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# Inter-individual Comparison of Gadobutrol and Gadoteridol Tissue Time-intensity Profiles for Dynamic Susceptibility Contrast Perfusion MR Imaging

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**Purpose:** Gadobutrol is a gadolinium-based contrast material (GBCM) with a high concentration of gadolinium and high relaxivity. Our purpose was to evaluate the signal intensity profiles in brain tissue for the bolus width and degree of signal change after bolus injection using an echo planar dynamic susceptibility contrast (DSC) sequence. We compared gadobutrol to gadoteridol using various injection speeds and saline flush volumes.

**Methods:** We studied 97 patients who underwent brain MRI. Datasets for perfusion studies were acquired using a 3T scanner with an echo planar imaging (EPI) sequence. The injection protocols were set up with combinations of injection speed and saline flush volume for both gadobutrol and gadoteridol. The full width at half maximum (FWHM) and the maximum signal change ratio ($SCR_{max}$) of the time intensity curves were measured.

**Results:** The FWHM did not show a statistically significant difference according to injection speed, flush volume, or type of GBCM. The $SCR_{max}$ showed a greater change with a faster injection speed, larger saline flush, and gadobutrol administration. The difference between gadobutrol and gadoteridol became smaller with a faster injection speed and a larger saline flush.

**Conclusion:** The maximum signal drop was larger with gadobutrol when the injection speed was slow and the saline flush was small. Thus, gadobutrol may be useful to obtain a better profile for DSC perfusion MRI in conditions requiring a slower injection speed and/or a smaller volume of saline flush.

**Keywords:** *gadobutrol, gadoteridol, injection speed, perfusion magnetic resonance imaging, saline flush*

## Introduction

Gadobutrol is a non-ionic, macrocyclic molecule that is used as gadolinium-based contrast material (GBCM). Gadobutrol has high pharmacokinetic stability, a high concentration of gadolinium (1.0 mol/L), and high relaxivity.[1–4] The relaxivity of gadobutrol is 107–131% higher for R1 and 91–244% higher for R2 than Gd-diethylenetriamine pentaacetic acid (DTPA).[5] In an experiment for rat brain glioma, greater tumor enhancement was noted with gadobutrol compared to both gadopentetate dimeglumine and gadoterate meglumine.[6] In a human study for primary and secondary brain tumors, 1.0 mol/L gadobutrol was proven to have significantly superior contrast enhancement characteristics in a routine MRI protocol compared to 0.5 mol/L GBCM.[7] These characteristics of gadobutrol are also beneficial in MR perfusion studies using dynamic susceptibility contrast (DSC), which requires a sharp bolus profile. Although several studies have described the characteristics of gadobutrol bolus injection for imaging the central nervous system, no report has described the signal change in tissue with different injection speeds.[8–10] The current study evaluated the tissue signal intensity profiles of the bolus width on brain images acquired with an echo planar DSC sequence. We investigated the degree of signal change by bolus injection with various injection speeds and two volumes of saline flush of gadobutrol in comparison to gadoteridol, which has a gadolinium concentration of 0.5 mol/L.

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## Materials and Methods

### *Subjects*

The study was approved by the institutional review board and ethics committee of our institute. The subjects were consecutive patients from October 2015 to September 2016 for which contrast-enhanced MRI studies were scheduled and who agreed to undergo the echo planar DSC sequence. We obtained permission from the institutional review board at our hospital, and written informed consent for the imaging study was obtained from all patients or their families after the nature of the procedures had been fully explained.

We investigated 97 patients (43 females and 54 males, age range 29–85 years, mean age 63 years, body weight range 38–83 kg, mean body weight 57.9 kg). All cases were assigned to either the gadobutrol or the gadoteridol group. The gadobutrol group consisted of 56 cases (25 females and 31 males, age range 35–85 years, mean age 64 years), and the gadoteridol group consisted of 41 cases (19 females and 22 males, age range 28–84 years, mean age 62 years). The underlying diseases for the perfusion study were as follows: metastatic brain tumor: 53 cases, glioblastoma multiforme: 6 cases, other gliomas: 7 cases, meningioma: 11 cases, vestibular schwannomas: 2 cases, other brain tumors: 3 cases, vasculitis: 11 cases, and other inflammatory diseases: 4 cases. Detailed background of gadobutrol group and gadoteridol group are summarized in Table 1.

### *Image acquisition*

The imaging studies were performed on a 3T clinical scanner (Magnetom Skyra with a 32-channel head coil; Siemens AG, Forchheim, Germany). The DSC perfusion datasets were acquired using an echo planar imaging (EPI) sequence (TR/TE = 1530/30 ms, flip angle = 60°, FOV: 220 mm, matrix: 128 × 128, section thickness: 5 mm, 15 slices, acquisition time = 1.58 s without parallel imaging) at 1.58 s intervals for 90 s. The GBCM was administered intravenously as a bolus through the cubital vein, generally from the right side, using a power injector (Sonic Shot 7, Nemoto Kyorindo co., Ltd, Tokyo, Japan). We used 20 or 22G injection needles and injection lines that were equipped with check valves so that the GBCM did not reflux into the saline chamber. The GBCMs used in the current study were gadobutrol (Gd-BT-DO3A, Gadovist gadolinium concentration: 1.0 mol/L; Bayer AG, Leverkusen, Germany) and gadoteridol (Gd-HP-DO3A, ProHance; gadolinium concentration: 0.5 mol/L; Bracco Imaging S.p.A., Milan, Italy). The injection dose for gadobutrol was 0.1 mmol per kg body weight and that for gadoteridol was 0.2 mmol per kg body weight. The injection protocol consisted of a combination of different injection speeds (1–4 ml/s) and two volumes of saline flush (20 and 50 ml). Thus, eight sets of the injection protocol were configured for the two GBCMs. The injection speeds of 1 and 2 ml/s were assigned in random order for cases in which perfusion MRI was not necessary, such as the detection of metastatic brain tumors or inflammatory lesions. The injection speeds of 3 and 4 ml/s were assigned in random order for cases in which perfusion MRI was necessary. These cases included the evaluation of glioblastomas or other brain tumors for which the assessment of cerebral blood volume (CBV) was needed. The volume of the saline flush was assigned in random order.

**Table 1** The background of gadobutrol group and gadoteridol group

| | Gadobutrol | Gadoteridol |
|---|---|---|
| a | | |
| Age (years old) | 63.9 ± 12.2 | 60.8 ± 13.4 |
| Sex | m: 31/f: 25 | m: 22/f: 19 |
| Body weight (kg) | 56.2 ± 10.2 | 60.3 ± 12.5 |
| Metastatic brain tumor | 31 | 22 |
| b | | |
| Glioblastoma multiforme | 4 | 2 |
| Other gliomas | 3 | 4 |
| Meningioma | 6 | 5 |
| Vestibular schwannomas | 2 | 0 |
| Other brain tumors | 2 | 1 |
| Vasculitis | 5 | 6 |
| Other inflammatory diseases | 3 | 1 |

(**a**) The demographics of the two groups. (**b**) The underlying diseases of the two groups.

### *Image analysis*

The DSC perfusion datasets acquired with the methods described above were evaluated by Mean curve software (Siemens AG) on the imaging console of the scanner. To acquire the time intensity curve, we placed a ROI in the basal ganglia in order not to be influenced by the signal from large vessels. The ROI was placed on the slice in which the basal ganglia, genu of internal capsule and thalamus are included. A circular ROI with an area of 1.1 ± 0.2 $cm^2$ was placed to touch the most lateral point of the right putamen unless there is lesion within the right basal ganglia. When there is lesion within the right basal ganglia, the left side was used for measurement. We also placed four ROIs in the background to estimate the noise level. The signal-to-noise ratios (SNRs) were calculated to generate the time intensity curve for the basal ganglia. We constructed the time intensity curves by calculating the signal change ratio (SCR) given by $SCR = SNR/SNR_{baseline}$. The $SNR_{baseline}$ was the mean value of the SNR of the images over the first 2–10 s. On the time intensity curve, we measured the full width at half maximum (FWHM) and the maximum signal change ratio ($SCR_{max}$) (Fig. 1). FWHM was calculated by linear fitting of the two time points under and above the half maximum value. We evaluated the FWHM and the $SCR_{max}$ values by

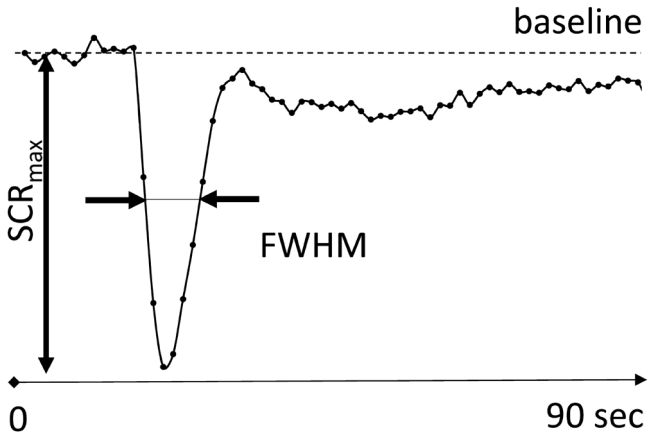


**Fig. 1** Time intensity curve after the bolus injection of gadolinium-based contrast media (GBCM). The full width at half maximum (FWHM) was measured to evaluate the bolus width, and the maximum signal change ratio ($SCR_{max}$) was measured as an index of the signal drop at the first pass after the GBCM administration.

making the following comparisons between gadobutrol and gadoteridol.

*Comparison by injection speed*

The FWHM and $SCR_{max}$ were compared by GBCM type (gadobutrol versus gadoteridol) for each injection speed (1–4 ml/s). Comparisons were made separately for each flush volume (20 and 50 ml). We performed an analysis of variance (ANOVA) for the FWHM and $SCR_{max}$ to identify statistically significant differences according to the different factors including the different GBCM types and the different injection speeds. We also compared GBCM types by performing an analysis of co-variance (ANCOVA) between the injection speed and the FWHM, and between the injection speed (dependent variable: FWHM; fixed variable: GBCM type; covariate: injection speed) and the $SCR_{max}$ (dependent variable: $SCR_{max}$; fixed variable: GBCM type; covariate: injection speed). In addition, we compared the flush volumes by performing an ANCOVA between the injection speed and the FWHM, and between the injection speed (dependent variable: FWHM; fixed variable: volume of saline flush; covariate: injection speed) and the $SCR_{max}$ (dependent variable: $SCR_{max}$; fixed variable: volume of saline flush; covariate: injection speed).

*Comparison by injection duration*

Since gadolinium concentration of gadobutrol is 1.0 mol/L and that of gadoteridol is 0.5 mol/L, the injection volume of GBCM is twice in gadoteridol. To equalize the difference of injection condition due to the difference of the concentration, we compared the injection duration for gadobutrol versus gadoteridol. We calculated the injection duration by dividing the administered volume of GBCM by the injection speed for each measurement. We performed an ANCOVA between the injection duration and the FWHM (dependent variable: FWHM; fixed variable: GBCM type; covariate: injection duration), and between the injection duration and the $SCR_{max}$ (dependent variable: $SCR_{max}$; fixed variable: GBCM type; covariate: injection duration).

## Results

Both contrast agents were well-tolerated, and no adverse effects were noted in any patient. Each contrast-based imaging study provided clinically useful information. For the cases that underwent the DSC perfusion study, perfusion images including CBV and CBF, which were processed by software on the scanner console, provided the clinically required information in all cases.

### *Comparison by injection speed*

Figure 2a shows the mean value and the standard deviation of the FWHM for each injection speed in the group with a 20-ml saline flush, and Fig. 2b shows that of the group with a 50-ml saline flush. The ANOVA indicated no statistically significant differences in the FWHM between the gadobutrol and the gadoteridol groups for any injection speed (1, 2, 3, or 4 ml/s), or with either a 20-ml saline flush (Fig. 2a) or a 50-ml saline flush (Fig. 2b). The ANCOVA revealed no statistically significant differences in the FWHM of the gadobutrol or the gadoteridol group for injection speeds of either a 20-ml saline flush or a 50-ml saline flush.

Figure 2c shows the mean value and the standard deviation of the $SCR_{max}$ for each injection speed in the group with a 20-ml saline flush. The ANOVA indicated that gadobutrol produced a statistically significant difference in $SCR_{max}$ ($P < 0.01$) compared to gadoteridol at injection speeds of 1–3 ml/s. We also found statistically significant differences in $SCR_{max}$ between injection speeds of 1 and 2 ml/s ($P < 0.05$), between 1 and 3 ml/s ($P < 0.05$), and 1 and 4 ml/s ($P < 0.05$) in the gadobutrol group. In the gadoteridol group, we found statistically significant differences in $SCR_{max}$ between 1 and 3 ml/s ($P < 0.05$), 1 and 4 ml/s ($P < 0.01$), and 2 and 4 ml/s ($P < 0.05$). The ANCOVA revealed a statistically significant ($P < 0.01$) difference between the regression lines of gadobutrol and gadoteridol, with a larger $SCR_{max}$ change over time for gadobutrol.

Figure 2d shows the mean value and the standard deviation of the $SCR_{max}$ for each injection speed in the group with a 50-ml saline flush. The ANOVA indicated that gadobutrol produced a statistically significant difference in the $SCR_{max}$ ($P < 0.01$) compared with gadoteridol only, at the injection speed of 1 ml/s. In addition, we found statistically significant differences in the $SCR_{max}$ between injection speeds of 1 and 3 ml/s ($P < 0.01$), and between 1 and 4 ml/s ($P < 0.01$) in the gadobutrol group. In the gadoteridol group, we found statistically significant differences in the $SCR_{max}$ between 1 and 2 ml/s ($P < 0.05$), 1 and 3 ml/s ($P < 0.01$), and 1 and 4 ml/s ($P < 0.01$). In a comparison of the regression lines for gadobutrol and gadoteridol, the ANCOVA indicated a statistically significant ($P < 0.01$) difference between the regression

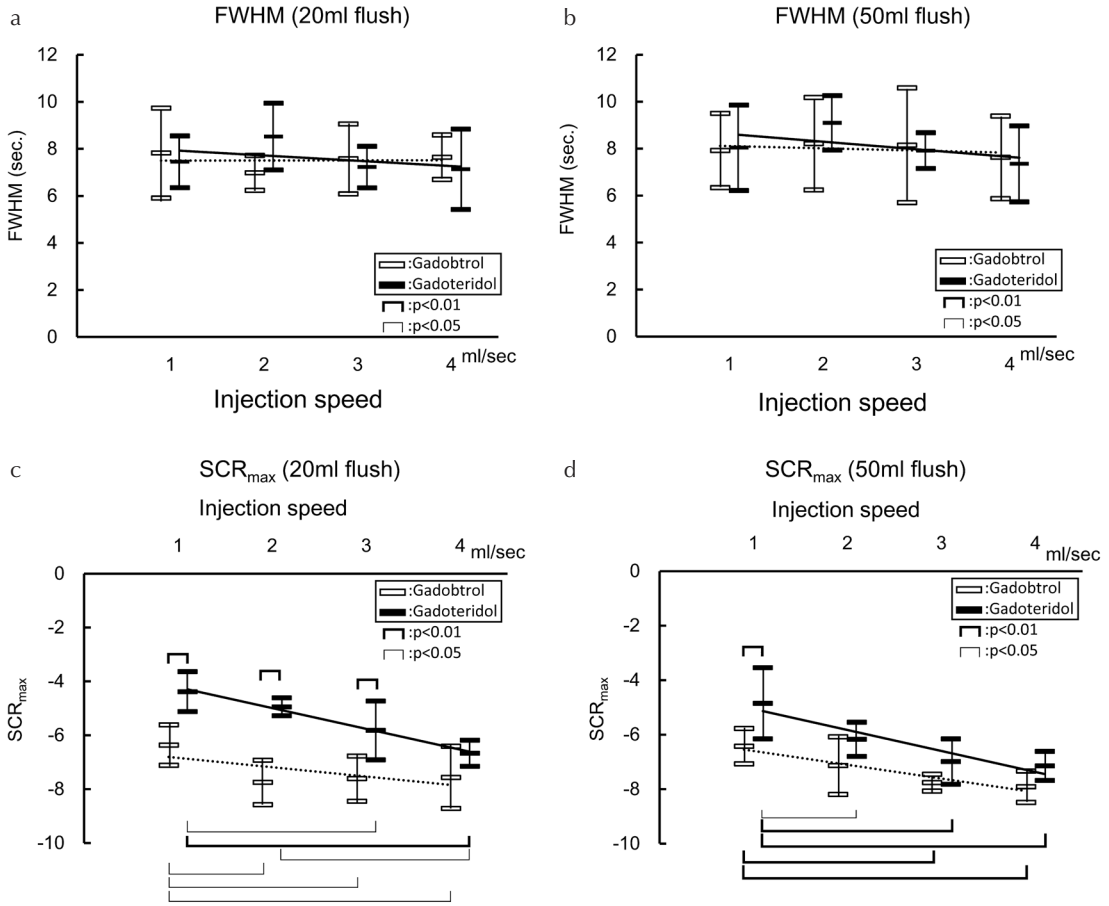


**Fig. 2** Comparison of injection speed. The full width at half maximum (FWHM) of the time intensity curve is plotted by injection speed in (**a**) (20 ml saline flush) and (**b**) (50 ml saline flush). The maximum signal change ratio ($SCR_{max}$) for various injection speeds is shown in (**c**) (20-ml saline flush) and (**d**) (50 ml saline flush). The mean values with 1 standard deviation for the measurements are presented. White markers and dotted regression lines represent the results for gadobutrol, and black markers and solid regression lines represent gadoteridol. Note that the FWHM does not show any statistical difference with the GBCM type, injection speed, or flush volume. However, the $SCR_{max}$ showed a correlation with the injection speed and flush volume. We found a statistically significant difference between the regression line for gadobutrol versus gadoteridol, indicating that gadobutrol had a larger signal drop compared to gadoteridol for both the 20 and 50 ml saline flush.

lines of gadobutrol and gadoteridol, with a larger $SCR_{max}$ difference over time for gadobutrol also for the 50 ml flush group.

We also made comparison of regression lines presented in Fig. 2c and 2d by flush volume to compare the effect of the saline flush volume (20 and 50 ml) in gadobutrol and gadoteridol. The ANCOVA indicated a statistically significant ($P < 0.01$) difference between the regression lines of 20 and 50 ml, with a larger $SCR_{max}$ increase over time for the 50 ml flush in the gadoteridol group. On the other hand, the ANCOVA indicated no statistically significant difference between the regression lines of 20 and 50 ml in the gadobutrol injection group.

### *Comparison by injection duration*

Figure 3a shows the value of the FWHM plotted against the injection duration in the group with the 20 ml flush. Figure 3b shows the group with a 50-ml saline flush. The ANCOVA revealed no statistically significant differences in the FWHM between the gadobutrol and the gadoteridol groups at any injection speed with either flush volume.

Figure 3c shows the value of the $SCR_{max}$ plotted against the injection duration in the 20 ml flush group and Fig. 3d shows the 50 ml flush group. The ANCOVA revealed a statistically significant ($P < 0.01$) difference between the regression lines for gadobutrol and gadoteridol, with a larger increase over time for gadobutrol. However, we found no statistically significant difference in the $SCR_{max}$ between the gadobutrol and the gadoteridol groups at any injection speed with a 50-ml saline flush.

## Discussion

Gadobutrol is the first GBCM with a gadolinium concentration of 1.0 mol/L, which is twice as high as other GBCMs. The *in vitro* relaxivity of gadobutrol is higher than that of

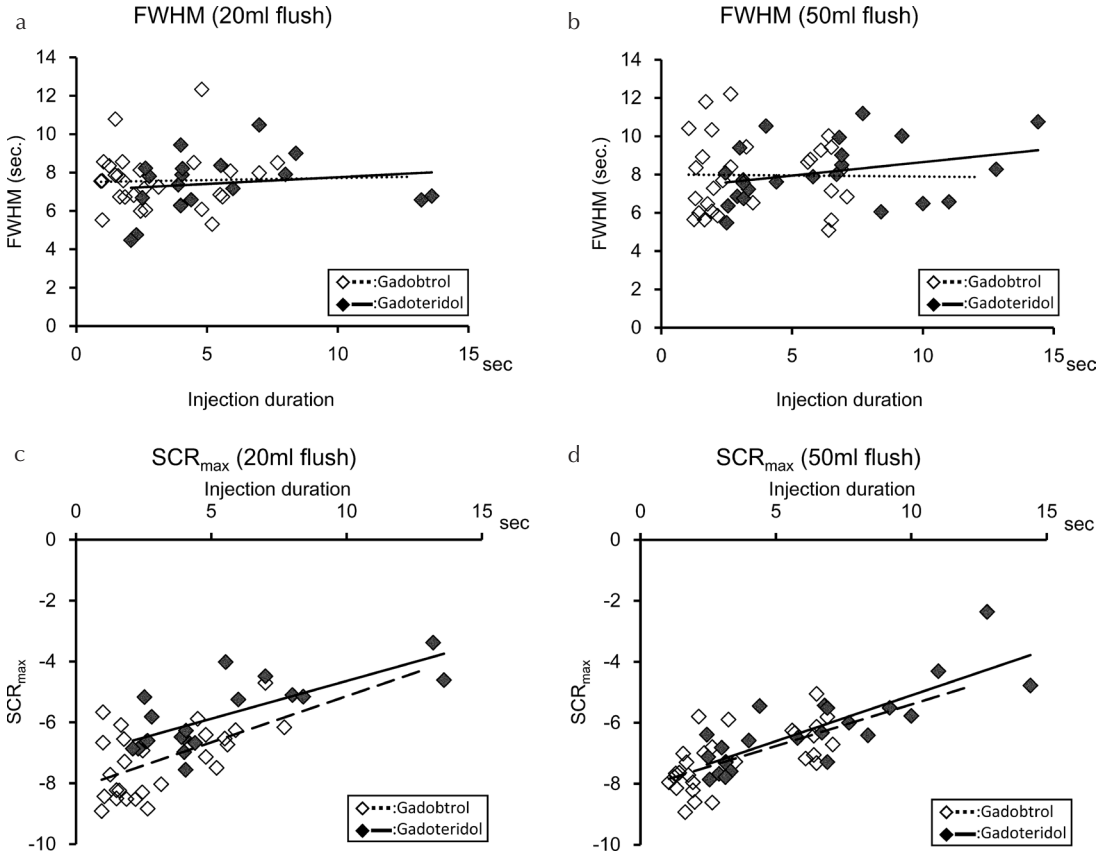


**Fig. 3** Comparison of injection duration. The comparison of injection duration canceled out the difference in concentration between gadobutrol and gadoteridol. The full width at half maximum (FWHM) of the time intensity curve is plotted by injection duration in (**a**) (20 ml saline flush) and (**b**) (50 ml saline flush). The maximum signal change ratio ($SCR_{max}$) plotted by injection duration is shown in (**c**) (20 ml saline flush) and (**d**) (50 ml saline flush). White markers and dotted regression lines represent the results for gadobutrol, and black markers and solid regression lines represent gadoteridol. We found no statistically significant difference in the FWHM between gadobutrol and gadoteridol according to injection speed for both the 20 and 50 ml saline flush. The regression line of the $SCR_{max}$ showed a statistically significant ($P < 0.01$), larger change only when the saline flush volume was 20 ml.

other non-protein-binding GBCMs.[11] The high concentration of gadobutrol is expected to reduce the bolus volume and thus be beneficial for DSC perfusion imaging. A previous study showed that the use of 1.0 mol/L gadobutrol resulted in a significantly smaller bolus width and a significant increase in the maximum change of the transverse relaxation rate compared to that obtained with 0.5 mol/L diluted gadobutrol with an injection speed of 5 ml/s and a 30-ml saline flush.[8] In contrast, another report comparing gadobutrol and gadobenate dimeglumine (Gd-BOPTA; 0.5 mol/L) indicated that the percentage of signal drop was similar for the two agents with the same dose (0.1 mmol/kg) at an injection speed of 5 ml/s and a 20-ml saline flush.[9] In the same report, the bolus width of gadobutrol was significantly less than that of gadobenate dimeglumine. Another report compared gadobutrol to gadopentetate dimeglumine at 0.5 mol/L and observed that the difference in maximal signal change for gray and white matter was significantly higher for gadobutrol at an injection speed of 5 ml/s and a 20 ml saline flush.[10] As indicated by the discrepancy in the findings of these previous studies, no consensus has been reached regarding the *in vivo* advantage of gadobutrol with its high relaxivity and a bolus administration of a high concentration for DSC perfusion MRI. This discrepancy in reports was the initial motivation for the current study in which we compared 1.0 mol/L gadobutrol to 0.5 mol/L gadoteridol and characterized the dynamics within brain tissue.

Another motivation for this study was to examine the effect of injection speed on GBCM. All of the above reports of DSC perfusion were performed with an injection speed of 5 ml/s. In general, a minimum of 3 ml/s (range, 3–5 ml/s) bolus injection rate of GBCM is recommended to allow a robust and compact bolus arrival in cerebral tissue, and this should be followed by a 25-ml (range, 10–30 ml) saline flush at the same rate to push the bolus toward the heart.[12] However, in clinical practice, particularly in older female patients, the cubital vein is often too thin to administer a bolus injection of 3 ml/s, but a perfusion image is still needed. To the best of our knowledge, only a limited number of reports have mentioned the behavior of GBCM at different injection

speeds. A study of a single subject (a 35-year-old male) indicated that injection speeds of <3 ml/s lead to underestimation of the observed CBF.[13] However, the CBF calculation in this study was not done with the block circulant single value deconvolution method, which is robust for the delay and dispersion of the bolus. In addition, the saline flush in the study was fixed at 20 ml, therefore, the influence of the flush volume was not considered. Because the flush volume improves the profile of the time intensity curve when the volume is equal to or greater than 30 ml,[14] it should be evaluated in addition to the injection speed. To evaluate the alterations in the time intensity curves in brain tissue after bolus injection of gadobutrol versus gadoteridol, we conducted this study at different injection speeds and with 2 volumes of saline flush.

In the current study, we evaluated the signal intensity change from GBCMs administered at different concentrations by plotting the time intensity curves in brain tissue. Our results indicated that the FWHM, which represents the bolus width and may have influence on perfusion map, did not change with respect to the concentration of GBCM, injection speed, or flush volume. The injection duration also did not alter the FWHM under the various injection conditions including the injection speed or the volume of saline flush. However, the $SCR_{max}$, which reflects the peak concentration of GBCM in brain tissue, showed correlations with the injection speed, injection duration, and volume of saline flush. Our comparison of the injection speeds showed that a faster speed resulted in a larger maximum signal change. With a 20-ml saline flush, gadobutrol showed a significantly larger signal drop compared to gadoteridol at injection speeds of 1–3 ml/s. However, we found no statistically significant difference between the two GBCMs at the injection speed of 4 ml/s. In total, the ANCOVA showed a statistically significant difference between the regression line for gadobutrol and gadoteridol, indicating that gadobutrol showed a larger signal drop compared to gadoteridol. When followed by a 50-ml saline flush, the faster injection speed also led to a larger maximum signal drop. Gadobutrol showed a significantly larger signal decrease compared to gadoteridol only at the injection speed of 1 ml/s, and we found no significant difference in the signal drop of the two GBCMs at the other injection speeds. In total, the ANCOVA indicated a statistically significant difference between the regression line for gadobutrol compared to that of gadoteridol, indicating that gadobutrol resulted in a larger signal drop. A comparison of the flush volume by the ANCOVA showed a statistically significant difference between the regression line for the 20 ml versus 50 ml flush, indicating that the 50 ml flush resulted in a larger signal drop compared to the 20 ml, but only with the gadoteridol injection. When we compared the injection duration, which canceled out the difference in GBCM concentrations, the ANCOVA showed that the regression line of gadobutrol was significantly larger change from that of gadoteridol, indicating a larger maximum signal drop during the bolus transition.

The results described above indicate that the bolus width was not different between gadobutrol and a GBCM at a 0.5 mol/L concentration, which contradicts the findings by Tombach et al.[8] and Essig et al.[9] In addition, neither the injection speed nor the flush volume produced a difference in the bolus width in our study. Previous studies showed a shortening of the bolus width in healthy, young volunteers (age range: 22–45 years; Tombach et al.[8], 19–34 years; Essig et al.[9]). The study by Tombach et al.[8] and Essig et al.[9] was an intra-individual comparison. However, our population consisted of patients with an age range of 29–85 years, and this heterogeneity is the reason for the large variation in the FWHM. This fact may be criticized as a limitation in the study design; however, this result represents the reality of bolus injection studies in clinical practice. The patients who undergo a contrast study are a very heterogeneous group and have different cubital vein thicknesses, brachial vein volumes, and pulmonary and cardiac circulation. Such inter-individual differences may have a greater influence on the FWHM than the differences due to the concentration of GBCM, injection speed, or flush volume. The timing of the injection with the heart pulse or respiration status may also be a factor in this large variation in bolus width represented by FWHM in the current study.

In contrast to bolus width, the maximum signal change ratio showed a clear correlation with several conditions despite the subject heterogeneity. In the comparison of the injection speeds, gadobutrol showed a higher signal change compared to gadoteridol. Interestingly, the difference between gadobutrol and gadoteridol was larger with the slower injection speed and smaller flush volume, and the difference decreased when a faster injection speed and larger flush volume was applied. Our finding from the comparison of the injection duration also showed a difference when the flush volume was small. All these results lead us to speculate that gadobutrol causes a larger signal change when the tissue concentration of GBCM is low, and the difference decreases when a faster injection speed and/or a larger flush volume is applied. The transverse relaxivity (R2) of gadobutrol is larger than that of gadoteridol (gadobutrol: 3.9 l/mmol·s, gadoteridol: 3.4 l/mmol·s) at 3T (Plasma at 37°C).[11] In another report, the relaxivity of gadobutrol was 91–244% higher for R2 than Gd-DTPA.[5] However, as far as we know, no *in vitro* or experimental data have been published on the comparison between gadobutrol and gadoteridol at various concentrations including a very low concentration. Thus, the detailed mechanism of our result cannot be elucidated clearly at this time.

Based on the result of this study, we can provide some recommendations for the administration of GBCM for brain imaging including DSC perfusion studies. Reducing the bolus width by altering the injection design is difficult because inter-individual variation is large in ordinary clinical practice. To obtain a good time intensity curve in brain tissue, attempting to improve the degree of signal drop in the first

pass would be the better option. When using gadoteridol, a faster injection ratio and larger flush volume will improve the degree of signal change. However, on the other hand, the results of the current study indicates that such an invasive injection protocol is not necessary. When we use gadobutrol, an injection speed as slow as 2 ml/s, or a flush volume as small as 20 ml, can produce almost the same result as a fast (4 ml/s) injection speed or a large flush volume (50 ml). These finding indicates that DSC perfusion study can be safely and effectively carried out even in the cases with thin surface vein and cannot tolerate high flow bolus injection.

The current study has some limitations. The population of the study was not large, and the number of cases for each injection condition was rather small. In addition, the subjects are patients who underwent an MRI study of the brain, and thus, the heterogeneity was large. We did not record heart rate during the injection which may influence the profile of time intensity curve. We used injection rates of 1 and 2 ml/s for cases that did not require a DSC perfusion study, which may have led to selection bias. We could not evaluate the effects of GBCM types or their injection method of the DSC perfusion study because we did not have data from positron emission tomography (PET) or single photon emission Computed tomography (SPECT) imaging as the gold standard for comparison, which may provide information on the influence of low flow rate infusion to the perfusion map.

## Conclusion

We evaluated the time intensity curve in brain tissue for gadobutrol and gadoteridol administration with various injection speeds and saline flush volumes. We found no difference in bolus length of the time intensity curve under any set of conditions. However, the maximum signal drop increased with gadobutrol when the injection speed was slow and the saline flush volume was small. Thus, gadobutrol may be useful in conditions requiring a slow injection and/or a small saline flush volume to obtain a better profile in the time intensity curve, which may be helpful in the patients with thin vessels.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

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