post-contrast MIP images. For quantitative analysis, the signal intensities were measured in the axial base 3D-TOF images, and then the relative contrast enhancement was calculated. The results of our studies were that: 1. Maximal signal intensities were obtained at 1 mmol/L of Gadomer-17 and 4 mmol/L of Gd-DTPA. 2. Flow-related signal loss was decreased by Gd-DTPA proportional to the concentration, but Gadomer-17 did not show such a dose accumulative effect. In conclusion, after comparing the results of Gd-DTPA, it was clear that improved MRA images and higher signal intensities of vessels were obtained when lower concentrations of Gadomer-17 were used.

Key Words: Magnetic resonance imaging, carotid flow phantom, magnetic resonance angiography, Gadolinium

INTRODUCTION

Following recent advances in magnetic resonance angiography (MRA), the non-invasive visualization of the internal vascular system is now possible. Two or three dimensional time-of-flight (TOF) MRA is one of the most commonly used MRA techniques which relies primarily on flow-related enhancement to distinguish moving from stationary spins in creating MRA. Blood that has flowed into the slice will not have experienced radio-frequency pulses and will therefore appear brighter than stationery tissue.[1,2] Three-dimensional TOF MRA offers a number of advantages over its two-dimensional counterpart. First, three-dimensional volume acquisition techniques offer superior signal-to-noise ratios. Second, they permit the prescription of very thin slices, thereby reducing voxel size and decreasing intravoxel dephasing. These advantages could make this approach superior to 2D TOF angiography for imaging aneurysms of the circle of Willis, arteriovenous malformations and intracranial vascular occlusive disease.[3]

To visualize the fine vasculature with a TOF MRA technique, the saturation effect should be compensated and high resolution MRA is needed. Saturation means the repeated application of radio-frequency pulses over a short period of time compared to the T1 of the tissue, producing incomplete realignment of the net magnetization with the static magnetic field. To minimize the saturation effect, contrast agents are used to shorten the intravascular T1 relaxation time.[4,5]

Although high resolution 3D-TOF MRA is mandatory for visualizing fine vasculature, an unwanted decrease of signal-to-noise ratio can occur after reducing the pixel size, which in turn lengthens the scan time. To solve these problems, new contrast agents are needed which have higher relaxivity and longer biologic half-life.

Gadopentetate dimeglumine (Gd-DTPA) (MW= 547 daltons) has been widely used as a clinical MR contrast agent. After injection, it rapidly spreads from the vascular compartment to the extracellular fluid

Received November 27, 1998
Accepted July 26, 1999

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space; the plasma half-life in rats is approximately 12 minutes. The T1 relaxivity of Gd-DTPA in water per gadolinium (III) ion is 4.9 $mmol^{-1}s^{-1}$ at 2 Tesla and 37°C.[6-8]

Gadomer-17 was developed as a new macromolecular blood pooling contrast agent with relaxivity four times higher than Gd-DTPA.[9] Relaxivity is the key element, which can promote proton relaxation time. The higher the relaxivity value of contrast agents, the brighter the signal intensities that can be obtained in MRA images. Another characteristic of Gadomer-17 is the blood pooling property due to a cascade polymer. This intravascular pooling effect of Gadomer-17 has the advantage over Gd-DTPA in that the time reservoir is wider for the visualization of minute vasculatures. Since most contrast agents escape to interstitial space in a short time when using Gd-DTPA, there is a narrower time reservoir for imaging.[10] For these reasons, Gadomer-17 would be a more effective contrast agent than the currently used Gd-DTPA for high resolution 3D-TOF MRA. However, there has so far only been phase 1 study about Gadomer-17. Its safety and biopharmacology have yet to be determined.

The work of Weinmann has provided the only available data about Gadomer-17 from in vivo experimental study using rabbits. However, there still remains the question about the higher relaxivity of Gadomer-17 compared to Gd-DTPA, because these data were derived from in vivo study.[9]

The purpose of this study was to compare the image quality of 3D-TOF MRA using Gadomer-17 with that using Gd-DTPA in a flow phantom model and to present the preliminary data about the proper dose concentration of Gadomer-17.

MATERIALS AND METHODS

To determine the optimal concentration for MRA, 0.5 mol/L of Gd-DTPA (Schering AG, Berlin, Germany) and Gadomer-17 (supplied by Weinmann, Schering AG, Berlin, Germany) were serially diluted with distilled water and the signal intensities were measured using high resolution single slab 3D-TOF MRA with slice interpolation technique in a 1.5 T MR device (Magnetom VISION; Siemens, Erlangen, Germany). To maintain magnetic homogeneity, the solutions of contrast agents were filled in 10 mL test tubes located at equal distance from the center of the gantry using custom-made testtube holders. To remove unwanted air in the testtubes, air was sucked out as much as possible. Therefore, we can reduce the susceptibility artifact. The signal intensities were measured at the mid-portion of each testtube and the curve of signal intensities and the concentration of contrast agents were obtained. A commercially available flow phantom model for carotid bifurcation and UHDC flow system (Quest Image Co., London, Canada) was filled with Gd-DTPA and Gadomer-17 in three different concentrations (1 mmol/L, 2 mmol/L, and 4 mmol/L, respectively). Because we obtained the highest signal intensity of Gadomer-17 solution and Gd-DTPA solution at 1 mmol/L and 4 mmol/L respectively, we chose three concentrations of solutions for the flow phantom model study. To maintain similar viscosity with human blood, a glycerine solution with distilled water (1.4 : 1) was used. The flow systems were operated on the pulsatile system (mean volume: 9.2 ml/sec, peak systolic volume: 30 ml/sec, stroke volume: 552 ml/min).[11] Two flow phantom models composed of normal and 70% stenosis at the proximal ICA area were used (Fig. 1). Using single slab 3D-TOF MRA with slice interpolation technique (TR/TE/FA: 35/6.4/15°, field of view: 220 mm, pixel size: 1.03×0.43 mm), an axial source image of 3D-TOF and MIP reconstructed images were obtained for each contrast agent, for each concentration, and for each phantom model. For the quantitative

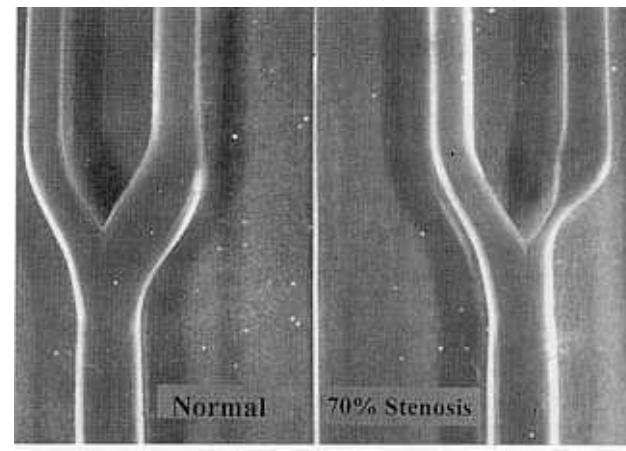

Fig. 1. Carotid bifurcation flow phantom models. Right, normal phantom and left, 70% stenosis phantom model for carotid bifurcation were filled with blood mimicking fluid to visualize the smooth inner lumen margin and architecture.

analysis, signal intensity was measured in the axial base 3D-TOF image. The region of interest (ROI) was positioned at the 1-cm distal portion of ICA from the carotid bifurcation area where the turbulent flow-related signal loss was most prominent on precontrast TOF MRA. Another ROI was positioned at the 3-cm distal area of ICA from the carotid bifurcation to evaluate the decrease in the saturation effect after contrast enhancement. The saturation effect decreased the signal intensity of the image. If we used the optimal concentration of contrast agents, then much brighter signal intensities could be obtained after post-contrast imaging. The percent enhancement was calculated as follows: RI (relative intensity)=Signal Intensity at ROI/Background Noise. Noise was measured based on background air. With these data, we obtained the percent enhancement in each area. [Percent enhancement=(RI of postcontrast - RI of precontrast)/RI of precontrast × 100].[12] As the value of background noise was similarly low, we used the measured data in practice. With MIP reconstructed images of the carotid bifurcation phantom, visual analysis was performed concerning the vessel conspicuity and the degree of the compensating effect of contrast agents over the flow-related signal loss above the bifurcation. The following scoring systems were used for the qualitative analysis of the phantom model. When comparing the noncontrast MRA image, if the flow-related signal loss was markedly reduced, we scored it as (++); not significantly different (+); and increased as (−). Another scoring system for the vessel conspicuity was compared with radiography; if the inner margin of phantom was equally focused, we scored it as excellent (++); less sharpness but acceptable as good (+); and unacceptable image quality as poor (−). Two radiologists (B-J Jo, T-S Chung) analyzed the images and the final interpretation was made by consensus.

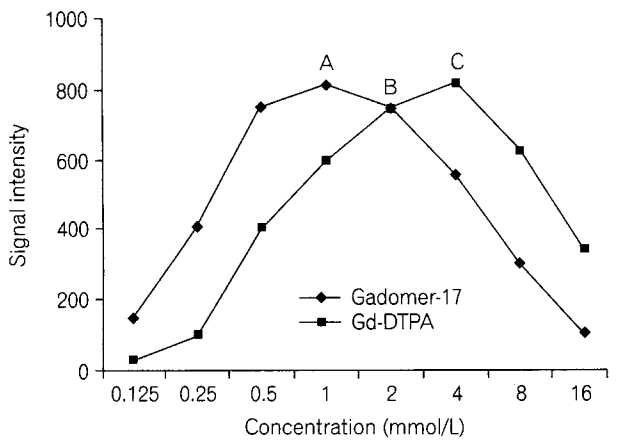

Fig. 2. Concentration-to-signal intensity curve of both contrast agents. This graph illustrates the relationship between concentrations of contrast agent and signal intensity. Gadomer-17 shows maximal signal intensity at a relatively lower concentration compared with Gd-DTPA. With this result, we selected 1,2 and 4 mmol/L of Gadomer-17 and Gd-DTPA solutions respectively for the flow phantom circulatory unit.

RESULTS

In dose-ranging study, we plotted the concentration/signal intensity curve for each contrast agent. Although the maximum signal intensity of the two contrast agents was similar, 4 mmol/L diluted Gd-DTPA and 1 mmol/L diluted Gadomer-17 solution

Table 1. Comparison of Percent Enhancement between Types of Contrast Agents

Location	Percent contrast enhancement(PCE)*			
	1 mmol/L		4 mmol/L	
	Gadomer-17	Gd-DTPA	Gadomer-17	Gd-DTPA
Distal portion†	180%	76%	45%	240%
Above bifurcation‡	210%	96%	0%	270%

* PCE=(SI of Postcontrast-SI of Precontrast)/SI of Precontrast × 100.

† Signal intensities were measured at the 3-cm distal area of ICA from the carotid bifurcation to evaluate the effect of contrast agent over the saturation effect at the distal part of the vessel.

‡ Signal intensities were measured at the 1-cm distal area of ICA above the carotid bifurcation, where flow-related signal loss was maximally demonstrated on precontrast MRA.

Table 2. Visual Analysis Score of Carotid Artery Bifurcation Phantoms on Variable Concentrations of Gadomer-17 and Gd-DTPA Solution

	1 mmol/L		4 mmol/L	
	Gadomer-17	Gd-DTPA	Gadomer-17	Gd-DTPA
Compensation over flow related signal loss*	(++)	(−)	(−)	(++)
Vessel conspicuity†	(++)	(−)	(−)	(++)

* When comparing with the noncontrast MRA image, if the flow-related signal loss is markedly reduced, we scored it as (++), not significantly different (+), and increased as (−).
† Vessel conspicuity was compared with radiography, if the inner margin of phantom was equally focused, we scored it as excellent (++), less sharpness but acceptable as good (+) and unacceptable image quality as poor (−).

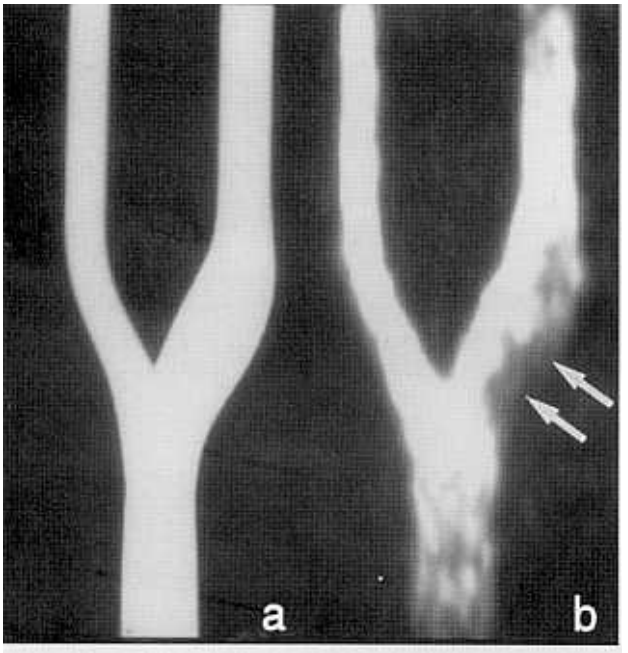

Fig. 3. Radiograph and MRA of normal carotid phantom model. Radiograph of normal carotid phantom model after filling with contrast agents shows good opacification of the vessel model with a smooth inner margin (a). 3D-TOF MRA without using contrast agent of normal carotid phantom (b). The arrows show turbulent flow-related signal loss at the proximal ICA.

showed the highest signal intensity in serially-diluted concentrations (Fig. 2). The peak signal intensity of Gadomer-17 was not significantly different from that of Gd-DTPA, but the concentration/signal intensity curve of Gadomer-17 was shifted to the left side compared to that of Gd-DTPA. The flow phantom study using a carotid bifurcation phantom model also showed peak signal intensity at 1 mmol/L concentration of Gadomer-17 and 4 mmol/L of Gd-DTPA

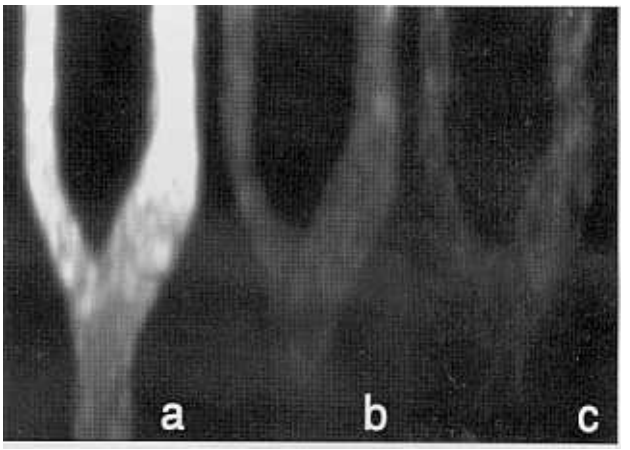

Fig. 4. Normal carotid MRAs using Gadomer-17 of different concentrations. Signal intensity of 1 mmol/L (a) concentration is higher than that of 2 mmol/L (b) and 4 mmol/L (c) on MIP image.

among three concentrations. Non-contrast-enhanced 3D-TOF MRA showed turbulent flow-related signal loss at the proximal ICA area, which had decreased after contrast enhancement. However, the highest signal reflecting the decrease of flow-related signal loss was observed at 4 mmol/L in Gd-DTPA, whereas, it was 1 mmol/L in Gadomer-17. The percent enhancement of Gadomer-17 was higher than that of Gd-DTPA in 1 mmol/L concentration (180% vs. 76%), but Gd-DTPA exhibited higher enhancement in 4 mmol/L concentration than Gadomer-17 (240% vs. 45%) (Table 1). Visual analysis of vessel conspicuity and the compensating effect of the contrast agent for turbulent flow-related signal loss were both excellent in 1 mmol/L concentration of Gadomer-17 and in 4 mmol/L concentration of Gd-DTPA (Table 2, Fig. 3-8).

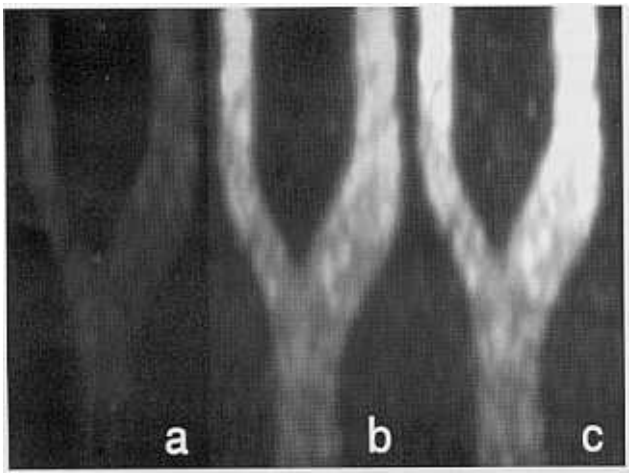

Fig. 5. Normal carotid MRAs using Gd-DTPA of different concentrations. Signal intensity of 4 mmol/L concentration (c) is higher than those of 1mmol/L (a) and 2 mmol/L (b) concentrations on MIP images. Superior vessel conspicuity is also demonstrated in the 4mmol/L solution.

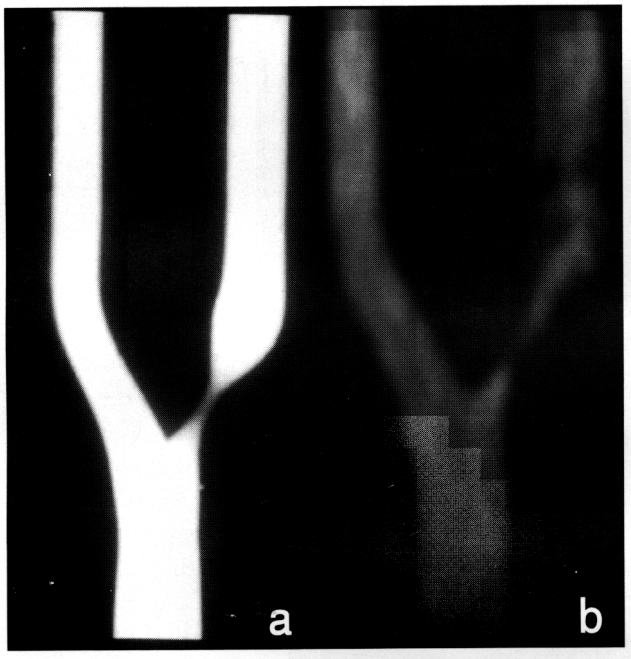

Fig. 6. Radiograph and MRA of stenotic carotid phantom. This carotid phantom model has 70% stenotic portion at the proximal ICA level. Radiograph (a) after filling with contrast agent shows good opacification of vessel model. 3D-TOF MRA (b) obtained without contrast agent also shows the stenotic portion. Compared with radiograph, it reveals flow-related signal loss areas in proximal ICA.

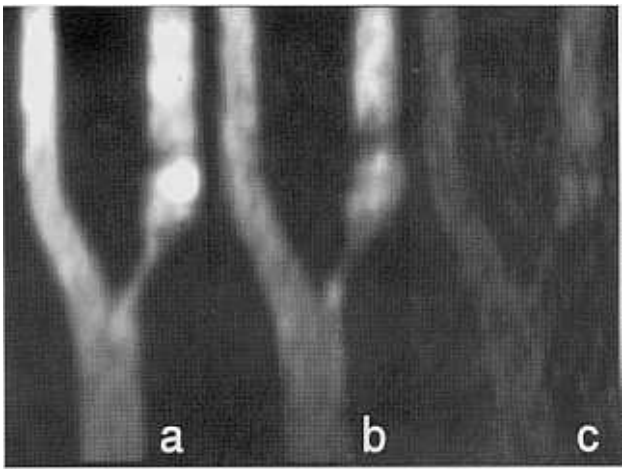

Fig. 7. Stenotic carotid MRAs using Gadomer-17 of different concentrations. Vessel conspicuity is superior in 1 mmol/L concentration (a) to concentrations of 2 mmol/L (b) and 4 mmol/L (c). Signal intensity of 1mmol/L (a) concentration is higher than those of 2 mmol/L (b) and 4mmol/L (c).

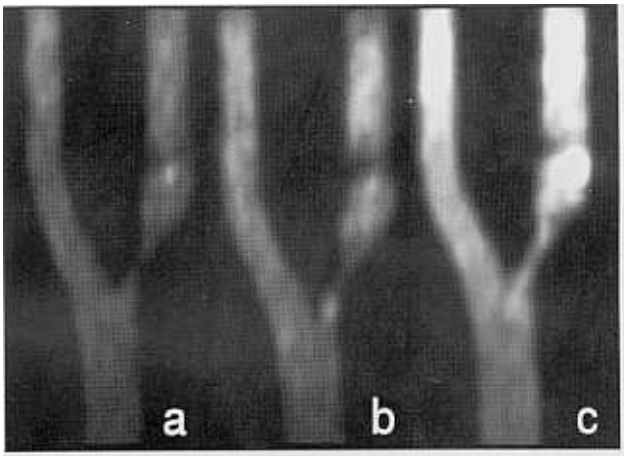

Fig. 8. Stenotic carotid MRAs using Gd-DTPA of different concentrations. Maximal intensity projection (MIP) images show greatest vessel conspicuity and higher signal intensity in 4 mmol/L (c) concentration than in those of 1 mmol/L (a) and 2 mmol/L (b).

DISCUSSION

3D-TOF MRA is a useful method for the visualization of small but fast flow vessels, and it is also effective in that it has a higher spatial resolution and higher signal-to-noise ratio. However, the saturation effect is still a grave limitation for 3D-TOF MRA.

Recently, to minimize the saturation effect, many researchers have used the TONE sequence and re-

duced the slab thickness. In addition to these methods, another effective method has been to reduce intravascular T1 relaxation time using MR contrast agents.[3]

To visualize the fine vasculature, high resolution MRA is needed. Although high resolution MRA can be achieved by reducing pixel size, which in turn results in an inevitable decrease of signal-to-noise ratio.[13] To compensate the decreased signal-to-noise ratio, high resolution MRA needs a longer scan time, which is a limitation for imaging vascular structures. Although contrast agent can be effective in high-resolution MRA, a longer scan time is still a limitation for imaging because Gd-DTPA, the currently-used contrast agent, has a very short half-life in the vascular space and very quickly escapes to interstitial space. For this reason, there is increased need for the development of new contrast agents with higher relaxivity and longer biologic half-life in the vascular space to better visualize the vasculatures with high-resolution MRA sequences. Contrast agents also have an advantage in that they can reduce the dephasing effect occurring in the tortuous vessel when applied to MRA.[14,15]

In our study, we used Gadomer-17, a new macromolecular blood-pooling contrast agent. Macromolecular paramagnetic contrast agents currently have the advantage in application to abdominal structures, such as the abdominal aorta, where the rapid shift of intravascular contrast into interstitial space by diffusion can occur when Gd-DTPA is used.[16-18]

Gadomer-17, a 24-cascade polymer has a molecular weight of 35 kDa and a T1/T2 relaxivity of 17.3 and 18.7 $Lmmol^{-1}sec^{-1}$ at 20 MHz.[9] In our study, we tried to reveal the different image quality between Gadomer-17 and Gd-DTPA depending on the difference in intrinsic relaxivity using high-resolution 3D-TOF MRA with slice interpolation technique. To our knowledge, apart from one preliminary report on Gadomer-17 by Weinmann, this study is the first detailed study concerning Gadomer-17. Since we were trying to demonstrate the difference in contrast between Gadomer-17 and Gd-DTPA by the difference in intrinsic relaxivity, we experimented in an in vitro flow phantom system where the variations of relaxivity in tissue could be minimized.

The percent enhancement of Gadomer-17 was higher than that of Gd-DTPA in 1 mmol/L concentration (180% vs. 76%), but Gd-DTPA exhibited higher enhancement in 4 mmol/L concentration than Gadomer-17 (240% vs. 45%). These results suggest that a relatively low concentration dose would be more effective in Gadomer-17 than Gd-DTPA for optimal contrast enhancement. Vessel conspicuity and the compensating effect of contrast agent for turbulent flow-related signal loss were excellent in 1 mmol/L concentration of Gadomer-17 and in 4 mmol/L concentration of Gd-DTPA. Visual analysis regarding vessel conspicuity showed no difference with Gd-DTPA, except there was a lower dose dependency for Gadomer-17. Flow-related signal loss was compensated by Gd-DTPA proportional to concentration, but Gadomer-17 did not show such a dose-accumulative effect in the optimal range of concentration for Gd-DTPA. These results suggest that a lower dose of Gadomer-17 can be equally effective in 3D-TOF MRA as a routine dose of Gd-DTPA. The reason why Gadomer-17 showed a greater decrease of signal intensity in a higher concentration of solution (4 mmol/L in our study) is not known. However, we can speculate that Gadomer-17 is more susceptible to T2 decay in a higher concentration of solution due to its intrinsic difference in molecular structure compared to that of Gd-DTPA.

Few studies about the relaxivity of MR contrast agents have been conducted using spectroscopic analysis or immunoassay in phantoms or in vivo. However, to our knowledge, there have been no previous reports about comparative studies between Gadomer-17 and Gd-DTPA using image analysis only. This study was based on the fact that Gadomer-17 has 4 times higher relaxivity than Gd-DTPA. We believe it is beyond the scope of our study to reveal the true relaxivity value of Gadomer-17. There still remains the task of revealing the pharmacology and kinetics of Gadomer-17. Generally, since the gadolinium complex has symmetrical structure, the gadolinium complex has stronger relaxivity. With this fact, we can presume that Gadomer-17 has a more symmetrical structure than Gd-DTPA.

In conclusion, this study showed that Gadomer-17, a new macromolecular paramagnetic contrast agent, can be used effectively to define the main carotid vasculature with relatively lower doses of contrast due to its higher T1 relaxivity. However, future clinical use of this contrast will focus on the distal, small vasculature, where Gadomer-17 has the advantage of

prolonged intravascular stasis.

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