

## Evaluation of Visibility of Celiac and Renal Arteries on Digital Subtraction Angiography Using Iodine, Gadolinium and Carbon dioxide Contrast Agents: A Porcine Experimental Study

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**Purpose:** To examine the differences in visibility of celiac, renal arteries and nephrogram on digital subtraction angiography (DSA) among 3 different contrast agents in a porcine model.

**Methods:** Six swine underwent percutaneous catheterization and DSA. Celiac and bilateral renal DSA angiograms with iodine, gadolinium and CO<sub>2</sub> were obtained by the same injection protocols for each swine. The arterial diameter, contrast enhancement and renal density were measured using the Image-J software. Assessment of visual quality of iodine, gadolinium and CO<sub>2</sub> images was done by 3 observers using a four-point grading scale. The Wilcoxon test was used to analyze among 3 contrast agents.

**Results:** The diameters of the main celiac/renal arteries were the largest on iodine-DSA ( $4.60 \pm 0.65$  mm/ $5.08 \pm 0.77$  mm), and larger on gadolinium-DSA ( $4.26 \pm 0.54$  mm/ $4.76 \pm 0.71$  mm) than CO<sub>2</sub>-DSA ( $3.33 \pm 0.37$  mm/ $3.48 \pm 0.77$  mm). The arterial enhancement of the main celiac/renal arteries was the highest on iodine-DSA ( $332 \pm 59/353 \pm 68$ ) and higher on gadolinium-DSA ( $113 \pm 21/122 \pm 31$ ) than CO<sub>2</sub>-DSA ( $39 \pm 14/37 \pm 14$ ). The nephrogram was denser on iodine-DSA ( $139 \pm 13$ ) than gadolinium-DSA ( $29 \pm 5$ ). Although visual quality was diagnostic on all DSA, iodine-DSA (mean celiac renal artery scores: 1.27 and 1.33) was the best, and gadolinium-DSA (mean celiac and renal artery scores: 1.83 and 1.71) was better than CO<sub>2</sub>-DSA (mean celiac and renal artery scores: 2.88 and 2.95). These differences were all significant ( $P < 0.05$ ).

**Conclusion:** Although gadolinium and CO<sub>2</sub> can be used as an alternative to iodine, the differences in image quality among them should be kept in mind when the diameters of visceral arteries, enhancement and nephrogram are assessed for diagnosis and therapeutic intervention.

**Key Words:** Digital subtraction angiography, Iodine, Gadolinium, Carbon dioxide

## Introduction

Iodine -enhanced digital subtraction angiography (DSA) is used clinically for angiographic examinations or endovascular therapies. Carbon dioxide (CO<sub>2</sub>) has been also used for DSA to reduce the iodine dosage<sup>1)</sup>, avoid allergy or renal failure<sup>2,3)</sup> and visualize the portal venous system from a peripheral segmental hepatic artery<sup>4)</sup>. Meanwhile, gadolinium diethylenetriaminepentaacetic acid (DTPA) for magnetic resonance imaging (MRI) was found to have a potential as an contrast agent for X-ray computed tomography (CT)<sup>5,6)</sup> and gadolinium based contrast agents have been also used for angiography as an alternative to iodine contrast medium<sup>7-14)</sup>. However, most of them were about clinical studies which compared two contrast agents and to our knowledge, only one animal study compared these 3 different contrast agents about the quality of DSA to assess renal artery stenosis in rabbits<sup>15)</sup>.

The aim of this study was to examine the differences in visibility of renal and celiac arteries and nephrogram on DSA among 3 iodine, gadolinium and CO<sub>2</sub> agents by an animal experimental study.

## Materials and Methods

This study was performed after approval by the Institutional Animal Experimental Committee. All animals used for this study received care according to the "Guide for the Care and Use of Laboratory Animals (1985)" prepared by the US Department of Health and Human Services and published by National Institutes of Health. The study was approved by the Institutional Animal Care and Use Committee (IACUC) of the Nationwide Children's Hospital with strict adherence to the IACUC guidelines regarding humane use of animals. Six female swine (average 32.85 kg: 31 – 34 kg) were used in this study. To achieve the relief of agony relating with all procedures, general anesthesia was used during all procedures. Animals were placed supine and then general anesthesia was performed with an intramuscular injection of mixing of ketamine hydrochloride (5 mg/kg Ketalar Intramuscular 500 mg; Daiichi Sankyo, Tokyo, Japan) and medetomidine chloride (80µg/kg Domitor; Zenoaq, Fukushima, Japan) and maintained with administration of halothane (4% Fluothane; Takeda Pharmaceutical, Osaka, Japan) using a mask. After anesthetic administration, an endotracheal tube was inserted and anesthesia was maintained with halothane (1.5%), nitrous oxide (1.5 l/min), and oxygen (1.5 l/min) through the tube.

Electrocardiography was used to monitor the heart rate and rhythm. Oxygen saturation and real-time blood pressure were monitored using a pulse oxymeter (BP-608V; OmronColin, Tokyo, Japan).

A 7 or 6 F vascular sheath was inserted into the femoral or carotid artery. A 4F vascular diagnostic catheter (C2 catheter, Medikit, Tokyo, Japan, outsidiameter :1.33mm, inside diameter: 1.05mm) was inserted into the celiac artery or the bilateral renal arteries. A subtraction angiography system (Allura Xper FD20, Philips, Eindhoven, Holland) was used to perform the procedure and antibiotics were administered continuously throughout this study. Celiac and renal artery DSA (80kV, 4 ~ 6mAs) was performed using a mechanical power injector. Both iodine (iodine concentration: 300 mg/ml, Iopamidol 300, Oypalomin 300, Konica Minolta, Tokyo, Japan) and gadolinium (gadolinium concentration:78.5 mg/ml, Omniscan, Gadodiamide hydrate, Daiichisankyo, Tokyo, Japan) were injected by the same injection volume and rate : total 8 ml and 4 ml/sec for the celiac artery and total 6 ml and 3 ml/sec for the renal artery. CO<sub>2</sub>-DSA was performed with forceful hand injection of 20 ml of CO<sub>2</sub> for the celiac and renal arteries. CO<sub>2</sub> gas was taken out from a gas cylinder.

## Measurements of arterial diameter and contrast enhancement (Figures 1-3)

A commercially available software (Image-J: public domain, Java-based image processing program developed at the National Institutes of Health, USA) was used to measure the diameter and contrast enhancement of the celiac and renal arteries on DSA obtained with 3 contrast agents. A circular region of interest (ROI) was put within the target artery and measured the mean pixel value and detected the most enhanced phase on iodine-DSA (Fig.1). Then, a straight line was drawn across the center of the circular ROI on the most enhanced phase to measure the arterial diameter and contrast enhancement (Fig.1). As the original pixel values were expressed inversely proportion to the value on the original density profile curve, i.e., the higher the value was, the lower its pixel value was (Fig. 2), we obtained the modified profile curve by plotting the each modified pixel value (maximum pixel value – each pixel value on the original profile curve). We defined the arterial diameter as the length at the half density of the maximum modified pixel value and the contrast enhancement of the artery as the difference between the

Figure 1

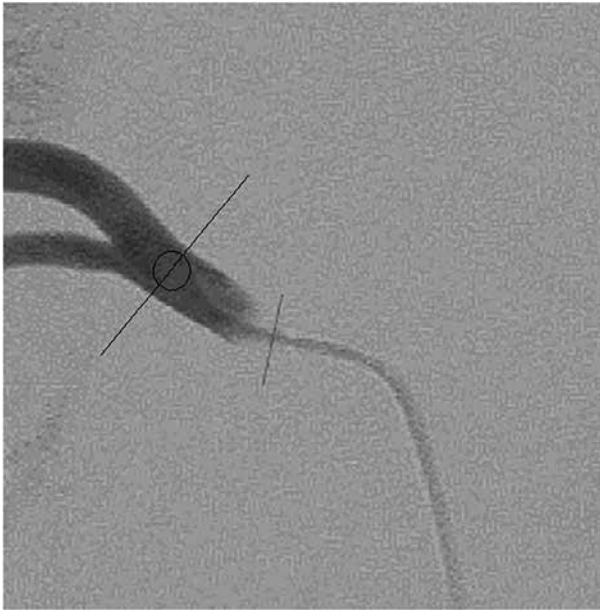


Figure 1: Methods to measure the arterial diameter and contrast enhancement

A circular region of interest (ROI) was put on the target vessel to detect the most enhanced phase (circle) on an iodine-DSA image. Then, a straight line was put at the center of the circular ROI perpendicularly to the long axis of the vessel (long line). The diameter of visible 4F vascular catheter near the target vessel was also measured (short line) to calibrate the vessel diameter. In this case, the diameter of the catheter was 1.98 mm and the true inside diameter was 1.05 mm. Thus the calibration factor was 0.53 (1.05/1.98) for the measured vessel diameter.

Figure 2

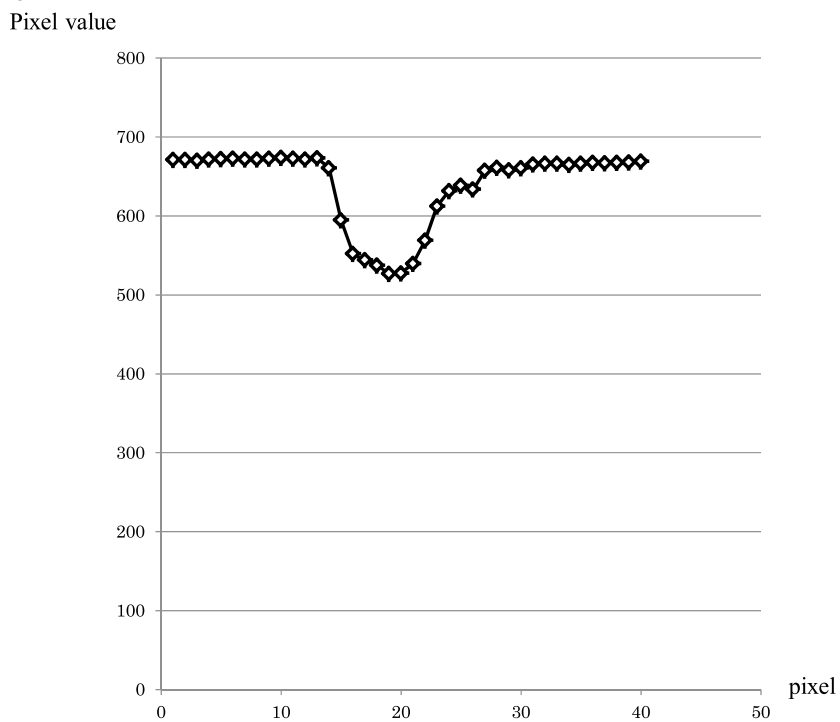


Figure 2: An example of the original pixel value profile curve of the line put on the vessel obtained by Image-J. When concentration becomes denser, the pixel value decreases. The distance (mm) between pixels on the horizontal axis is determined by using the calibration factor for each vessel.

Figure 3  
Modified pixel value

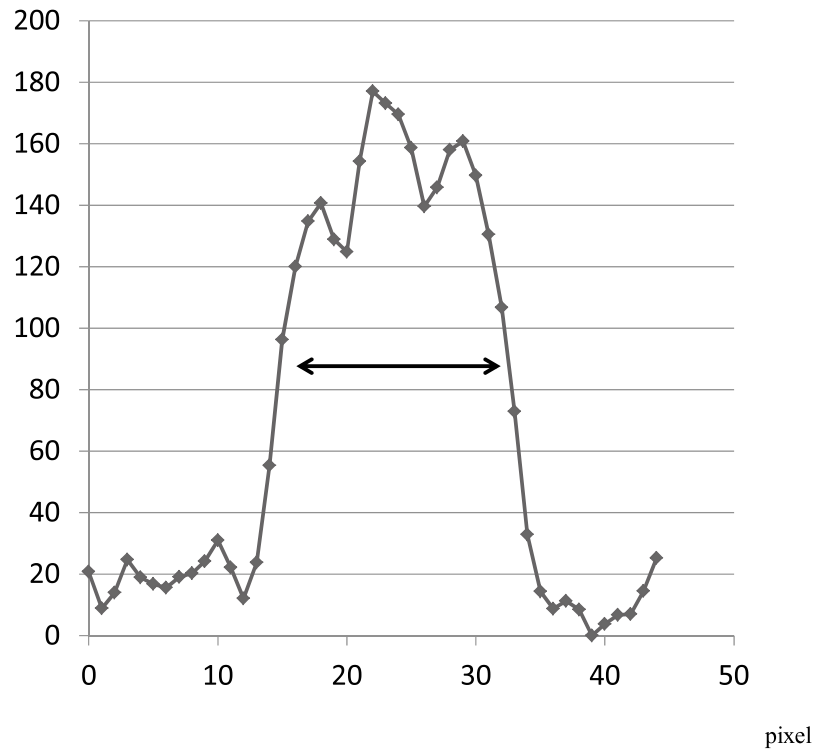


Figure 3: The modified pixel value profile curve of Fig.1.

The arterial diameter is defined as the length at the half density of the maximum modified pixel value (two way arrow) from this curve.

maximum and minimum pixel values (Fig.3). An arterial diameter was measured five times and the averaged diameter was used as the arterial diameter on each contrast agent DSA image. The diameter of the iodine visible 4F vascular catheter near the target artery was also measured 5 times and its averaged value was used to calibrate the arterial diameter. The inside diameter of the 4F vascular catheter was 1.05 mm. Thus the calibration factor was 1.05 mm/ the measured iodine catheter diameter. This factor was used to calibrate the diameters of arteries obtained by iodine-, gadolinium- and CO<sub>2</sub>-DSA. The diameter of the iodine-DSA artery was used as a standard to obtain the relative percentage of the arterial diameter on the gadolinium- and CO<sub>2</sub>-DSA images.

#### The density of Nephrogram

The density of the nephrogram was measured by setting manually a ROI which surrounded the entire nephrogram on iodine- and gadolinium-DSA images (Fig.4). The density of the nephrogram was obtained as follows: the maximum pixel value - the minimum pixel value.

#### Visual image quality assessment

The visual quality of celiac and renal arteries was evaluated by 3 radiologists (Y.B., S.H., S.I.) in consensus using the following four-point grading scale (16): 1, complete contrast agent filling with clear delineation of small vessels; 2, complete contrast agent and clear anatomic detail, but

Figure 4



Figure 4: An example of an ROI for the nephrogram. The nephrogram density was also measured by the ROI which enclosed the kidney.

moderately reduced contrast and/or reduced anatomic detail; 3, circumscribed filling defects and/or reduced contrast and/or reduced anatomic detail with still-unaffected diagnostic image quality; 4, nondiagnostic because of multiple or large filling defect and /or markedly reduced contrast with global deterioration in image quality.

**Statistical analysis**

The value was expressed as mean ± standard deviation (SD). The Wilcoxon signed-rank test was used to analyze

the differences in the arterial diameter and enhancement, nephrogram and visual assessment among 3 contrast agents with Statview-J 5.0 software (SAS Institute, Cary, NC) software packages. A two-tailed P value<0.05 was considered significant.

**Results**

The celiac arterial diameter and contrast enhancement among iodine-, gadolinium- and CO2-DSA are summarized in Table 1. The diameter of the main celiac artery was significantly larger on iodine-DSA than gadolinium-DSA (P=0.0273) and CO2-DSA (P=0.0277), and on gadolinium-DSA than CO2-DSA (P=0.0277). The arterial enhancement was significantly higher on iodine-DSA than gadolinium-DSA (P=0.0277) and CO2-DSA (P=0.023) and gadolinium-DSA than CO2-DSA (P=0.0277). The renal arterial diameter, contrast enhancement and nephrogram among iodine-, gadolinium- and CO2-DSA are summerized in Table 2. The diameter of the renal artery was significantly larger on iodine-DSA than gadolinium-DSA (P=0.0051) and CO2-DSA (P=0.0033) and on gadolinium-DSA than CO2-DSA (P=0.0033).The arterial enhancement was significantly higher on iodine-DSA than gadolinium-DSA (P=0.0033) and CO2-DSA (P=0.0033) and on gadolinium-DSA than CO2-DSA (P=0.0033). The nephrogram was significantly denser on iodine-DSA than gadolinium-DSA (P=0.001) (Figure 5).

The results of visual image quality assessment are listed in Table 3. Iodine- DSA was significantly superior to gadolinium-DSA (celiac artery; P=0.0077, renal artery, P=0.0047 ) and CO2-DSA (celiac artery; P=0.0003, renal artery; P<0.0001) (Figs.6 and 7). Gadolinium-DSA was significantly superior to CO2-DSA (celiac artery; P=0.0007, renal artery; P=0.0001).

Table 1. Real and relative diameters and contrast enhancement of the celiac artery (N=6) on DSA

Contrast agent	Real diameter	Relative diameter*	Contrast enhancement
Iodine	4.60 ± 0.65mm	100%	332 ± 59
Gadolinium	4.26 ± 0.54mm	92.6 ± 11.7	113 ± 21
CO2	3.33 ± 0.37mm	72.3 ± 8.0%	39 ± 14

Note) mean ± SD, \*Contrast agent diameter/ iodine diameter  
 P values for a-f were as follows; a: 0.0273, b: 0.0277, c: 0.0277, d: 0.0277, e: 0.0277 and f: 0.0273

Table 2. Real and relative diameters and contrast enhancement of the renal artery (N=12) and nephrogram (N=12) density on DSA

Contrast agent	Real diameter	Relative diameter*	Contrast enhancement	Nephrogram density
Iodine	5.08 ± 0.77mm	100 %	353 ± 68	139 ± 13
Gadolinium	4.76 ± 0.71mm	93.7 ± 6.6 %	122 ± 31	29 ± 5
CO2	3.48 ± 0.77mm	68.5 ± 5.2%	37 ± 14	

Note) Mean ± SD, \*Contrast agent diameter/ iodine diameter

P values for a-g were as follows; a: 0.0051, b: 0.0033, c: 0.0033, d: 0.0033, e: 0.0033, f: 0.0033 and g:0.001

Figure 5a

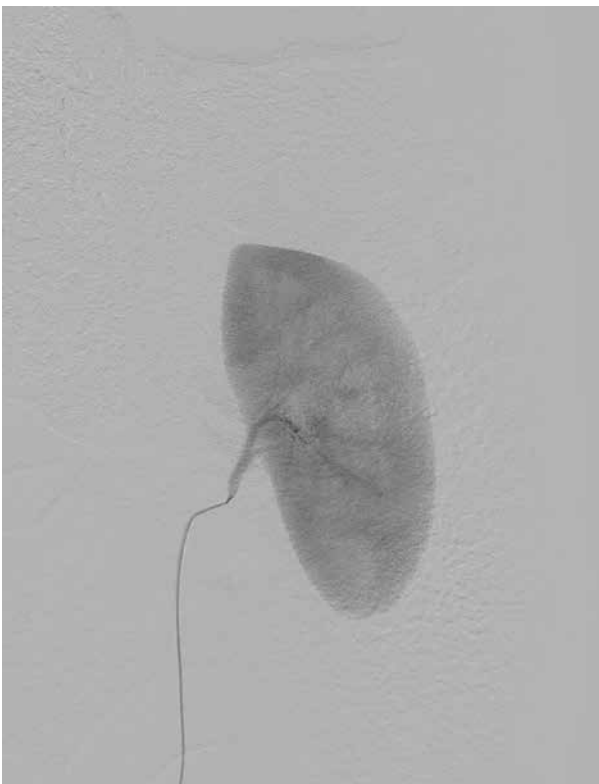


Figure 5b

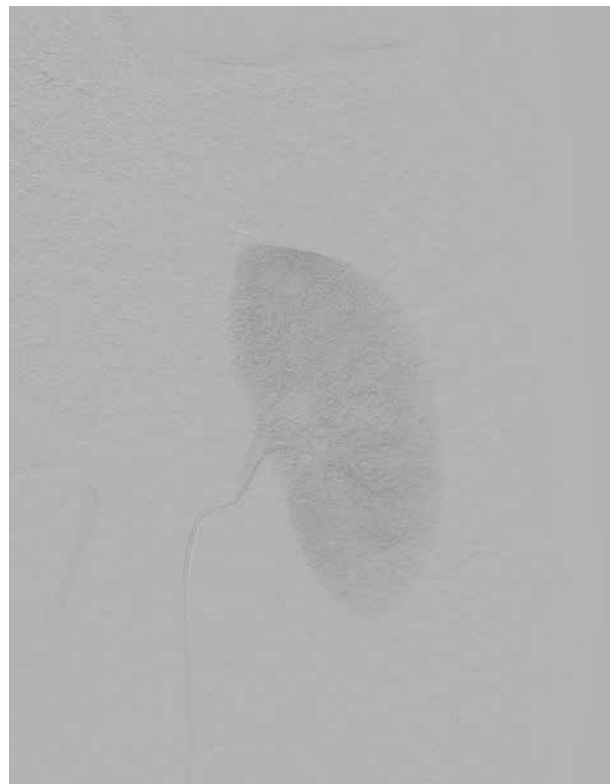


Figure5. Examples of left renal nephrograms on iodine- and gadolinium-DSA.

The left renal nephrogram density was 139 on iodine-DSA (a) and 35 on gadolinium-DSA (b) in this case.

Figure 6a



Figure 6b



Figure 6c



Figure 6. Celiac arteriograms on iodine- (a), gadolinium- (b) and CO<sub>2</sub>- (c) DSA in a swine. The average visual score was 1.33 (a), 2 (b) and 3.3 (c) in this case.

Figure 7a



Figure 7b

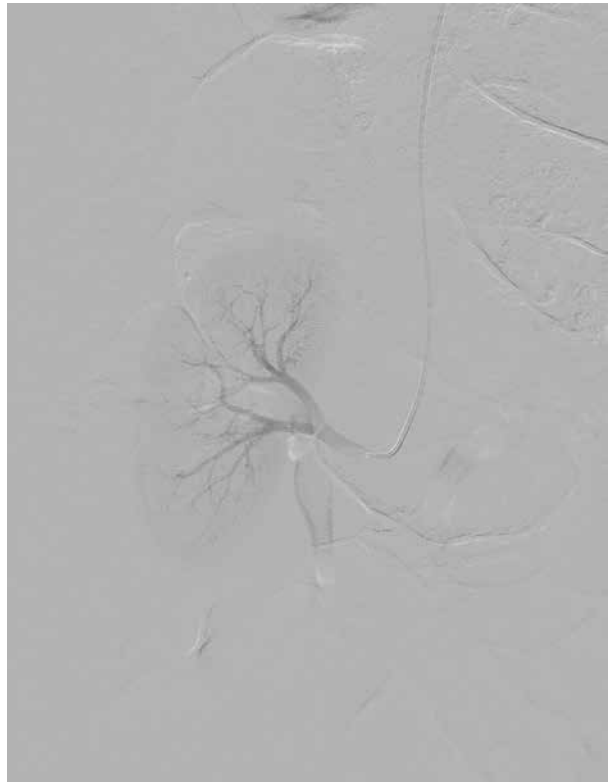


Figure 7c

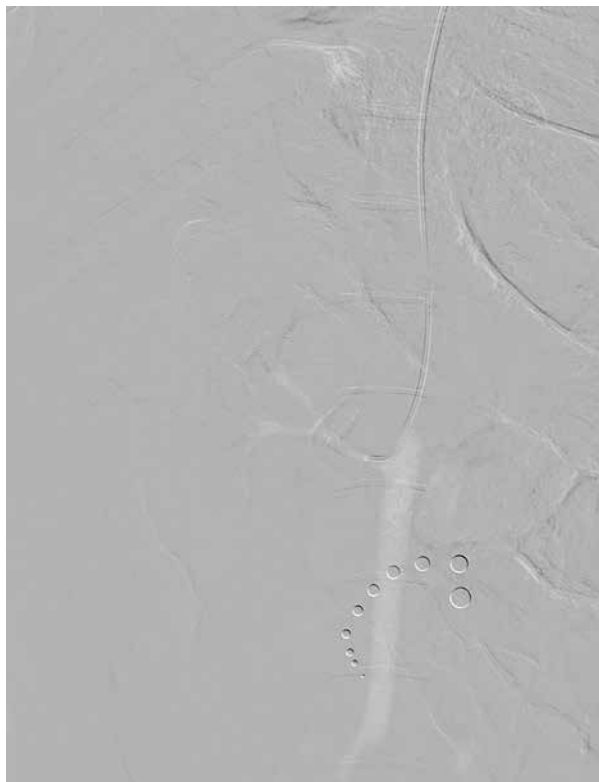


Figure 7. Renal arteriograms on iodine- (a) , gadolinium- (b) and CO<sub>2</sub>- (c) DSA. The average visual score was 1 (a), 2 (b) and 2.7 (c) in this case.



## Discussion

Dosage of contrast agents used in our study was almost the same as that used in the ordinal clinical practice<sup>4, 9, 10</sup>. Meanwhile, a larger dosage (100 ml) of CO<sub>2</sub> was used previously in the previous porcine model study because it was injected into a larger vessel, abdominal aorta<sup>16</sup>. Therefore, to our knowledge, this is the first report of animal experimental study using a smaller dose of CO<sub>2</sub> (< 20 ml) in the same condition as selective visceral arteriography is performed in human.

In our study, analysis of arterial diameter and enhancement was performed using the software of Image-J. We defined the vessel diameter as the length at the half density of the maximum modified pixel value and the contrast enhancement of the vessel as the difference between the maximum pixel value and the minimum pixel value. Fischer et al. measured meningeal blood vessel diameter of rats with the software of image-J and estimated the vessel diameter by a full width at half-maximum algorithm like ours<sup>17</sup>. Harden et al. reported a method of measuring of vessel diameter using a solder pointed guide wire on DSA<sup>18</sup>. For example, the measured aortic diameter was 13 mm above the stenosis and the measured distance between 2 solder points of the guide wire was 24 mm which was 22 mm in actual distance. Thus the estimated actual diameter was 12 (13 x 22/24) mm. In our study, the inside diameter of the 4F vascular catheter filled with iodine near the target vessel was used as the standard for calibration of the measured vessel diameter on iodine-, gadolinium- and CO<sub>2</sub>-DSA. This could eliminate nearly completely the effect of difference in each target artery position on magnification of each target artery. The inside diameter of the 4F vascular catheter was 1.05 mm. However, it was measured between 1.41 mm and 2.83 mm according to each target artery and the calibration factor ranged between 0.37 and 0.74 (average; 0.5), in other words, the magnification ranged between 1.34 and 2.70 (average; 2.0). Although the exact reasons are unknown, iodine concentration, the injection volume and rate, the angle of the catheter to the X-ray pathway might have affected on the catheter lumen.

Arterial enhancement on iodine-DSA was almost 3 times as dense as that on gadolinium-DSA in spite of the same injection volume and rate for both DSA in our study. Gierada et al.<sup>19</sup> compared between an iodinated contrast agent and a gadolinium contrast agent for CT attenuation in vitro study.

They revealed that 1mg/ml yield 28 HU for iodine and 38 HU for gadolinium. The concentration used in our study was 300 mg of iodine/ml and 78.5 mg of gadolinium/ml, respectively. Thus the iodine contrast agent would have a concentration 2.82 (28 x 300/ 38 x 78.5) times as dense as that of the gadolinium concentration. Le Blanch et al.<sup>15</sup> injected iodixanol at the concentration of 320 mg/ml and Gd-DOTA which contains 90.62 mg of gadolinium oxide (78.6 mg of gadolinium)/ml with 2 ml and a flow rate of 2 ml/sec and measured the iodine/gadolinium density ratio in rabbit renal arteries by using a stenosis measurement software and reported the iodixanol contrast density was 3.5 times as dense as the gadolinium contrast density in rabbit renal arteries. The iodine/gadolinium density ratio was about 3 in our study. Thus our result was consistent with these previous ones.

The average diameters of the celiac and renal arteries were 93% and 94% on gadolinium- DSA and 72% and 69% on CO<sub>2</sub>-DSA when compared with those on iodine- DSA in our study. To our knowledge, no previous papers are available for direct quantitative comparison of relative arterial diameters among these 3 DSA images. McLennan et al.<sup>20</sup> reported that there was no significant difference in diameters of the aorta, iliac arteries between iodine and CO<sub>2</sub>-DSA angiograms in a porcine model. They injected an iodine contrast agent (300mg/ml) at a rate of 8 mL for a total of 16 ml and 35 ml of CO<sub>2</sub> into the juxtarenal aorta and measured the diameters directly on DSA films. Thus the vessel diameters may differ according to the used contrast agent, injection method, catheter position and measurement method. In addition, CO<sub>2</sub> has the characteristics of low viscosity and high diffusion compared with iodine contrast agent. Thus it may be difficult to fill the visceral arterial lumen with CO<sub>2</sub> to result in underestimation of arterial diameter compared with iodine.

In our visual assessment, image quality was rated to be the best for iodine- DSA, better for gadolinium-DSA and good for CO<sub>2</sub>-DSA. These results were similar to the previous rabbit study<sup>15</sup>, suggesting that gadolinium and CO<sub>2</sub> agents can be used as contrast agents clinically. However, it may be difficult to use CO<sub>2</sub>-DSA when precise assessment of vascular lumen is required to deploy the stent or coil for embolization. Meanwhile, gadolinium could be available to evaluate the assessment of vascular lumen. But we must pay attention to renal toxicity due to gadolinium contrast agent<sup>21</sup>.

There are some limitations in this study. At first, the number

of examined vessels were small. Second, CO<sub>2</sub>-DSA was performed by manual hand injection which could not ensure the constant injection rate. Third, although the inner diameter of a 4F catheter near each target vessel was used as the standard reference of diameter, it needs to prove the change in diameter between with and without each contrast agent with different injection protocols in future.

In conclusion, although gadolinium and CO<sub>2</sub> can be used as an alternative to iodine, the differences in image quality among them should be kept in mind when the diameter of visceral arteries, enhancement and nephrogram are assessed for diagnosis and therapeutic intervention.

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## 実験用豚を用いた3種の造影剤（ヨード、ガドリニウム、二酸化炭素）における腹腔・腎動脈血管造影（DSA: Digital Subtraction Angiography）の描出能の検討

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**目的:** 実験用豚を用い、血管造影法 (digital subtraction angiography (DSA)) における腹腔、腎動脈及び腎実質相の描出の違いを、3つの異なる造影剤間において評価することにある。

**方法:** 6匹の豚を用い、経皮的にカテーテルを挿入し、DSAを行った。腹腔、両側腎動脈造影がヨード造影剤 (Io)、ガドリニウム (Gd)、二酸化炭素 (CO<sub>2</sub>) をそれぞれの豚において同じ撮影条件にて行われた。動脈径、造影効果、腎実質濃度を Image-J software で測定した。Io, Gd, CO<sub>2</sub> の視覚的評価は3人の独立した評価者によって、4点評価測定にて行われた。Wilcoxon test を用いて3つの造影剤間の比較がなされた。

**結果:** 腹腔および腎動脈は Io-DSA にて最も大きく描出され ( $4.60 \pm 0.65$  mm/ $5.08 \pm 0.77$  mm), そして Gd-DSA ( $4.26 \pm 0.54$  mm/ $4.76 \pm 0.71$  mm) は CO<sub>2</sub>-DSA ( $3.33 \pm 0.37$  mm/ $3.48 \pm 0.77$  mm) より大きく描出された ( $P < 0.05$ )。腹腔及び腎動脈の造影効果は Io-DSA ( $332 \pm 59/353 \pm 68$ ) で最も高く、Gd-DSA ( $113 \pm 21/122 \pm 31$ ) は CO<sub>2</sub>-DSA ( $39 \pm 14/37 \pm 14$ ) より高かった ( $P < 0.05$ )。腎実質相は Io-DSA ( $139 \pm 13$ ) で Gd-DSA ( $29 \pm 5$ ) よりも濃度が高かった ( $P < 0.05$ )。視覚評価は3つの造影剤にて診断に値するものであったが、Io-DSA (平均スコア: 1.27 (腹腔)、1.33 (腎)) が一番スコアが低く (画質が良い)、Gd-DSA (平均スコア: 1.83 (腹腔)、1.71 (腎))、CO<sub>2</sub>-DSA (平均スコア: 2.88 (腹腔)、2.95 (腎)) の順であった ( $P < 0.05$ )。

**結語:** ガドリニウム、二酸化炭素はヨード造影剤に代わりうるものであるが、造影剤間の画像の質の違いを念頭に置いて動脈径、造影効果、腎実質相の評価を行うべきである。

