Abstract: The aim of this study was to compare differences in imaging quality at different injection rates of gadobutrol (Gadovist® 1.0M) for dynamic supra-aortic imaging by contrast-enhanced magnetic resonance angiography (CEMRA). In 6 healthy volunteers, dynamic CEMRA examinations were performed twice at a 7 d interval with a gadobutrol dose of 0.1 mmol given to 1 kg body mass. For the two examinations, the contrast medium was injected at rates of 1.5 mL/s and 2.0 mL/s, followed by 20 mL normal saline injected at the same rate. Using a GE Signa 3.0T MR apparatus and the time-resolved imaging of contrast kinetics (TRICKS) technique, scanning was performed continuously for 15 phases at a time resolution of about 2.4 s. Vascular reconstruction was undertaken by multiplane reconstruction and maximum intensity projection techniques. Two radiologists experienced in CEMRA diagnosis subjectively evaluated the contrast effect, vascular detail, and pseudo-shadow of all images, and graded them via a 5-point scale. With the two drug injection rates, the image quality, peak signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) were compared for imaging of the infra-aortic arch, brachiocephalic trunk, subclavian artery (left/right), common carotid artery (left/right), internal carotid artery (left/right), and external carotid artery (left/right). Characteristics of the time-signal-intensity (T-S-I) curves were also analyzed at the two injection rates. All studies were performed successfully, without any complications. There was good image quality with both gadobutrol injection rates of 1.5 mL/s and 2.0 mL/s, and subjective scores for image quality, SNR and CNR were not significantly different between the two rates ($P > 0.05$). The time-to-peak (TTP) from the hand dorsal vein injection site to the carotid artery ranged from 16.0 s to 27.1 s (mean 21.7 s $\pm$ 3.4 s) in the 6 subjects, and was also not significantly different between the two drug injection rates ($P > 0.05$). We conclude that dynamic CEMRA examination of the supra-aortic arch with gadobutrol injection at a rate of 1.5 mL/s was feasible, and satisfactorily reflected vascular shape and dynamic blood flow information.

Keywords: gadobutrol; supra-aortic imaging; magnetic resonance imaging

1 Introduction

Magnetic resonance angiography (MRA) is well-accepted by both clinicians and patients for its advantages of ease and simplicity of use, noninvasiveness, safety, and freedom from x-rays. With the development of MR techniques and the application of contrast media, especially the recently developed 4-D contrast-enhanced MRA (CEMRA) technique, MRA is able to scan cavities continuously, obtain good spatial/time resolution, improve vascular contrasts with surrounding tissues, display vascular lesions better, and provide a diagnostic capability comparable to that of digital subtraction angiography (DSA) $^{[1-3]}$. 

Gadobutrol (Gadovist® 1.0 mol/L, Schering, Berlin, Germany) is a non-ionic, water-soluble, gadolinium (Gd)-based MR contrast medium that has rapid extracellular distribution, tissue nonspecificity and electrical neutrality. It has high relaxivity, good stability, low viscosity, and low permeability, is eliminated mainly by glomerular filtration, and has low toxicity \cite{6-8}. As gadobutrol is available at a concentration twice that of other Gd-based contrast media and has higher $T_1$ relaxivity, it provides better image contrasts, can be injected at a slower rate (with consequent milder vascular injury) and in a volume half that of other Gd-based contrast media, and can achieve a more concern-trated blood drug-signal peak. Therefore, the scanning protocol with gadobutrol in terms of the drug injection rate and the scanning delay time can be modified.

Currently, a 0.5 mmol/L Gd-based preparation injected at a rate of 3.0 mL/s is commonly used as the contrast medium for supra-aortic CEMRA examination \cite{7-9}. As the volume injected is reduced by half with 1.0 mol/L gadobutrol, the present study was undertaken to determine whether gadobutrol can be injected intravenously at a rate of 1.5 mL/s. By scanning with a 3.0T MRI apparatus, two different injection rates (1.5 mL/s and 2.0 mL/s) were studied to explore the optimal scanning protocol, analyze the characteristics of the time-signal-intensity (T-S-I) curves at the two injection rates, and determine whether a rate of 1.5 mL/s can be applied clinically.

2 Materials and methods

2.1 Subjects

Six healthy volunteers, 3 males and 3 females ranging in age from 35 a to 42 a (mean 39 a) were recruited for the study. The research was approved by the Ethics Committee of our Hospital, and all subjects signed informed consent forms.

Inclusion criteria for enrollment in the study were: 1) age older than 18 a, male or female gender, and good general health status with no cardiovascular diseases; 2) no use of contrast media within the past week; 3) no contraindications for contrast-enhanced MR examinations; and 4) agreement to undergo two CEMRA examinations, and provision of signed informed consent. Exclusion criteria were allergy or previous allergy to any Gd-based contrast medium or the presence of bronchial asthma; lactation, pregnancy or suspected pregnancy; the presence of a pacemaker or previous implantation of metal/magnetic objects; uncooperative or claustrophobic behavior; and an estimated glomerular filtration rate (eGFR) of more than 60 mL/min per 1.73 m².

In all 6 healthy volunteer, two CEMRA examinations of the carotid artery were performed at a 7 d interval to enable intraindividual comparisons of gadobutrol injection rates of 1.5 mL/s and 2.0 mL/s at a dose of 0.1 mmol given to 1 kg body mass with the same scanning array and parameters. Blood pressure and heart rate were measured before CEMRA examination and 30 min after the examination; blood creatinine levels were also measured before CEMRA examination and at 3 d to 5 d after injection of the contrast medium. Adverse effects were monitored and were considered to have occurred when there were clinically significantly abnormal laboratory test results, subjective patient discomfort, or unstable vital signs during the CEMRA examinations and within 24 h after the examinations.

2.2 MR imaging

All CEMRA examinations were performed with the 3.0T MR system (Signa Excite; GE Medical Systems, USA) 8-channel neurovascular (NV) array coil ranging from the aortic arch to the circle of Willis, using the time-resolved imaging of contrast kinetics (TRICKS) technique with parallel imaging (asset factor of 2.0) in the coronal orientation. Scanning parameters: 3-D volume acquisitions; TR 3 ms, TE 0.8 ms, flip angle 35°; bandwidth: 100 kHz; matrix: 300x160; NEX: 1; FOV: 32 cmx25.6 cm; section thickness: 2.4 mm interpolated to 1.2 mm. A central k-space refresh rate (frame rate equivalent to an effective temporal resolution of the resultant 3-D volumes) was 2.4 s and a total of 15 consecutive data sets were acquired. After acquisition of the mask, the TRICKS sequence was initiated simultaneously with the intravenous injection. The total scan time was approximately 49 s, including 13 s for the mask.

Using an automatic power injector (Optistar; Liebel-Flarsheim, Cincinnati, OH, USA), gadobutrol 1.0 mol/L (Gadovist® 1.0M, Schering, Berlin, Germany) was injected intravenously in a dose of 0.1 mmol/kg body mass at a rate of either 1.5 mL/s or 2.0 mL/s for the first CEMRA examination and the alternative rate for the second examination, followed by 20 mL normal saline injected at the same rate. A
randomization procedure was applied to deciding the injection rate order. Intravenous access was obtained with a 20-gauge intravenous catheter located in the hand dorsal vein. For 3 subjects, the gadobutrol injection was given into the left hand for the first examination and the right hand for the second; for the other three subjects, the injection was given into the right hand for the first examination and the left hand for the second.

2.3 Data analysis

Through multiplane reconstruction and maximum intensity projection techniques, vascular reconstruction was performed on the original images with the best enhanced effect for the carotid artery, and all images were stored in DICOM (digital imaging and communications in medicine) format. Two radiologists experienced in CEMRA diagnosis subjectively evaluated the image quality, and graded the images on a 5-point rating scale \(^9\): 0 = very poor image quality, unclear artery, and completely unsuitable for diagnostic analysis; 1 = poor image quality, unclear vascular contour and signal, and unsuitable for diagnostic analysis; 2 = moderate image quality, coarse vascular contour, uniform signal, and moderately suitable for diagnostic analysis; 3 = good image quality, clear or slightly coarse vascular contour, moderate signal, and suitable for diagnostic analysis; and 4 = excellent image quality, clear, sharp vascular contour, uniform signal, and preferably suitable for diagnostic analysis.

Two radiologists who were blinded to the injection rate measured the peak signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) of images. Signal intensity time curves were calculated for the following vascular segments: the aortic arch, brachiocephalic trunk, subclavian artery (left/right), common carotid artery (left/right), internal carotid artery (left/right), and external carotid artery (left/right). From the signal intensity time curves, the peak SNR and CNR of each vascular segment were calculated. SNR and CNR were calculated as follows:

\[
SNR = \frac{SI_{\text{vascular}}}{SD_{\text{background}}}
\]

where \(SI_{\text{vascular}}\) is the peak signal intensity in the artery after contrast application; and \(SD_{\text{background}}\) is the standard deviation of the background noise.

\[
CNR = \frac{SI_{\text{vascular}} - SI_{\text{peripheral tissue}}}{SD_{\text{background}}}
\]

where \(SI_{\text{vascular}}\) is the peak signal intensity in the artery after contrast application; and \(SI_{\text{peripheral tissue}}\) is the mean signal intensity in peripheral tissue. Regions of interest (ROIs) were placed in vessels with sizes adjusted to cover as much of the vascular lumen as possible (mean number of pixels 80±50). All measurements were repeated three times and averaged.

Hemodynamic evaluate were analyzed for the following vascular segments: aortic arch, common carotid artery, carotid branch, and common jugular vein. The enhancement start time and TTP (time-to-peak) were analyzed for the aortic arch, carotid artery and jugular vein.

2.4 Statistical analysis

All data were processed using SPSS 13.0 software (SPSS, Inc., Chicago, IL). A paired-sample t-test was applied for the subjective scores of image quality, SNR, CNR and TTP, and \(P < 0.05\) was considered to indicate a significant difference.

3 Results

3.1 Safety evaluation

The 6 volunteers satisfactorily completed the two CEMRA examinations without any adverse drug effects. Blood pressure, heart rate and the blood creatinine level were not significantly different before and after the examination.

3.2 Image quality, SNR and CNR

Following gadobutrol injection at rates of 1.5 mL/s and 2.0 mL/s using the TRICKS technique, the image quality was good; all images had maximum intensity projection (MIP) scores of 3 to 4 and all images were rated suitable for clinical diagnostic analysis. In both injection rate groups, the mean image quality score was 3.50, and there was no significant difference between the two groups (\(P>0.05\)). In addition, SNR and CNR were also not significantly different between the two groups (\(P>0.05\)) as shown in Table 1.

3.3 Hemodynamic evaluation

In the 6 volunteers, the TTP from the hand dorsal vein to the carotid artery ranged from 16.0 s to 27.1 s.
(mean 21.7 ± 3.4 s). With the two injection rates, the mean TTP values were 21.9 ± 3.6 s and 21.5 ± 3.5 s for the 1.5 mL/s and 2.0 mL/s groups, respectively, as shown in Fig. 1; the difference between the two groups was not significant (P>0.05). For both the carotid artery and the aortic arch, the mean TTP was 21.7 ± 3.4 s, and the time resolution was 2.4 s. In other words, the enhanced peak value showed no more than 2.4 s difference between the aorta and the carotid artery (Fig. 2).

Jugular vein enhancement started only after the peak enhancement of the carotid artery (Fig. 3). Theoretically, there is always a time phase for imaging of the carotid artery without any imaging of the jugular vein (pure artery phase). The mean TTP for the jugular vein was 32.3 ± 4.7 s. With the two injection rates, the mean jugular vein TTP values were 33.7 ± 4.6 s and 30.8 ± 4.9 s for the 1.5 mL/s and 2.0 mL/s groups, respectively (significantly different; P<0.05). The mean time window was 10.6 ± 4.1 s for the carotid artery and jugular vein. With the two injection rates, the values were 11.7 ± 2.6 s and 9.4 ± 5.1 s for the 1.5 mL/s and 2.0 mL/s groups, respectively (not significantly different; P>0.05).

3.4 Influence of drug injection site

Following drug injection into the left hand, 2 of 6 subjects (33.3%) showed pseudo-shadow mostly at the initial part of the supra-aortic arch (Fig. 4). However, with injection into the right hand, the aortic branches were not affected.

4 Discussion

At present, Gd-based chelates are the most commonly used contrast media for CEMRA examinations as they shorten the relaxation time of protons. Gadobutrol is a Gd-based compound with a macro ring, and is a nonspecific extracellular contrast medium. In this study, we used 1.0 mol/L gadobutrol which doubles the concentration of other available Gd-based contrast media. In China and most countries in Europe and America, gadobutrol has been approved for use and is widely applied in clinical practice [4]. This agent is more than 90% eliminated by the kidney within 12 h, and has a half-life in the body of 1.3 h to 2.1 h that is independent of its dose and concentration. As shown in numerous clinical trials, the adverse effects of gadobutrol are not significantly different from those of other Gd-based contrast media [4-6]. In this study, no adverse effects occurred with gadobutrol during 12 CEMRA examinations in 6 subjects.

| Signal-to-noise ratios (SNRs) and contrast-to-noise ratios (CNRs) at different gadobutrol injection rate (r) |
|-------------------------------------------------|--------|----------|--------|--------|----------|--------|----------|--------|--------|
| SNR                                             | r=1.5 mL/s | r=2.0 mL/s | t-Value | P-Value | r=1.5 mL/s | r=2.0 mL/s | t-Value | P-Value |
| Aortic arch                                      | 79.6±9.6   | 70.2±22.1  | 0.958   | 0.121   | 71.8±11.2 | 64.6±18.0  | 0.833   | 0.424   |
| Left subclavian artery                          | 65.6±10.6  | 71.2±20.7  | −0.587  | 0.315   | 60.1±9.1  | 64.8±20.1  | −0.523  | 0.612   |
| Right subclavian artery                         | 71.3±22.5  | 67.9±18.7  | 0.282   | 0.906   | 66.1±21.3 | 62.6±18.0  | 0.305   | 0.767   |
| Left common carotid artery                      | 74.3±19.6  | 84.6±22.3  | −0.846  | 0.840   | 68.2±18.4 | 75.3±20.8  | −0.624  | 0.547   |
| Right common carotid artery                     | 65.4±24.5  | 75.0±16.7  | −0.793  | 0.261   | 60.0±24.3 | 69.7±15.9  | −0.814  | 0.434   |
| Left internal carotid artery                    | 63.4±13.6  | 55.0±25.0  | 0.689   | 0.549   | 58.4±12.8 | 49.8±23.1  | 0.795   | 0.445   |
| Right internal carotid artery                   | 61.6±18.6  | 52.3±17.8  | 0.884   | 0.504   | 57.0±18.0 | 47.7±17.2  | 0.912   | 0.383   |
| Left external carotid artery                    | 49.5±13.2  | 45.8±10.8  | 0.528   | 0.507   | 44.1±11.7 | 41.4±10.4  | 0.418   | 0.685   |
| Right external carotid artery                   | 46.7±12.9  | 41.5±11.8  | 0.728   | 0.507   | 42.0±12.4 | 37.0±11.9  | 0.711   | 0.493   |
Fig. 1 Time-signal-intensity (T-S-I) curves for the left carotid branch at the injection rate of a) 2.0 mL/s and b) 1.5 mL/s, where the signal intensity is in terms of MR units.

Fig. 2 Regions of interest (ROI) in the aortic arch and left common carotid artery in one subject: a) placements; and b) their time-to-peak (TTP) curves, where the signal intensity is in terms of MR units.
Fig. 3 Regions of interest (ROI) in the carotid artery and jugular vein in one subject: a) placements; and b) their time-signal-intensity (T-S-I) curves, where the signal intensity is in terms of MR units

As blood circulates very quickly to the head/neck and circulation times vary greatly between individuals, it is important for the success of routine CEMRA examinations to accurately determine the delay between the start of the contrast medium injection and the start of scanning. In the 6 healthy volunteers who participated in this study, the TTP from the hand dorsal vein to the carotid artery ranged from 16.0 s to 27.1 s.
There would be not ideal artery enhancement if scanning was started too early, but contaminated veins would be evident if scanning was started too late. In comparison with other Gd-based contrast media, 1.0 mol/L gadobutrol is injected in half the volume, achieves a more concentrated peak blood drug-signal value, and has been found to have a narrower bolus injection peak than gadopentetate dimeglumine (Magnevist®) [10-13].

In this study, the problem of a scanning time delay was effectively solved by using a time-resolution 4-D CEMRA imaging technique (TRICKS) to ensure that all images were qualified for clinical diagnostic analysis and provided good hemodynamic information. Thus, 4-D CEMRA examination plus a high-concentration contrast medium can effectively enhance imaging of the carotid artery, and improve the success rate of the examination.

The drug injection rate is an important factor influencing imaging quality. In the past, gadopentetate dimeglumine (Magnevist®) has been injected at a rate of 3.0 mL/s for supra-aortic CEMRA examinations [14-15], while gadobutrol has been injected at a rate of 2.0 mL/s [10,16]. By reducing the volume injected by half, 1.0 mmol/L gadobutrol can be injected intravenously at 1.5 mL/s. In this study, in which gadobutrol was injected at rates of 1.5 mL/s and 2.0 mL/s, we found that image quality, SNR and CNR were not significantly different between the two injection rates. Theoretically, an injection rate of 1.5 mL/s requires a longer injection time and will attain a wider bolus injection peak, which will provide greater benefits for MRI imaging. It is astonishing that the SNR and CNR values for the 2 mL/s injection protocols do show a larger difference between the common carotid arteries and the internal carotid arteries than the 1.5 mL/s protocol. This indicated that a lower injection rate would be even better. In addition, the lower drug injection rate may be potentially safer for patients, particularly for hand injections or small veins. Consequently, we now recommend the lower injection rate for clinical use.

The hemodynamic information attained was very similar with the 1.5 mL/s and 2.0 mL/s injection rates. As shown by the images, jugular vein enhancement started only after the peak enhancement of the carotid artery. Theoretically, there is always a time phase for significant enhancement of the carotid artery without any contamination from the jugular vein. At injection rates of 1.5 mL/s and 2.0 mL/s, the time window for the carotid artery and jugular vein became wider, which might improve the success rate of CEMRA imaging, and the enhanced peak was almost synchronous at <2.4 s difference for the aortic arch and carotid artery, indicating very fast blood flow in the supra-aortic arch. Therefore, this study has provided a theoretical basis for clinical application of the fluoroscopic-triggered CEMRA technique.

The optimal drug injection site was also investigated in this study. With injection into the left hand in 2 of the 6 subjects, the contrast medium level was higher in the vein of the left arm which affected imaging of the supra-aortic arch branch. However, with injection into the right hand, all images were good. This difference results from anatomic factors. As has been reported in some studies, contrast media should be injected into the affected side in people with venous occlusive disease [17-18]. The optimum site of injection was not completely studied.

As this study involved only a small number of subjects, verification of its findings in a larger sample is necessary. In addition, all subjects were healthy, and a further study in diseased patients needs to be undertaken.

In conclusion, 1.0 mol/L gadobutrol is a safe and effective contrast medium. When used at a low dose and low injection rate with the TRICKS technique, gadobutrol can clearly display blood vessels of the supra-aortic arch, ensure the success rate of CEMRA examination, and play an important role in clinical investigation of vascular diseases of the neck.

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References


