RADIOLOGY OPEN

ELSEVIER

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

Kuniharu Imai[a],[*], Mitsuru Ikeda[a], Yoshiki Satoh[a], Keisuke Fujii[a], Chiyo Kawaura[a], Takuya Nishimoto[b], Masaki Mori[b]

[a] *Department of Radiological and Medical Laboratory Sciences, Nagoya University Graduate School of Medicine, 1-20 Daikominami 1-chome, Higashi-ku, Nagoya, 461-8673, Japan*
[b] *Division of Radiological Technology, Nagoya University Hospital, 65 Tsurumai, Showa-ku, Nagoya, 466-8560, Japan*

ARTICLE INFO

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 H_2O) [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

---

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; Eizai, 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:

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

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

$$\omega_H = \frac{2 \times [H]}{[H_2O]} = \frac{2}{18} \tag{2}$$

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

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

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,

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

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

$$\int \mu(E)S(E)dE \tag{5}$$

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