Online October 28, 2022
Journal of Neuroendovascular Therapy 2022; 16: 586–592 DOI: 10.5797/jnet.oa.2022-0041

Original Article

Relationship between Dilution Magnification of Non-Ionic Iodinated Contrast Medium and Amplification Effect of Radiation Dose

Kuniharu Imai,[1] Kento Takeda,[1] Keisuke Fujii,[1] Chiyo Kawaura,[1] Takuya Nishimoto,[2] Masaki Mori,[2] Yuki Yamamoto,[3] and Takashi Izumi[4]

Objective: Neuroendovascular treatments are less invasive than surgical clipping. However, the number of fluoroscopy runs may be greater when a contrast medium is used than when routine angiography is performed. Several recent studies have suggested that an iodinated contrast medium causes an increase in the radiation dose. Therefore, it is clinically important to identify physical factors causing amplification of the radiation dose. The purpose of this study was to investigate how dilution of a contrast medium with water influences the amplification effect of the radiation dose using simulation analysis.

Methods: Three different types of commercially available contrast media, namely, iopamidol, iohexol, and iodixanol, were diluted 1.7–3.3 times with water and placed in the left brain parenchyma of a numerical brain phantom. Using the Monte Carlo simulation method, the phantom was exposed to X-ray beams under constant exposure conditions, and the energy absorbed in the entire region of the left brain parenchyma was estimated. At the same time, the content and volume of a contrast medium in the cerebral vessels were predicted on the basis of pharmacokinetic and fractal analyses.

Results: The increase in absorbed energy was attributed to secondary electrons emitted from the contrast medium and varied depending on its content and volume. Interestingly, the amount of energy absorbed increased with increasing dilution of the contrast medium. Furthermore, the amplification effect of the radiation dose varied according to the type of contrast medium used.

Conclusion: These results suggest that the amplification effect of the radiation dose is closely related to an increase in the cross-sectional area in which the X-rays interact with the contrast medium, which is caused by increased distribution of contrast medium in the cerebral vessels. When the contrast medium is diluted with water, its spread in the cerebral vessels plays a more important role than its content in the amplification effect of the radiation dose.

Keywords ▶ non-ionic iodinated contrast medium, radiation dose, amplification, dilution

[1]*Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan*
[2]*Division of Radiological Technology, Nagoya University Hospital, Nagoya, Aichi, Japan*
[3]*Division of Radiological Technology, Fujita Health University Okazaki Medical Center, Nagoya, Aichi, Japan*
[4]*Department of Neurosurgery, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan*

Received: June 23, 2022; Accepted: September 2, 2022
Corresponding author: Kuniharu Imai. Department of Integrated Health Sciences, Nagoya University Graduate School of Medicine, 1-1-20, Daikominami, Higashi-ku, Nagoya, Aichi 461-8673, Japan
Email: imai@met.nagoya-u.ac.jp

Introduction

Neuroendovascular treatments for intracranial aneurysms, such as coiling and stent placement, are safe, effective, and less invasive than surgical clipping. However, given that these treatments involve advancement of a catheter through a cerebral artery under fluoroscopic guidance, patients are inevitably exposed to radiation. Furthermore, the positional relationship between the cerebrovascular lesion and the catheter tip needs to be determined precisely; therefore, the number of fluoroscopy runs may be greater with neuroendovascular treatment than with routine angiographic examination. In line with the increased amount of radiation exposure, there is an increase in the amount of contrast medium used, which increases the risk of adverse

reactions.[1–3] In particular, there is an increase in the risk of dose-dependent adverse reactions such as nausea, vomiting, and sensation of heat. Therefore, a contrast medium is usually diluted with saline to reduce the risk of dose-dependent adverse reactions in patients undergoing fluoroscopy examinations.

At present, a non-ionic iodinated contrast medium is more widely used than an ionic iodinated contrast medium and is less likely to cause adverse reactions. However, mild symptoms, such as nausea, vomiting, and sensation of heat, are common even when a non-ionic contrast medium is used. Several researchers have recently identified that the use of an iodinated contrast medium is closely associated with an increase in the radiation dose to patients and may amplify radiation damage at the genetic level.[4,5] This phenomenon may be as damaging as the chemical toxicity associated with the use of a contrast medium. Therefore, the amplification effect of the radiation dose is considered to be an adverse reaction in the same way as nausea, vomiting, and heat sensation. Although it is clinically important to be able to identify the physical factors responsible for this effect, there have been no in-depth investigations of the amplification effect of radiation dose caused by a contrast medium.

Some investigators have measured the radiation dose delivered to an anthropomorphic phantom using a radiophotoluminescence glass dosimeter or semiconductor dosimeter.[6,7] The radiation dose can be assessed with high reliability using this method. However, the amplification effect of the radiation dose caused by a contrast medium needs to be evaluated at a molecular level and it is difficult to assess this effect using a dosimeter. Another method for evaluation of the radiation dose is simulation analysis, which is usually based on the Monte Carlo method.[7] Simulation analysis using this method makes it possible to evaluate the radiation dose at a molecular level and to investigate the amplification effect of radiation dose caused by a contrast medium.

Therefore, in this study, we investigated how dilution of a non-ionic iodinated contrast medium with water contributes to the amplification effect of the radiation dose in cerebral vessels during a fluoroscopy-guided examination using simulation analysis.

Materials and Methods

Numerical brain phantom

The radiation dose can be evaluated with high reliability using a target object with an area similar to that of human blood vessels. However, it is difficult to accurately reproduce blood vessel area. In many simulation analyses of radiation dose, a target object with a simple shape, such as a medical internal radiation dose phantom, is used.[8] Moreover, given that an aim of this study was to investigate how the amplification effect of the radiation dose varies according to the contrast medium content, it was considered unnecessary to reproduce the blood vessel area exactly. Therefore, a numerical brain phantom with an elliptical cylindrical shape (**Fig. 1**) was used as the target object for evaluating the amplification effect of radiation dose. For the purposes of simulation analysis, we considered the brain parenchyma and cerebrospinal fluid to be equivalent to water. Therefore, the simulated brain parenchyma of a numerical brain phantom that measured 8.5 cm in length × 7.5 cm in width × 9 cm in height was filled with water and surrounded by a bone-equivalent material with a thickness of 1 mm. As shown in **Fig. 1**, an elliptical cylinder with dimensions of 6.5 cm in length × 3.6 cm in width × 9 cm in height was prepared as the region occupied by the contrast medium in the simulated left brain parenchyma.

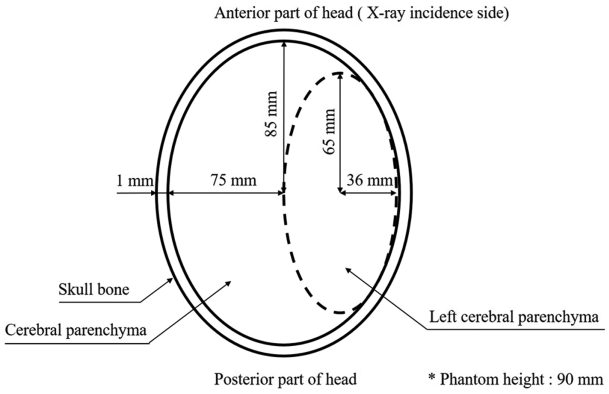

Fig. 1 Cross-sectional view of the numerical brain phantom. Water is regarded as a material equivalent to that of cerebral parenchyma. The constituent elements of the skull bone are hydrogen, carbon, nitrogen, oxygen, fluorine, and calcium with a mass ratio of H:C:N:O:F:Ca = 1.00: 1.45:42.33:32.40:7.37:14.74, as recommended by the High Energy Accelerator Research Organization (KEK).

Pharmacokinetic estimation of mass and volume of contrast medium in the vessel

Iopamidol with an iodine concentration of 300 mg/mL, iohexol with an iodine concentration of 300 mg/mL, and iodixanol with an iodine concentration of 270 mg/mL were prepared to investigate the amplification effect of radiation dose. In a previous study, a two-compartment model (**Fig. 2**) was found to be suitable for analyzing the pharmacokinetics of iodinated contrast medium in cerebral vessels.[9,10] Hence, the material balance based on the model is given by

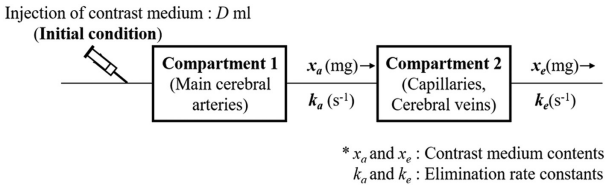

Fig. 2 Illustration of the two-compartment model. Compartments 1 and 2 are considered to be the main cerebral arteries and capillaries, respectively. Contrast medium is manually injected through the catheter and the injection volume is 10 mL.

equation (1), in which x_e is the contrast medium content that distributes in cerebral vessels:

$$\frac{dx_a}{dt} = -k_a x_a$$
$$\frac{dx_e}{dt} = k_a x_a - k_e x_e \quad (1)$$

where x_a and x_e represent the contrast medium content in compartments 1 and 2, respectively, and k_a and k_e are the elimination rate constants for the contrast medium in compartments 1 and 2. When a neuroendovascular procedure is performed, a small dose of the contrast medium is manually injected to check the position of the catheter tip in a cerebral artery. This confirmatory maneuver can be regarded as the initial condition of equation 1, which, in this analysis, is given as the contrast medium content per 10 mL of water solution. On this occasion, the contrast medium was diluted with saline. Thus, the dilution magnification for each type of non-ionic iodinated contrast medium was set to 1.7-fold, 2.0-fold, 2.5-fold, and 3.3-fold.

Viscosity also changes in response to an increase in the dilution magnification of contrast medium. It is widely known that the viscosity of a liquid is inversely proportional to the flow velocity and is governed by the Arrhenius equation:

$$\eta = A\exp(\alpha x) \quad (2)$$

where η is viscosity, x is the concentration of a solute in a solution, and A and α are constants. In order to demonstrate the validity of equation (2), the relationship between viscosity and iodine concentration for each type of contrast medium was investigated on the basis of the nominal values mentioned in the interview forms. Plots of the viscosity of each type of contrast medium as a function of iodine concentration are shown on a semi-logarithmic scale (so-called Arrhenius plots) in **Fig. 3**. For each type of contrast medium, there was a positive linear relationship between viscosity and the iodine concentration, which followed the Arrhenius

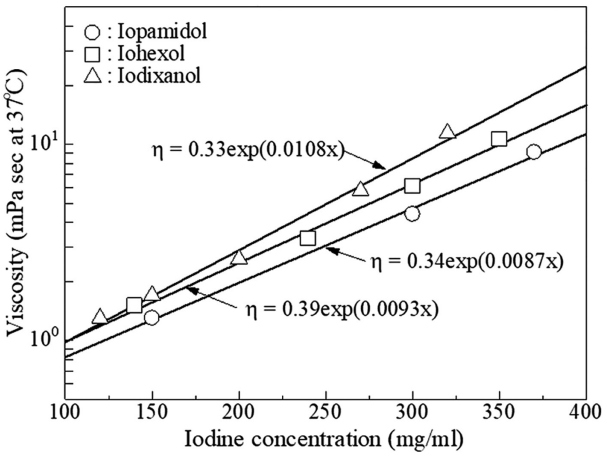

Fig. 3 Relationship between viscosity of the contrast medium and iodine concentration. The correlation coefficients for the Arrhenius plots were p >0.996. The empirical formula for the viscosity of each type of contrast medium is shown.

equation. Therefore, the empirical formula of viscosity for each type of contrast medium was derived from the characteristic curve shown in **Fig. 3**. The viscosity of the contrast medium for each dilution magnification was estimated by calculating the iodine concentration corresponding to the iodine content in the diluted contrast medium.

In addition to analysis of the pharmacokinetics of each type of contrast medium based on the use of the two-compartment model, the efficacy of contrast enhancement was investigated by fractal analysis. We found a linear correlation between the area enhanced on a cerebral DSA image and the fractal dimension. Furthermore, to investigate the flow of contrast medium in cerebral vessels, the elimination rate constants for the different types of contrast medium in compartments 1 and 2 were estimated based on these results.[10] The elimination rate constant for the contrast medium in compartment 1 was estimated to be 0.50 (s^{-1}) for iopamidol with an iodine concentration of 300 mg/mL, 0.37 (s^{-1}) for iohexol with an iodine concentration of 300 mg/mL, and 0.39 (s^{-1}) for iodixanol with an iodine concentration of 270 mg/mL, and was inversely proportional to viscosity for all three types of contrast media. However, the elimination rate constant for the contrast medium in compartment 2 remained unchanged regardless of the type of medium used and was estimated to be 0.35 (s^{-1}). These results suggested that the flow of contrast medium in the main cerebral arteries, such as the internal carotid artery and middle cerebral artery, was governed by viscosity, whereas that in the capillaries and cerebral veins was limited by the velocity of red blood cells.

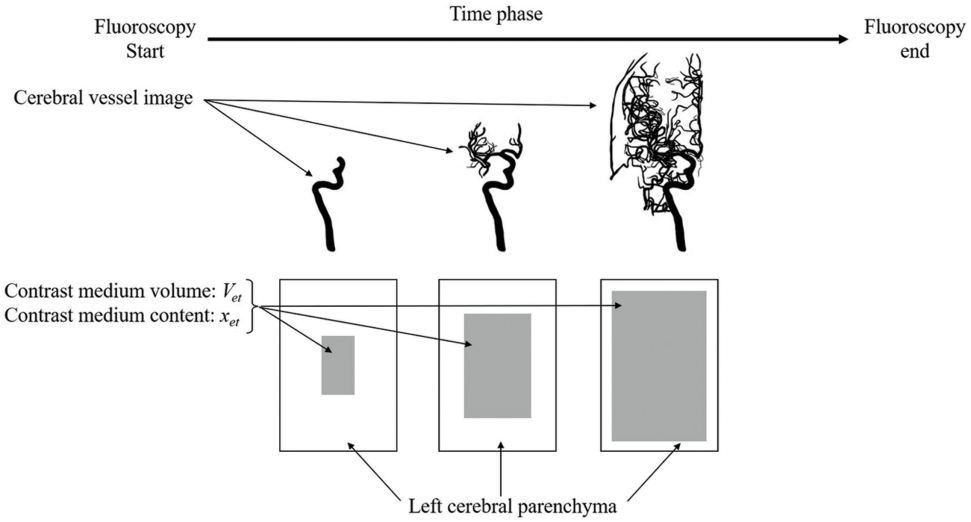

Fig. 4 Schematic diagram showing the change in contrast medium volume with passage of time. The upper panels show cerebral vessel images corresponding to the contrast medium volumes in the lower panels.

In view of the above results, after calculation of the viscosity of contrast medium for a given dilution magnification using the empirical formula based on the Arrhenius equation, the elimination rate constant for compartment 1 was estimated using equation (3):

$$k_{ad} = \frac{\eta_0}{\eta_d} k_{a0} \tag{3}$$

where k_{ad} and k_{a0} are elimination rate constants for dilution magnifications of d and non-dilution (e.g., k_{a0} = 0.50 (s^{-1}) for iopamidol with an iodine concentration of 300 mg/mL), respectively, and η_d and η_0 are viscosities for dilution magnification of d and non-dilution, respectively. The elimination rate constant for the contrast medium in compartment 2 was set to 0.35 (s^{-1}), and the pharmacokinetics of the contrast medium were analyzed according to various dilution magnifications on the basis of the two-compartment model.

As mentioned above, the enhanced area on cerebral DSA images correlated with the fractal dimension of the cerebral vessel. This finding means that the volume of contrast medium in the cerebral vessels can be estimated from the fractal dimension of cerebral DSA images. In general, the fractal dimension of plane images is 2;[11] that is, cerebral DSA images with a fractal dimension of 2 imply that the cerebral vessels are completely filled with a contrast medium. This notion can be also applied to fluoroscopic images of cerebral vessels because these images are also considered to have a fractal dimension of 2 when the contrast medium content in cerebral vessels reaches a maximum value in pharmacokinetic characteristics of the contrast medium. Furthermore, the contrast medium content in cerebral vessels has a linear relationship with the efficacy of contrast enhancement and, as such, can be used as a substitute for the fractal dimension.[12] For these reasons, the contrast medium volume (i.e., spread of contrast medium) can be given by equation (4):

$$V_e : V_{max} = x_e : x_{max} \qquad \therefore V_e = \frac{x_e}{x_{max}} V_{max} \tag{4}$$

where V_e and V_{max} (= π × 6.5 cm × 3.5 cm × 9 cm in the present study) are the contrast medium volumes for x_e and maximum content x_{max} in pharmacokinetic characteristics of contrast medium diluted with water, respectively.

Evaluation of radiation dose using the Monte Carlo simulation technique

In this study, the radiation dose was evaluated using the Electron Gamma Shower computer code system (version 5; High Energy Accelerator Research Organization), which is one of the Monte Carlo simulation codes. The simulation conditions of X-ray irradiation were as follows: tube voltage, 80 kVp; fluoroscopy time, 1 s; irradiated area, 15 cm × 9 cm; and distance between the X-ray source and numerical brain phantom, 50 cm. Incident X-ray photons were set to 10^6 and their statistical errors were estimated to be within 5%. Furthermore, the spectrum of X-rays was simulated by the Tucker equation.

Figure 4 shows the contrast medium volumes corresponding to frontal views of the cerebral vessels for a variety of time phases. Now, let x_{et} and V_{et} be the content and volume of a contrast medium for a given time t, which are calculated from equations (1) and (4), respectively. An

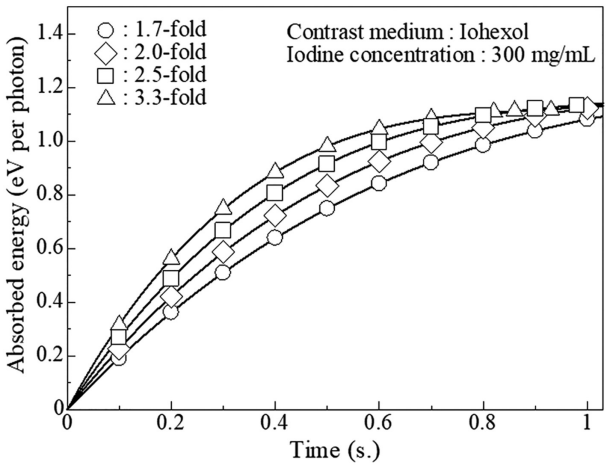

Fig. 5 Time-dependent characteristics of absorbed energy. Time-dependent curves of absorbed energy for iohexol are drawn as an example. Similar characteristics were obtained for iopamidol and iodixanol.

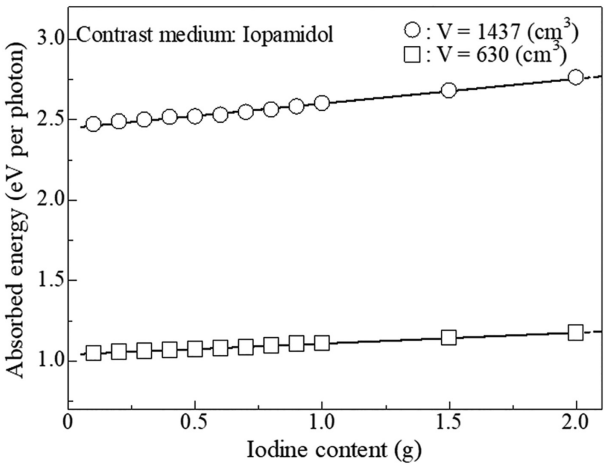

Fig. 6 Relationship between absorbed energy and contrast medium content using iopamidol as an example. Similar characteristics were obtained for iopamidol and iodixanol.

elliptical cylinder with a volume of V_{et} was used as the target object for analysis of the amplification effect of radiation dose, and the spread of contrast medium according to time was represented using the shapes of the simulated left brain parenchyma. A mixture of the contrast medium content of x_{et} and water was placed to uniformly distribute in the elliptical cylinder with a volume of V_{et}, and the cylinder was set to the center of the simulated left brain parenchyma as shown in **Fig. 1**. Under the geometric arrangement of the contrast medium, the numerical brain phantom was exposed virtually to X-ray beams in the anterior–posterior direction at arbitrary time intervals.

Several studies have suggested that the photoelectric interaction between X-ray photons and the contrast medium (that is, the photoelectric effect) is closely related to the amplification effect of radiation dose.[4,13] In view of these reports, the absorbed energy attributed to secondary electrons emitted from the contrast medium, and the X-ray photons that passed through the contrast medium were calculated over the entire region of the simulated left brain parenchyma and converted to absorbed energy per incident X-ray photon.

Results

The time-dependent change in absorbed energy for each type of contrast medium according to dilution magnification is shown in **Fig. 5**. The absorbed energy indicates the characteristics with the maximum value in a given time phase regardless of the dilution magnification and type of contrast medium. The finding that the absorbed energy was not constant regardless of time phase suggests that the amplification effect of radiation dose was induced by the contrast medium. Furthermore, the amplification effect of contrast medium is strongly correlated with its content and volume. The influence of contrast medium content on the increase in radiation dose was then evaluated while maintaining a constant volume of medium (**Fig. 6**). Although the absorbed energy increased linearly with the increase in the contrast medium content, the increments were very small. The increment in absorbed energy was affected to a greater extent by the volume of contrast medium than by its content. For example, even though the contrast medium content increased by 2-fold, the absorbed energy only increased by approximately 1.05-fold. In contrast, the absorbed energy increased by approximately 2-fold when the volume of contrast medium increased by 2-fold. Therefore, the spread of contrast medium in the cerebral vessels had a marked effect on the increase in the radiation dose.

Table 1 Relationship between the area under the curve and dilution magnification of three types of contrast media

	1.7-fold	2.0-fold	2.5-fold	3.3-fold
Iopamidol	0.745	0.802	0.866	0.875
Iohexol	0.678	0.742	0.798	0.840
Iodixanol	0.692	0.758	0.815	0.857

The time to maximum absorbed energy decreased as the dilution magnification increased (**Fig. 5**). To make the effect of the dilution magnification clear, the area under the time-dependent curve for the absorbed energy (AUC; i.e., the average absorbed energy over fluoroscopy time) was calculated for each type of contrast medium. As shown in **Table 1**, the AUC increased as the dilution magnification increased, regardless of the type of contrast medium used.

Furthermore, iopamidol had the largest AUC of the three types of non-ionic iodinated contrast media, and iohexol had almost the same AUC as iodixanol. These findings suggested that the dilution magnification of the contrast medium also had a strong effect on the increase in radiation dose and that its amplification effect varied in accordance with the type of contrast medium used.

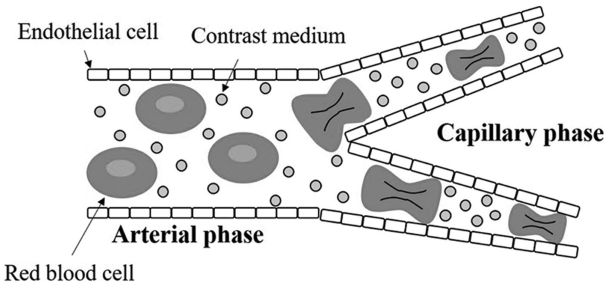

Fig. 7 Schematic diagram showing the flow of contrast medium flow at the border between a cerebral artery and a capillary. A contrast medium with high viscosity pools in this region, whereas a contrast medium with low viscosity passes smoothly through this region along with the red blood cells.

Discussion

Several studies have suggested that the amplification effect of radiation dose is caused by secondary electrons emitted from the contrast medium.[4,13] In line with those reports, in the present study, the absorbed energies of the secondary electrons and transmission X-ray photons were used as physical indices to investigate the amplification effect of radiation dose. However, it is uncertain whether or not the secondary electrons contributed to the increase in radiation dose. Therefore, the interaction of X-ray photons with the simulated cerebral parenchyma was investigated further based on the results obtained in the simulation analysis. The vast majority of incident X-ray photons were converted to secondary electrons by interaction with the contrast medium and accounted for 95% of the absorbed energy regardless of the dilution magnification of the contrast medium. This finding indicates that the increase in radiation dose was induced by secondary electrons emitted from the contrast medium. Furthermore, the secondary electrons increased as the volume of contrast medium increased and were mostly emitted from the surface of the X-ray incidence side of the contrast medium region (elliptical cylinder with the volume of V_{et}). That is, the surface area for the X-ray incidence side of the contrast medium region can be regarded as the cross-section of X-ray interactions with the contrast medium. Indeed, in regions other than the surface, the contrast medium did not contribute to emission of secondary electrons. These events are consistent with the finding that the amplification effect of radiation dose was more dependent on the spread of contrast medium rather than by its content.

The radiation dose delivered to the simulated cerebral parenchyma was shown to increase with increasing dilution magnification of the contrast medium. As previously mentioned, the value of the elimination rate constant (k_a) in the main cerebral arteries decreased with increasing viscosity of the non-ionic iodinated contrast medium, regardless of type, whereas that in the capillaries and cerebral veins remained constant and was lower than that in the main cerebral arteries. This finding indicates that the elimination rate constant in the capillaries and cerebral veins depends on the flow velocity of red blood cells and not on the viscosity of the contrast medium. Therefore, a contrast medium with low viscosity would flow steadily in the main cerebral arteries until reaching the capillary region. However, as shown in **Fig. 7**, the contrast medium starts to pool at the border between the main artery and the capillaries because of the slow movement of red blood cells in the capillaries. Consequently, the cross-sectional area of X-ray interactions with the contrast medium becomes larger in accordance with expansion of the region in which the contrast medium becomes pooled, resulting in an increase in the radiation dose. Furthermore, the area in which the flow of contrast medium is slow becomes larger because it is easier for large amounts of the contrast medium to pool at the border between the main artery and capillaries in accordance with the reduction in the viscosity of the contrast medium. However, the high-viscosity contrast medium flows in the cerebral vessels in the same way as the low-viscosity contrast medium, which increases the area within which the contrast medium pools. If the viscosity of the contrast medium was slightly higher than or almost equal to that of red blood cells, the contrast medium would flow smoothly without pooling near the border between the main artery and capillaries; consequently, the amplification effect of the radiation dose would be low. Therefore, dilution of the contrast medium with water could account for the increase in the radiation dose.

The radiation dose delivered to the simulated cerebral parenchyma was higher for iopamidol than for iohexol or iodixanol. This finding can be explained by the difference in viscosity between the three types of contrast media. Iopamidol is the least viscous, and in view of the previously mentioned mechanism associated with the increase

in the radiation dose, it is more prone to pooling than iohexol or iodixanol, thus resulting in the highest amplification effect of radiation dose. Furthermore, our finding that iohexol delivered almost the same radiation dose to the simulated cerebral parenchyma as iodixanol can be attributed to the fact that there is little difference in viscosity between these two types of contrast media.

This study has some limitations. First, the amplification effect of the radiation dose caused by the different types of contrast media was investigated by simulation analysis and not measured using a dosimeter. Second, the target object used for this analysis was a numerical brain phantom, which has a simplified shape and does not accurately simulate cerebral vessels. Third, an additional filter was not included in the simulation geometry. These shortcomings need to be overcome in future studies of the amplification effect of radiation dose.

Conclusion

We have investigated the influence of dilution of a contrast medium on the amplification effect of radiation dose using the Monte Carlo simulation technique. We found that the radiation dose increased with an increasing dilution of the contrast medium. The main reason for this effect was the spread of contrast medium in the cerebral vessels rather than its content.

Funding

This work was supported by JSPS KAKENHI Grant Number 18K12129.

Disclosure Statement

The authors declare that they have no conflicts of interest.

References

1) Del Favero C, Rossini G, Martegani A. A comparison of iopamidol and ioxaglate in CT enhancement. *Eur Radiol* 1993; 3: 77–82.
2) Stacul F, Thomsen HS. Nonionic monomers and dimers. *Eur Radiol* 1996; 6: 756–761.
3) Stacul F. Current iodinated contrast media. *Eur Radiol* 2001; 11: 690–697.
4) Grudzenski S, Kuefner MA, Heckmann MB, et al. Contrast medium-enhanced radiation damage caused by CT examinations. *Radiology* 2009; 253: 706–714.
5) Piechowiak EI, Peter JW, Kleb B, et al. Intravenous iodinated contrast agents amplify DNA radiation damage at CT. *Radiology* 2015; 275: 692–697.
6) Imai K, Ikeda M, Kawaura C, et al. Dose reduction and image quality in CT angiography for cerebral aneurysm with various tube potentials and current settings. *Br J Radiol* 2012; 85: e673–e681.
7) Fujii K, Nomura K, Muramatsu Y, et al. Correlation analysis of organ doses determined by Monte Carlo simulation with dose metrics for patients undergoing chest-abdomen-pelvis CT examinations. *Phys Med* 2020; 77: 1–9.
8) Snyder WS, Fisher HL Jr., Ford MR, et al. Estimates of absorbed fractions for monoenergetic photon sources uniformly distributed in various organs of a heterogeneous phantom. *J Nucl Med* 1969; 10(Suppl 3): 7–52.
9) Naito K, Yamamot Y, Fujii K, et al. Kinetic analysis of iodinated contrast media on the basis of fractal of cerebral arteries. *IEICE Technical Report* 2014; 114: 23–28. (in Japanese)
10) Naito K, Imai K, Nishimoto T, et al. Pharmacokinetics and pharmacodynamics analysis of non-ionic iodinated contrast medium in cerebral vessels. Proceedings of the 31st Annual Meeting of the Japanese Society for Neuroendovascular Therapy, Okayama, 2015; O4–2. (in Japanese)
11) Rathore MK, Kumar M, Yadav S, et al. Estimation of fractal dimension of digital images. *IJETR* 2014; 2: 176–181.
12) Imai K, Ikeda M, Satoh Y, et al. Contrast enhancement efficacy of iodinated contrast media: effect of molecular structure on contrast enhancement. *Eur J Radiol Open* 2018; 5: 183–188.
13) Sahbaee P, Abadi E, Segars WP, et al. The effect of contrast material on radiation dose at CT: Part II. A systematic evaluation across 58 patient models. *Radiology* 2017; 283: 749–757.