Contrast-Enhanced Magnetic Resonance Angiography in Rats with Gadobenate Dimeglumine at 3T

Jo-Chi Jao, Yen-Ku Chen, Twei-Shiun Jaw, Po-Chou Chen

Abstract—This study aimed to investigate the magnetic resonance (MR) signal enhancement ratio (ER) of contrast-enhanced MR angiography (CE-MRA) in normal rats with gadobenate dimeglumine (Gd-BOPTA) using a clinical 3T scanner and an extremity coil. The relaxivities of Gd-BOPTA with saline only and with 4.5% human serum albumin (HSA) were also measured. Compared with Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), Gd-BOPTA had higher relaxivities. The maximum ER of aorta (ERa) appeared at 1.2 min and decayed to half at 10 min after Gd-BOPTA injection. This information is helpful for the design of CE-MRA study of rats.

Keywords—Contrast-Enhanced Magnetic Resonance Angiography, Gd-BOPTA, Gd-DTPA, Rat.

I. INTRODUCTION

CARDIOVASCULAR diseases, one of the major cause of death and disability in the world, has to be diagnosed early and accurately for better prognosis of treatment. Magnetic resonance imaging (MRI) can demonstrate a high contrast between soft tissues and has no radiation. Therefore, MRI plays an important role in lesion detection. Contrast agents can improve the signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of MR images. Nowadays, contrast-enhanced magnetic resonance angiography (CE-MRA) is commonly used for the detection of vascular lesions [1]-[5].

The first MRI contrast agent approved by the United States Food and Drug Administration (FDA) is Gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) in 1988. Gd-DTPA can reduce both of the spin-lattice relaxation time (T1) and transversal relaxation time (T2). For T1 measurement, the echo time (TE) was 14 ms fixed and the repetition time (TR) was 2000 ms fixed and the TE varied from 20 to 120 ms. Other MRI parameters for T1 and T2 measurements are the same: the field of view (FOV) was 20 cm, the matrix size was 256×256, and slice thickness was 5 mm. All the acquired images were transferred to an Advantage Windows Workstation (General Electric Company, Milwaukee, WI) and the MR images were analyzed by a radiologist.

Gadobenate dimeglumine (Gd-BOPTA) and gadoxetate disodium (Gd-EOB-DTPA) are both commercially available MRI contrast agents. Gd-BOPTA and Gd-EOB-DTPA can be taken up by hepatocytes and are used in liver MRI for the detection of hepatic mass. In addition to the kidney system, Gd-BOPTA and Gd-EOB-DTPA are partially excreted by the hepatobiliary system [7]. Yoshikawa et al. demonstrated higher image quality of MRA in rats with Gd-EOB-DTPA than with Gd-DTPA using a 1.5 T MRI scanner [8].

High-field MRI is expected to show higher signal intensity of MR images than lower MRI. The aim of this study was to evaluate the enhancement of MRA both in rats with Gd-BOPTA compared with Gd-DTPA at 3T. The relativity values of Gd-BOPTA solution with saline or 4.5% human serum albumin (HSA) was also measured.

II. MATERIALS AND METHODS

A. Phantom MRI

This study was performed on a 3T clinical whole-body scanner (General Electric Company, Milwaukee, WI). Fifteen test tubes containing various concentrations (0-10 mM) of Gd-BOPTA (Multihance, Bracco Imaging, Milan, Italy) in saline were prepared and put into a quadrature head coil. One coronal image was acquired using a conventional spin echo (CSE) pulse sequence to evaluate longitudinal relaxation time (T1) and transversal relaxation time (T2). For T1 measurement, the echo time (TE) was 14 ms fixed and the repetition time (TR) varied from 30 ms to 12000 ms. For T2 measurement, the TR was 2000 ms fixed and the TE varied from 20 to 120 ms. Other MRI parameters for T1 and T2 measurements are the same: the field of view (FOV) was 20×20 cm, the matrix size was 256×128, and slice thickness was 5 mm. All the acquired images were transferred to an Advantage Windows Workstation (General Electric Company, Milwaukee, WI) and the MR signal intensity of each tube were measured. The T1 and T2 values of contrast agents with varied concentrations were determined by least square curve fitting the MR signal intensity (S) according to (1) and (2) respectively [9].

\[ S = M(1 - 2\exp(\frac{TR - 0.5TE}{T1}) + \exp(-\frac{TR}{T1})) \]  
(1)

\[ S = M\exp(-\frac{TE}{T2}) \]  
(2)

where M is the magnetization including electric gains.

The longitudinal and transversal relaxivity \( r_1 \) and \( r_2 \) were obtained by linear regression according to (3) and (4), respectively.

\[ \frac{1}{T1} = \frac{r_1}{M} + \frac{1}{T1_0} \]  
(3)

\[ \frac{1}{T2} = \frac{r_2}{M} + \frac{1}{T2_0} \]  
(4)

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1/\(T_1\) = 1/\(T_{10}\) + \(r_1 \cdot C\)  
1/\(T_2\) = 1/\(T_{20}\) + \(r_2 \cdot C\)  

where \(C\) is the concentration of the contrast agent.

The \(r_1\) and \(r_2\) values of Gd-BOPTA with 4.5% HSA were obtained as the same procedure mentioned above. The \(r_1\) and \(r_2\) values of Gd-DTPA (Magnesvit, Schering, Berlin, Germany) with saline or 4.5% HSA were obtained from the published data.

**B. Animal CE-MRA**

The protocol of animal use was approved by the Institutional Animal Care and Use Committee (IACUC).

Six normal male Sprague Dawley rats were divided into two groups: one for Gd-BOPTA-enhanced MRA (\(n = 3\)) and the other for Gd-DTPA-enhanced-MRA (\(n = 3\)). Each rat was anesthetized with 50 mg/kg ketamine, 10 mg/kg xylazine and 1 mg/kg atropine and underwent CE-MRA. For each scan only one rat was put inside the knee coil in a prone position. The enhanced fast gradient echo 3-dimensional (efgre3D) pulse sequence was used for the CE-MRA with flip angle (FA) = 30°, FOV = 12× 10.8 cm, matrix size = 320 × 160, and slice thickness = 1 mm. Each MRA took 24s. After one pre-contrast scanning, 0.1 mmol/kg Gd-BOPTA or Gd-DTPA was bolus injected through the rat’s tail vein and MRA was performed sequentially for 30 min. All acquired images were transferred to the GE Advantage Windows Workstation. Regions of interest (ROIs) in the aorta, liver, kidney, muscle and background were selected. The SNR of each organ as a function of time were calculated as follows:

\[
\text{SNR}(t) = \frac{S(t)}{\sigma}
\]

where \(S(t)\) is the signal intensity obtained at time \(t\) after the injection of contrast agents, and \(\sigma\) is the standard deviation of the background.

The signal enhancement ratio (ER) of the aorta, liver, kidney and muscle as a function of time were calculated as:

\[
\text{ER}_i(t) = \frac{\text{SNR}(t)/\text{SNR}_0}{\text{SNR}_i(t)/\text{SNR}_0}
\]

where \(\text{SNR}(t)\) and \(\text{SNR}_i(t)\) is the SNR obtained at time \(t\) after and before the injection of contrast agents, respectively. The suffix \(i\) represents each organ: aorta, kidney, liver or muscle.

Nonparametric statistics and the Mann-Whitney tests were used to compare the ER and ERR of the Gd-BOPTA-enhanced MRA and Gd-DTPA-enhanced MRA, which were conducted using SPSS software (version 14.0, SPSS Inc. Chicago, IL, USA). There was a significant difference if \(p < 0.05\).

**III. RESULTS**

**A. Phantom MRI**

Table I lists the \(r_1\) and \(r_2\) values of Gd-BOPTA and Gd-DTPA with saline or 4.5% HSA. There was good linearity between the relaxation rates (1/\(T_1\) and 1/\(T_2\)) and the concentration of each contrast agent. Both Gd-BOPTA and Gd-DTPA with 4.5% HAS had higher relaxivities than those with plain saline. Furthermore, Gd-BOPTA had higher relaxivities than Gd-DTPA.

**B. Animal CE-MRA**

Figs. 1 and 2 show the representative maximum intensity projection (MIP) images of two normal rats before and after Gd-BOPTA or Gd-DTPA injection. Figs. 3-6 show the ER in aorta (\(E_{Ra}\)), kidney (\(E_{Rk}\)), liver (\(E_{Rl}\)) and muscle (\(E_{Rm}\)) before and after Gd-BOPTA or Gd-DTPA injection. After Gd-BOPTA injection, \(E_{Ra}\) was 2.68 ± 0.83 at 0.4 min and up to maximum value 4.56 ± 1.09 at 1.2 min. Afterwards, \(E_{Ra}\) decreased to 2.27 ± 0.52 at 10 min and to 1.40 ± 0.34 at 30 min. On the other hand, after Gd-DTPA injection, \(E_{Ra}\) was 2.05 ± 0.26 at 0.4 min, which was lower than Gd-BOPTA group, but the difference was not significant (\(p > 0.05\)). The maximum value \(E_{Ra}\) 2.47 ± 0.26 also happened at 1.2 min, and then decreased faster than Gd-BOPTA group to 1.64 ± 0.17 at 10 min and to 1.30 ± 0.30 at 30 min. There was significant difference from 1.2 to 15 min (\(p < 0.05\)). After 20 min, the difference was not significant (\(p > 0.05\)). For kidney, after Gd-BOPTA injection, clear enhancement started at 1.2 min with \(E_{Rk}\) value 1.50 ± 0.46, increased to maximum value 7.63 ± 1.57 at 2.4 min, and then decreased to 2.23 ± 0.59 at 30 min. For Gd-DTPA group, obvious enhancement also started at 1.2 min with \(E_{Rk}\) value 4.74 ± 0.26, which was lower than that of Gd-BOPTA group. The maximum \(E_{Rk}\) value 5.73 ± 0.23 at 2.4 min and declined to 3.29 ± 0.14, which became higher than that of Gd-BOPTA group. From 1.2 to 4.0 min and at 30 min, the \(E_{Rk}\) values were significantly different between these two groups. For liver, right after Gd-BOPTA injection, the enhancement was not clear. But \(E_{Rl}\) value was 4.13 ± 0.48 at 1.2 min, then decayed slowly to 3.73 ± 0.44 at 10 min and 2.00 ± 0.22 at 30 min. From 1.2 to 10 min, \(E_{Rl}\) values were similar. For Gd-DTPA group, \(E_{Rl}\) was 1.18 ± 0.26 at 0.4 min, which was similar to that of Gd-BOPTA group, but the maximum \(E_{Rl}\) value 2.09 ± 0.38 happened at 1.2 min, which was much less than that of Gd-BOPTA group. Afterwards, the \(E_{Rl}\) declined, which was only 1.21 ± 0.27 at 30 min. The \(E_{Rl}\) values were significantly different between Gd-BOPTA and Gd-DTPA groups for 1.2 min to 30 min (\(p < 0.05\)).The \(E_{Rm}\) was smaller than \(E_{Rk}\) and \(E_{Rl}\) for both groups. Gd-BOPTA group had higher \(E_{Rm}\) than that of Gd-DTPA group. The maximum \(E_{Rm}\) were 1.79 ± 0.37 and 1.20 ± 0.20 for Gd-BOPTA and Gd-DTPA group respectively. There was significant difference between these two groups from 0.4 min to 30 min.

**IV. DISCUSSION**

In the phantom study, we have shown that the \(r_1\) and \(r_2\) relaxivities of Gd-BOPTA with 4.5% HSA were higher than those with saline only. The \(r_1\) and \(r_2\) relaxivities of Gd-BOPTA with 4.5% HAS were also higher than those of Gd-DTPA with 4.5% HSA or saline only. These results demonstrate that Gd-BOPTA has stronger binding with HSA than Gd-DTPA. In the animal study, the maximum of \(E_{Ra}\), \(E_{Rk}\), \(E_{Rl}\) and \(E_{Rm}\) with Gd-BOPTA were higher than those with Gd-DTPA.
Fig. 1 Representative coronal MIP images of a normal rat before and after Gd-BOPTA

Fig. 2 Representative coronal MIP images of a normal rat before and after Gd-DTPA

Fig. 3 ER of aorta before and after contrast agents injection

Fig. 4 ER of kidney before and after contrast agent’s injection

Fig. 5 ER of liver before and after contrast agents injection

Fig. 6 ER of muscle before and after contrast agents injection
Hepatic cells can uptake Gd-BOPTA. Therefore, Gd-BOPTA is used as a hepatobiliary contrast agent. Gd-BOPTA can also be used for CE-MRA due to the high binding with HSA. After 0.1 mmole/kg Gd-BOPTA injection, the maximum ER appeared at 1.2 min and dropped to half at 10 min. This information suggests that the best time window to complete image acquisition is with 10 min after Gd-BOPTA injection.

The ER varies with species, injected Gd-BOPTA dosage, imaging acquisition time after injection, magnetic field of MR scanners, coil types, MRI pulse sequences and parameters [11]-[13]. In this study, the efgre3D pulse sequence with a commercialized extremity coil at 3T was used for rat CE-MRA. Different situations of CE-MRA may have various results and need further studies.

Rats are often used for studies of diseases causes and development of new diagnostic or therapeutic drugs. CE-MRA is helpful for monitor the vessel status longitudinally. MR scanners specific for animal studies has been developed using very high magnetic fields and can get very good quality of images. However, animal specific MR scanners are still rare for researchers. Using clinical MR scanners with optimized coils, pulse sequences, scanning parameters and contrast agents can still obtain images with high quality and be a good choice for animal studies.

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**REFERENCES**


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