



Contrast enhancement efficacy of iodinated contrast media: Effect of molecular structure on contrast enhancement

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ABSTRACT

Purpose: To investigate the contrast enhancement in DSA images based on the X-ray absorption characteristics of iodinated contrast media.

Methods: We have derived a new formula of predicting the pixel value ratio of two different contrast media and designate it as “Contrast Enhancement Ratio (CER)”. In order to evaluate the accuracy of CER, we have evaluated the relationship between CER and pixel value ratio for all combinations of eleven iodinated contrast media. The non-ionic iodinated contrast media, iopamidol, iomeprol, iopromide, ioversol, iohexol, and iodixanol, were evaluated in this study. Each contrast medium was filled in the simulated blood vessel in our constructed anthropomorphic phantom, and DSA images were obtained using an angiographic imaging system. To evaluate the contrast enhancement of the contrast medium, the mean pixel value was calculated from all pixel values in the vascular image.

Results: CER was indicated to agree well with the pixel value ratio of two different contrast medium solutions and showed a good accuracy. CER was also shown to have a good linear relation to the pixel value ratio when the iodine concentration was constant. This means that the molecular structure of the contrast media affects contrast enhancement efficacy. Furthermore, in evaluation of contrast enhancement of iodinated contrast media by using the weight factor (that is a key factor in CER) ratio, Iodixanol, and iopamidol, and iomeprol have the same ability of contrast enhancement in DSA images, and iohexol shows the lowest ability.

Conclusions: We have derived a new formula (CER) of predicting the pixel value ratio of two different contrast medium solutions, and shown that CER agreed well with the pixel value ratio for blood vessel filled with eleven contrast media.

1. Introduction

Iodinated contrast media play an important role in digital subtraction angiography (DSA) and computed tomography angiography (CTA) examinations [1–12]. In general, iodinated contrast media are classified into two different types (ionic and non-ionic contrast media), and non-ionic iodinated contrast media are now the mainstream. Among them, non-ionic monomers, such as iohexol, iopamidol, iomeprol, iopromide, and ioversol have been commercially marketed for long periods, and their safety has been confirmed clinically [14,15]. Thus, these monomeric contrast media are widely used, especially when performing the X-ray angiographic examinations which need a high injection rate and dose of contrast media. However, it has been pointed out that the

contrast enhancement effect is lowered by intravascular dilution of non-ionic monomeric contrast media, because their osmolality is more than two times of blood (290 mOsm/kg H₂O) [13].

Iodixanol is a non-ionic, dimeric, hexaiodinated contrast medium developed by Nycomed AS, Oslo, Norway. In iodixanol, electrolyte solutions are added in the equivalent ratio in blood to make the injected solution isosmotic to blood. The osmolality of iodixanol is less than half that of the non-ionic monomeric contrast media, and iodixanol has been proven to be at least as safe as the non-ionic monomeric contrast media [16–18]. Additionally, due to the osmolality difference, non-ionic dimers are expected to be less diluted than monomers. In fact, Pannu et al. have reported that there was no statistically significant difference in mean aortic attenuations between dimeric iodixanol and monomeric

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iohexol, although iodixanol (320 mgI/ml) has lower iodine concentration than iohexol (350 mgI/ml), and have concluded that this result supports the hypothesis that there is less intravascular dilution of iso-osmolar iodixanol compared with iohexol [13]. However, Jared et al. have shown that iodixanol (320 mgI/ml) provided statistically significant lower vascular contrast than iopamidol (370 mgI/ml) [11]. Aside from these reports, experience shows that in cerebral angiography examinations, iopamidol of 300 mg iodine /ml has higher contrast enhancement efficacy than iohexol of 300 mg iodine /ml even through their osmolality is almost the same. Thus, when considering the above-mentioned reports, a following question arises: can the reduction of contrast enhancement in DSA and CTA images be explained adequately only by the plasma dilution of iodinated contrast media?

The contrast enhancement of arteries in DSA and CTA images is provided mainly by X-ray absorption by iodine in contrast media. However, the vascular enhancement has not been investigated in the light of the interaction of X-ray photons with iodine molecules embedded in contrast media, whereas the concept of a directly proportional relationship between iodine content and vascular enhancement is well established [11,12]. In this study, we have derived a new formula for comparing the contrast enhancement efficacy of iodinated contrast media in DSA images, based on the X-ray absorption characteristics of iodinated contrast media, and evaluated the accuracy of this new formula by using phantom.

2. Materials and methods

2.1. DSA phantom image acquisition

The head phantom was employed as the target object for evaluating the contrast enhancement efficacy. The phantom was composed of simulated brain parenchyma, intracranial arteries with several aneurysms, and skull bone [19]. In this phantom, the brain parenchyma was made of polyurethane polymer with 2.5% calcium phosphate and its attenuation coefficient was equivalent to that of human brain parenchyma; the intracranial arteries were bored through it; and, the skull bone was made of gypsum and enveloped by polyurethane polymer having the same attenuation coefficient as soft tissue.

The following eleven commercially available non-ionic contrast media were used in this study: iopamidol with iodine concentrations of 300 and 370 mg/ml (Iopamirom 300 and 370; Bayer, Tokyo, Japan), iomeprol with iodine concentration of 350 mg/ml (Iomeron; Eisai, Tokyo, Japan), iopromide with iodine concentrations of 300 and 350 mg/ml (Iopromide 300 and 350; Fuji Film RI Pharma, Tokyo, Japan), iohexol with iodine concentrations of 240, 300, and 350 mg/ml (Omnipaque 240, 300, and 350; Daiichi Sankyo, Tokyo, Japan), ioversol with iodine concentrations of 320 and 350 mg/ml (Optiray 320 and 350; Fuji Pharma, Tokyo, Japan), and iodixanol with iodine concentration of 270 mg/ml (Visipaque 270; Daiichi Sankyo, Tokyo, Japan). Before contrast media were put into the simulated blood vessel, the phantom mask image was obtained using an angiographic imaging system (Artis Zee and Syngo X-Workplace; Siemens, Berlin, Germany) with auto-exposure control unit under a constant tube voltage of 64 kV (Fig. 1(a)). Then, each contrast medium with a volume of 10 ml was filled in the simulated right internal carotid artery and eleven kinds of vascular images were acquired under the same exposure condition (Fig. 1(b)), whereas non-ionic iodinated contrast media with iodine concentrations of 320, 350, and 370 mg/ml are not usually administered into the blood vessels in cerebral angiography examinations. Since the pixel values created by the image processing software installed in the angiographic imaging system were not appropriate to quantitatively evaluate the contrast enhancement efficacy of contrast media, we acquired DSA images by subtracting the mask image from the vascular images through the image processing software “Image J” (Fig. 1(c)), so that a pixel value in DSA images was proportional to an attenuation coefficient in the pixel.

2.2. Formula for comparing contrast enhancement of iodinated contrast media in DSA images

Now we derive a new formula for comparing the contrast enhancement of two different iodinated contrast media in DSA images, based on the interaction between iodine and X-ray photons. Let CM-A and CM-B be two different iodinated contrast media.

The mass attenuation coefficient of a molecule, μ/ρ , is given by the following equation:

$$\mu/\rho = \frac{1}{A_M} \sum a_n A_n (\mu/\rho)_n = \sum \omega_n (\mu/\rho)_n \quad (1)$$

where $(\mu/\rho)_n$ is the mass attenuation coefficient of an atom n which constitutes the molecule M , a_n is the ratio of the atom n , A_n is the atomic mass of the atom n , A_M is the molecular mass of the molecule M , and $\omega_n = \frac{a_n A_n}{A_M}$. Here, we refer to ω_n as “weight factor” of element n , and it is a key factor of our formula. For example, the weight factor of hydrogen in a water molecule is given by

$$\omega_H = \frac{2 \times [H]}{[H_2O]} = \frac{2}{18} \quad (2)$$

where $[H]$ and $[H_2O]$ are the atomic mass of hydrogen and the molecular weight of water, respectively.

Let $(\mu/\rho)_{A,E}$ and $(\mu/\rho)_{B,E}$ denote the mass attenuation coefficient of iodinated contrast medium CM-A and CM-B for a monochromatic X-ray energy E , respectively. Then, if solvent is neglected, the measured attenuation coefficient ratio of CM-A and CM-B solution for E , α , is expressed by

$$\alpha = \frac{\mu_A(E)}{\mu_B(E)} = \frac{(\mu/\rho)_{A,E} \rho_A l_A}{(\mu/\rho)_{B,E} \rho_B l_B} = \frac{\sum \omega_{nA} (\mu/\rho)_{n,A,E} \rho_{nA} l_A}{\sum \omega_{nB} (\mu/\rho)_{n,B,E} \rho_{nB} l_B} \quad (3)$$

where $\mu_A(E)$ and $\mu_B(E)$ are the measured attenuation coefficient of CM-A and CM-B solution for E , respectively; ρ_A and ρ_B are the volumetric mass density of CM-A and CM-B, respectively; l_A and l_B are the volume of CM-A and CM-B in blood vessels, respectively; and, $(\mu/\rho)_{n,A,E}$ and $(\mu/\rho)_{n,B,E}$ are the mass attenuation coefficients of atom n constituting of CM-A and CM-B for E , respectively. As for the iodinated contrast medium, the iodine term constitutes mainly of the mass attenuation coefficient, expressed in the Eq. (1), and the other terms except for iodine can be neglected in the calculation of the mass attenuation coefficient. For example, the mass attenuation coefficients of iopamidol and its iodine component at a monochromatic X-ray energy of 40 keV are 4.721 and 4.696, respectively, and the difference between them is 0.530% [= (4.721 - 4.696)/ 4.721 × 100]. As another example, the difference is 0.528% for iodixanol. As these examples show, the difference in mass attenuation coefficient between with and without the other terms except for iodine is less than 1% for the iodinated contrast medium. Thus, α , given as the Eq. (3), can be approximated as,

$$\alpha = \frac{\mu_A(E)}{\mu_B(E)} = \frac{\sum \omega_{nA} (\mu/\rho)_{n,A,E} \rho_{nA} l_A}{\sum \omega_{nB} (\mu/\rho)_{n,B,E} \rho_{nB} l_B} \cong \frac{\omega_{IA} (\mu/\rho)_{I,E} \rho_{IA} l_A}{\omega_{IB} (\mu/\rho)_{I,E} \rho_{IB} l_B} = \frac{\omega_{IA} \rho_{IA} l_A}{\omega_{IB} \rho_{IB} l_B} \quad (4)$$

where $(\mu/\rho)_{I,E}$ is the mass attenuation coefficient of iodine for E ; ω_{IA} and ω_{IB} are the weight factor of iodine in CM-A and CM-B, respectively; and, ρ_{IA} and ρ_{IB} are the mass concentrations of iodine in CM-A and CM-B, respectively. The last equation of the equation set (4) is independent of X-ray energy, and we express it as β for the moment.

Whereas the Eq. (4) is derived for monochromatic X-ray, DSA examination systems use polychromatic X-ray source. The attenuation coefficient for polychromatic X-ray is given by

$$\int \mu(E) S(E) dE \quad (5)$$

where $\mu(E)$ is the attenuation coefficient for energy component E and S (E) is the incident X-ray energy spectrum. Thus, the measured attenuation coefficient ratio of CM-A and CM-B solution for

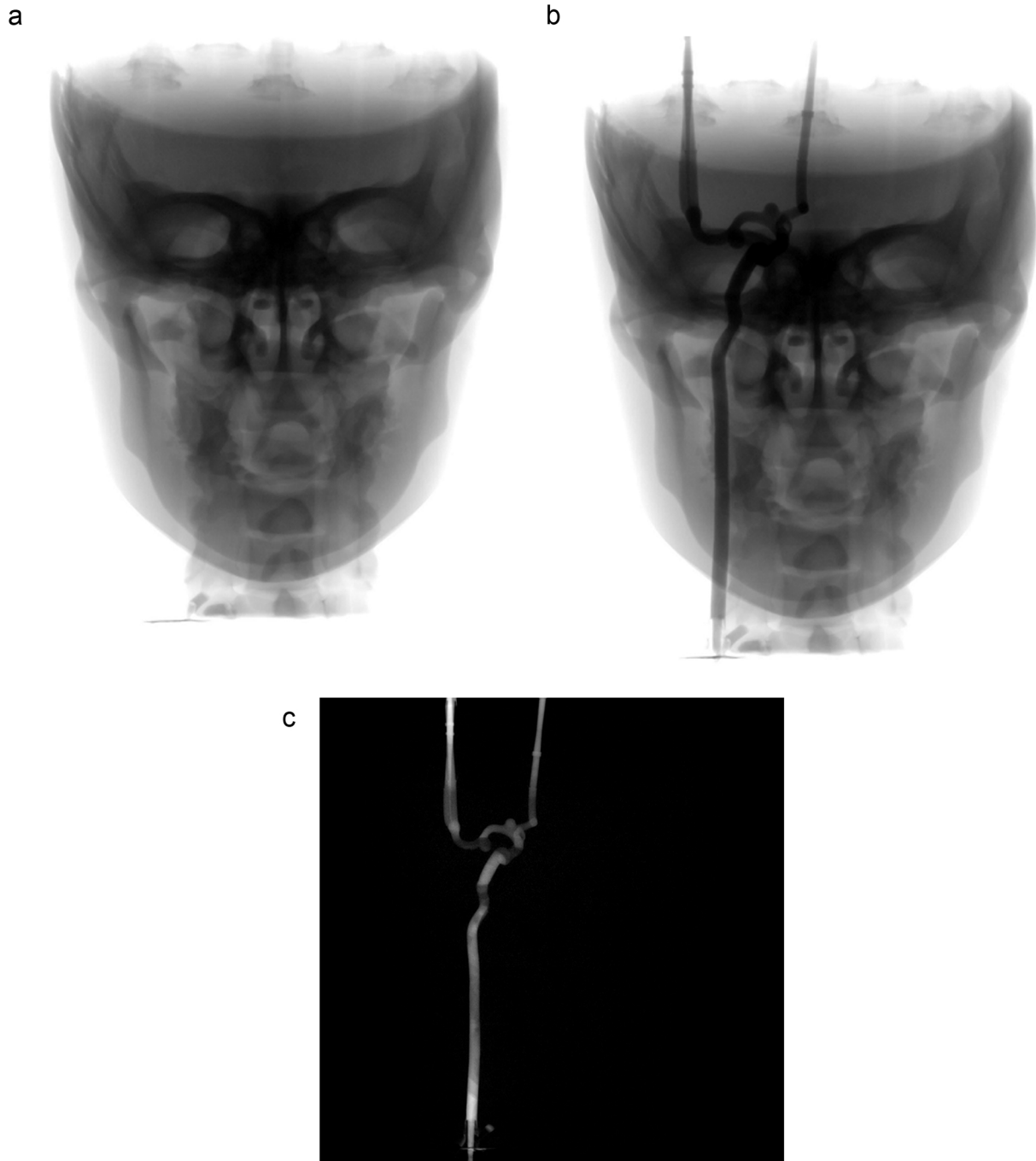


Fig. 1. Digital radiography of anthropomorphic phantom. (a) Mask image, (b) Vascular image, and (c) DSA image.

polychromatic X-ray is as follows:

$$\frac{\int \mu_A(E)S(E)dE}{\int \mu_B(E)S(E)dE} \tag{6}$$

Since the Eq. (4) holds for each energy component of polychromatic X-ray spectrum and $\frac{\mu_A(E)}{\mu_B(E)} = \beta$,

$$\mu_A(E)S(E) = \beta\mu_B(E)S(E) \tag{7}$$

Substituting the Eq. (7) into the Eq. (6) gives the following equation:

$$\frac{\int \mu_A(E)S(E)dE}{\int \mu_B(E)S(E)dE} = \frac{\int \beta\mu_B(E)S(E)dE}{\int \mu_B(E)S(E)dE} = \beta \tag{8}$$

As presented by Eq. (8), β [defined as the last equation of the equation set (4)], also approximates the measured attenuation

coefficient ratio (i.e., pixel value ratio) of the contrast media CM-A and CM-B solutions for any polychromatic X-ray source. Therefore, we consider β as a new formula for approximating the pixel value ratio of two different contrast medium solutions and designate it as “contrast enhancement ratio (CER)”:

$$CER = \frac{\omega_{IA}\rho_{IA}l_A}{\omega_{IB}\rho_{IB}l_B} \tag{9}$$

As is clear in the Eq. (9), contrast enhancement efficacy of iodinated contrast media in DSA images is determined by not only iodine concentration but also molecular structure, and the weight factor ratio $\left(\frac{\omega_{IA}}{\omega_{IB}}\right)$ can be considered to reflect an intrinsic difference in contrast enhancement between two different iodinated contrast media.

In this study, the accuracy of CER was evaluated by using pixel

Table 1
Weight Factor Ratio ($\frac{\omega_A}{\omega_B}$) for Each Combination of Six Contrast Media.

CM-B CM-A	iopamidol	iomeprol	ioversol	iohexol	iopromide	iodixanol
iopamidol	1.000	1.000	0.964	0.946	0.982	1.003
iomeprol	1.000	1.000	0.964	0.946	0.982	1.003
ioversol	1.037	1.037	1.000	0.982	1.019	1.040
iohexol	1.057	1.057	1.019	1.000	1.038	1.059
iopromide	1.018	1.018	0.981	0.963	1.000	1.021
iodixanol	0.997	0.997	0.962	0.944	0.980	1.000

values in vascular portion on DSA images. Here, the pixel uniformity of the vascular images was low, as illustrated in Fig. 1(c). However, this low uniformity can be compensated by increasing the area used for evaluation (that is, increasing sample size). The mean pixel value calculated from all pixel values in the vascular portion on DSA images can be also considered to reflect the contrast enhancement efficacy which is attributed to contrast medium. Thus, the ratio of mean pixel values of blood vessel filled with two different contrast media was used as an evaluation index, and the relationship between CER and this pixel value ratio was investigated to evaluate the accuracy of CER.

3. Results

Table 1 shows the weight factor ratios for all combinations of the six contrast media assessed in this study. The weight factor ratios for the combinations of iodixanol, iopamidol, and iomeprol are approximately one, and our formula indicates that these three contrast media have almost the same ability of contrast enhancement. Furthermore, the weight factor ratio to iodixanol is 0.980 for iopromide, 0.962 for ioversol, and 0.944 for iohexol. Thereby, our formula indicates that iohexol has the lowest contrast enhancement ability of the six contrast media.

Fig. 2 shows the relationship between CER and the pixel value ratio. There was a strong linear correlation between CER and the pixel value ratio, and the slope (m) of the estimated linear regression line between them and their Pearson’s correlation coefficient (r) were $m = 0.985$ and $r = 0.943$. To clarify the characteristics of our derived formula, CER, we focused on the relationship between CER and the pixel value ratio when $\frac{\omega_A}{\omega_B} = 1$ and when $\frac{\rho_{IA}^A}{\rho_{IB}^A} = 1$ (Fig. 3). This reason was that the influence of iodine contents on contrast enhancement efficacy can be investigated when $\frac{\omega_A}{\omega_B} = 1$ and the influence of molecular structure of contrast media on it can be investigated when $\frac{\rho_{IA}^A}{\rho_{IB}^A} = 1$. Where confined

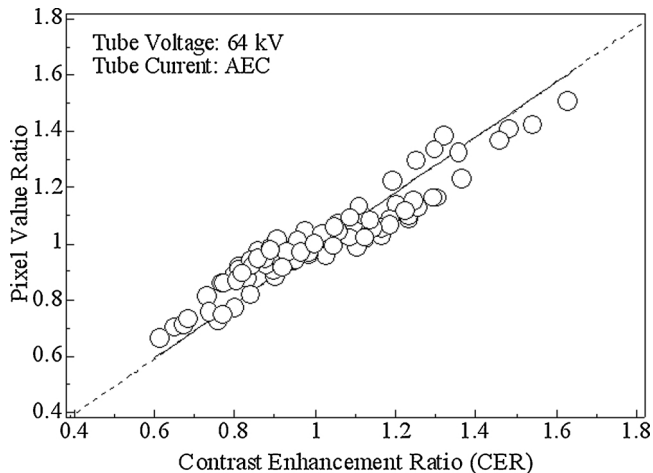


Fig. 2. Contrast enhancement ratio (CER) versus pixel value ratio for each combination of eleven non-ionic iodinated contrast media.

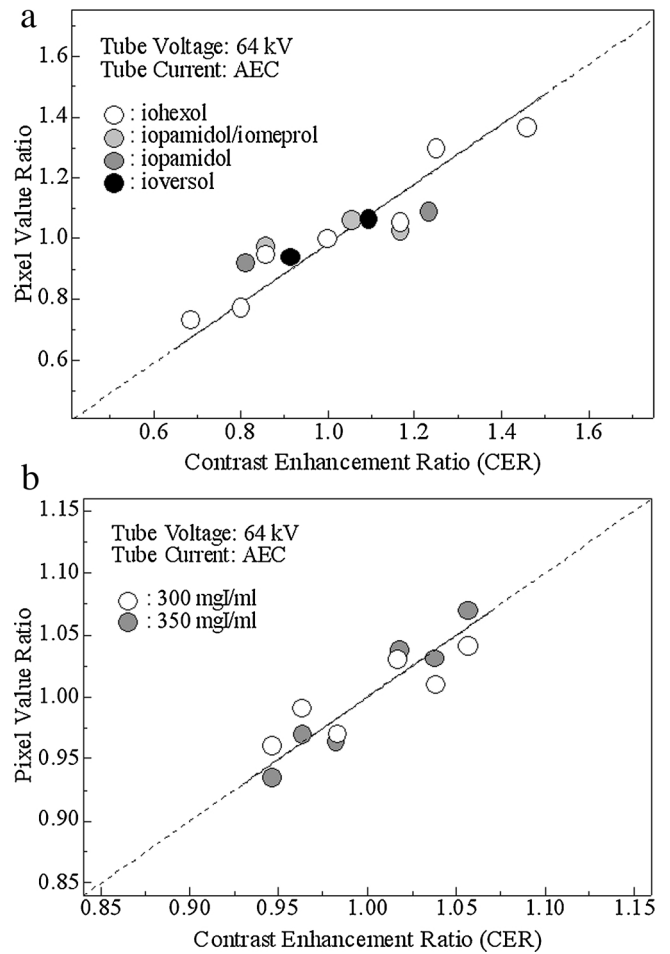


Fig. 3. Relationship between contrast enhancement ratio (CER) and pixel value ratio. (a) Iodine content dependence of contrast enhancement efficacy and (b) Molecular structure dependence of contrast enhancement efficacy. In (a), iodine contents were changed under same molecular weight (i.e., molecular weight of 777 (iopamidol and iomeprol), 806 (ioversol), and 821 (iohexol)). In (b), molecular weights of contrast media were changed under same iodine contents (i.e., iodine concentration of 300 and 350 mg/ml).

to $\frac{\omega_A}{\omega_B} = 1$, there was also a strong linear correlation between CER and pixel value ratio, and the slope (m) of the estimated linear regression line between them and their Pearson’s correlation coefficient (r) were $m = 0.983$ and $r = 0.925$ (Fig. 3(a)). Furthermore, where confined to $\frac{\rho_{IA}^A}{\rho_{IB}^A} = 1$, the pixel value ratio showed also a strong linear correlation with CER, and the slope (m) of the estimated linear regression line between them and their Pearson’s correlation coefficient (r) were $m = 1.000$ and $r = 0.920$ (Fig. 3(b)).

4. Discussions

We have investigated the intrinsic contrast enhancement ability of iodinated contrast media in DSA images on the basis of their X-ray absorption characteristics and derived a new formula (CER) of predicting the pixel value ratio of two different contrast medium solutions. This study showed that CER agreed well with the pixel value ratio for blood vessel filled with the six contrast media and had a good accuracy. These results indicate that vascular enhancement in DSA images is governed by the X-ray absorption characteristics of iodinated contrast media. Furthermore, as shown in Fig. 3, CER overturns the generally accepted opinion that contrast enhancement efficacy will increase in proportion to iodine contents, because the pixel value ratio is not 1 when $\frac{\rho_{IA}^A}{\rho_{IB}^A} = 1$, whereas CER supports this opinion when $\frac{\omega_A}{\omega_B} = 1$. This

also supports that the molecular structure of non-ionic iodinated contrast medium is a factor affecting contrast enhancement in DAS images. Thus, CER is expected to be very useful when comparing the contrast enhancement efficacy of two different iodinated contrast media in DAS images.

In evaluation of contrast enhancement of iodinated contrast media by using the weight factor ratio ($\frac{\omega_{IA}}{\omega_{IB}}$), iodixanol, iopamidol, and iomeprol will have the same ability of contrast enhancement in vascular DSA images. Iodixanol is a non-ionic dimeric contrast medium with an osmolality similar to human plasma, whereas iopamidol and iomeprol are non-ionic monomeric contrast media with higher osmolality than human plasma. Because of the iso-osmolality, iodixanol will suffer less from plasma dilution than iopamidol and iomeprol [20]. Thus, the contrast enhancement reduction caused by plasma dilution will be smaller for iodixanol than iopamidol and iomeprol. Since iodixanol has a larger molecular weight than iopamidol and iomeprol, the leak to interstitium will be also smaller for iodixanol than iopamidol and iomeprol [13,21]. In addition, Justesen et al. have confirmed the benefit of reducing injection-related pain for iodixanol [22]. Thus, iodixanol can suppress the degradation of vascular images that is attributed to motion artifacts [21]. Totally, iodixanol can be considered to have higher contrast enhancement efficacy in DSA images than iopamidol and iomeprol, whereas the weight factor ratio implies that these three iodinated contrast media have the same contrast enhancement ability. Here, the iodine concentrations of commercially available iodixanol are 270 and 320 mgI/ml and relatively low compared with iopamidol and iomeprol. Therefore, iodixanol with higher iodine concentrations is highly expected to be developed.

From the weight factor ratio, iohexol will be the lowest in the contrast enhancement ability in DSA images among the six contrast media. However, iohexol has a benefit of relatively low osmolality, compared with the other non-ionic monomeric contrast media. The osmolality of non-ionic materials decreases with the increase of molecular weight. Indeed, the molecular weight of commercially available iohexol is 821 and higher than any other non-ionic monomeric contrast media (777 for iopamidol and iomeprol, 791 for iopromide, and 806 for ioversol). In these non-ionic monomeric contrast media, three iodine atoms are embedded in the molecule (i.e., triiodobenzene). Therefore, as indicated by the weight factor, the absorption of X-ray photons by iodine does not take place effectively in iohexol, because the characteristic groups which are contributed to the reduction in osmolality, such as hydroxyl group, amino group, and methyl group, occupy a larger portion in iohexol compared with the other non-ionic monomeric contrast media. The difference in contrast enhancement ability between iohexol and iodixanol can be also explained for the same reason. That is, although the molecular weight of iodixanol is larger than that of iohexol, six iodine atoms are contained in iodixanol because of dimeric structure with two triiodobenzenes. From these discussions, one must bear in mind that the molecular structure of non-ionic iodinated contrast medium also has a great effect on contrast enhancement in DSA as well as the effect of plasma dilution and leak to interstitium.

As motioned above, our derived formula of contrast enhancement efficacy is formed by the following two terms: weight factor and iodine content ratios. So, when a new contrast medium is developed, the difference in contrast enhancement efficacy between new and existing contrast media will be able to be predicted by this formula. Therefore, our derived formula would be also useful for the development of new contrast media.

There are some limitations in this study. The difference in contrast enhancement between two different iodinated contrast media was investigated using the anthropomorphic phantom. Therefore, the influence of plasma dilution and leak to interstitium on the contrast enhancement efficacy was not taken into account in this study. However, as mentioned above, CER is a physical index which shows the difference in contrast enhancement ability between two different iodinated

contrast media. If CER is not in agreement with pixel value ratio for clinical DSA images, the difference between them can be considered to reflect the physiological effects such as plasma dilution. In this context, our derived formula can be theoretically applied to evaluation of contrast enhancement for not only DSA images but also CTA images, and the influence of plasma dilution and leak to interstitium on the contrast enhancement efficacy may be investigated in CTA images and deserves future analysis. Furthermore, except for iodine content, molecular structure, plasma dilution, and leak to interstitium, flow rate of contrast media in blood vessel affects contrast enhancement in DSA images. Particularly, the viscosity of non-ionic iodinated contrast media can be considered to play an important role in contrast enhancement efficacy because it is in inverse proportion to flow rate. However, the relationship between contrast enhancement efficacy and viscosity of non-ionic contrast media was not investigated in this study and this is a future work.

In conclusion, we have derived a new formula (CER) of predicting the pixel value ratio of two different contrast medium solutions, and shown that CER agreed well with the pixel value ratio for blood vessel filled with the six contrast media. Through this study, we have shown that the contrast enhancement in DSA images is affected by the molecular structure of non-ionic iodinated contrast medium.

Conflict of interest

All authors do not have any conflicts of interest, except for a Grant-in-Aid for Scientific Research (C) (JSPS KAKENHI Grant Number 18K12129).

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