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# Efficacy of CO<sub>2</sub> Infusion for Preoperative Computed Tomographic Angiography with Computed Tomographic Colonography

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Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** Computed tomographic colonography (CTC) is useful for patients for whom colonoscopy may be difficult to perform and is widely employed to examine the vasculature prior to colorectal cancer surgery. Computed tomographic angiography (CTA) was shown to be beneficial intraoperatively to manipulate blood vessels and prevent vascular injury. Three-dimensional (3D)-CTA combined with CTC (3D-CTA with CTC) is useful for preoperative evaluations of the anatomy of mesenteric vessels, colon, and lymph nodes. We observed that when the intestine was dilated with carbon dioxide (CO<sub>2</sub>), the arteriovenous delineation was often more pronounced than without CO<sub>2</sub>. To clarify the effects of gas injection with and without CO<sub>2</sub> on hemodynamics and vascular passage, we compared the effect of contrast for blood vessels.

**Material/Methods:** Thirty patients with resectable colorectal cancer who underwent a preoperative CT examination at our institution from January to October 2019 were study participants. Of these, 15 underwent 3D-CTA and 15 had 3D-CTA with CTC. Three board-certified radiologists independently and blindly evaluated 18 blood vessels. CT values for each blood vessel were measured on each image.

**Results:** CT values for 3D-CTA with CTC were significantly higher with CO<sub>2</sub> than without CO<sub>2</sub>. The quality of 3D-CTA with CTC images for visualization of blood vessels was also significantly greater than that of 3D-CTA, especially those of arterial and intramesenteric venous systems.

**Conclusions:** Based on the higher image quality and CT values obtained by 3D-CTA with CTC for vessels, compared with by 3D-CTA imaging, 3D-CTA with CTC imaging might be useful in evaluating colorectal cancers.

**Keywords:** **Carbon Dioxide • Colonic Neoplasms • Colonography, Computed Tomographic**

**Abbreviations:** **CTC** – computed tomographic colonography; **CTA** – computed tomographic angiography; **ROI** – region of interest; **SMA** – superior mesenteric artery; **MCA** – middle colic artery; **RCA** – right colonic artery; **ICA** – ileocolic artery; **SIA** – small intestinal artery; **IMA** – inferior mesenteric artery; **LCA** – left colonic artery; **SA** – sigmoidal artery; **SRA** – superior rectal artery; **SMV** – superior mesenteric vein; **MCV** – middle colonic vein; **RCV** – right colonic vein; **ICV** – ileocolic vein; **IMV** – inferior mesenteric vein; **LCV** – left colonic vein; **SV** – sigmoidal vein; **SRV** – superior rectal vein; **kVp** – kilovolt peak; **SD** – standard deviation; **mA** – milliamperere; **HU** – Hounsfield unit; **BMI** – body mass index

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## Background

Computed tomographic colonography (CTC) is a diagnostic imaging technique in which carbon dioxide (CO<sub>2</sub>) is injected into the anus to inflate the intestinal tract, after which computed tomography (CT) is performed and three-dimensional (3D) image processing is performed at a workstation. CTC is highly accurate, with an accuracy very close to that of colonoscopy. Because of its superior performance, higher patient compliance, and lower dose exposure, CTC has completely replaced the barium enema [1]. CTC is useful for patients in whom colonoscopy is difficult owing to stenosis or post-surgical adhesions and whose positional relationship is difficult to grasp because of meandering of the intestinal tract; CTC also has advantages in the elderly because it is less invasive [2,3]. Identifying the mesenteric artery, venous anatomy, and lymph node structure using 3D computed tomographic angiography (3D-CTA) was reported to be useful not only for manipulating blood vessels, but also for preventing vascular injury during surgery [4,5,6]. In our hospital, we had previously obtained information on blood vessels by performing 3D-CTA before colorectal cancer surgery. Also, preoperative 3D-CTA combined with CTC (3D-CTA with CTC) is helpful to evaluate lesions within the intestinal tract as well as the anatomy of mesenteric vessels, colon, and lymph nodes.

We noticed that when the intestine was dilated by CO<sub>2</sub>, the arteriovenous delineation was often more pronounced than without CO<sub>2</sub>. High concentrations of CO<sub>2</sub> have been used for some time in European countries to treat a variety of diseases [7]. Its effect on cutaneous circulation depends primarily on vasodilatation [7]. It was shown that CO<sub>2</sub>-enriched water induces peripheral vasodilatation, which increases cutaneous blood flow [8,9]. The ability of CO<sub>2</sub> to improve blood flow in the brain was also suggested [10]. Based on these findings, we considered the effects of CO<sub>2</sub> infusion on the hemodynamics and vascular passages in CTC.

We hypothesized that CO<sub>2</sub> makes the blood vessels in the insufflated colon easier to delineate because of its high absorbability and vasodilatory properties. Through conducting a comparative study, we assessed differences in blood flow in the distended colon between 3D-CTA and 3D-CTA with CTC. We also examined the vasodilating effects of CO<sub>2</sub> in the distended colon.

## Material and Methods

### Patients

Study participants were 30 patients with resectable colorectal cancer who underwent preoperative CT examination at our institution from January to October 2019. All study patients had

operable colorectal cancer diagnosed at colonoscopy using tissue samples. **Table 1** shows the location, macroscopic type, and stage of tumors in the study patients. The macroscopic type was assessed based on the Japanese Classification of Gastric Cancer [11]. We excluded patients with contraindications for CTC because of risks of perforation of the large bowel [1]. Also excluded were those patients with contrast medium allergy, renal dysfunction, pregnancy, and underlying bowel diseases such as ulcerative colitis and Crohn's disease. In total, 15 patients underwent 3D-CTA and 15 patients underwent 3D-CTA with CTC, before which, surgery was performed.

### 3D-CTA

For the CT examination, we used a 320 multi-slice CT (Aquilion One Vision Edition, Canon Medical Systems Corporation, Tokyo, Japan). Scan parameters were as follows: tube voltage, 120 kilovolt peak (kVp); exposure milliampere (mA), automatic exposure control (standard deviation, 12); gantry rotation time, 0.5 ms; pitch factor, 1; and collimation, 1 mm. Simple CT and dynamic CT scans were performed with patients in the supine position, and the imaging range was from the diaphragm to the pubis. A 20-gauge or 22-gauge indwelling needle was inserted into the medial cubital vein. The amount of non-ionic iodine contrast agent (Iohexol 300 mgI/mL or Iopamidol 300 mgI/mL) was 600 mgI/kg/body weight, and the contrast agent's automatic injector (Dual Shot GX7, Nemoto Co., Tokyo, Japan.) was used for 30 to 35 s. The arterial phase was imaged using the bolus tracking method. The region of interest (ROI) was placed at the descending aortic level, the threshold was set at 150 Hounsfield units (HU), and the arterial phase was imaged 8 s after the threshold was reached. The portal phase was taken 20 s after the arterial phase, and the venous phase was taken 120 s after the start of infusion. Volume data on all phases obtained from the imaging were transferred to Ziostation2 (Ziosoft Inc., Tokyo, Japan). 3D-CTA images of the mesenteric artery, portal vein, and mesenteric vein were reconstructed from the volume data.

### 3D-CTA with CTC

On the day before the 3D-CTA with CTC, patients took 5 mg mosapride citrate hydrate tablets (Gasmotin®) 30 min before each meal and 24 mg Sennoside (Pursennid®) at 9: 00 PM. There were no dietary restrictions for breakfast and lunch the day before the examination, and dinner was completed by 8: 00 PM on the day before the examination. On the day of the examination, the patients drank polyethylene glycol with ascorbic acid solution (Moviprep®, EA Pharmaceuticals, Tokyo, Japan) at a rate of about 1 L/h from 8: 00 AM. After that, patients were prohibited from eating or drinking until after the examination. In addition, we did not use antispasmodics to suppress peristalsis of the intestinal tract and fecal tagging

**Table 1.** Demographic and clinical characteristics of the study population.

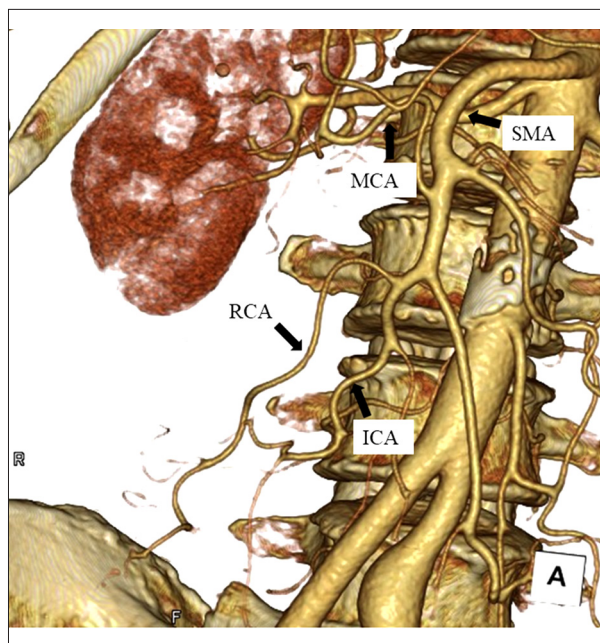
Characteristic	3D-CTA group (n=15)	3D-CTA with CTC group (n=15)
<b>Sex:</b> Male: Female	10: 5	11: 4
<b>Age [y]:</b> Mean±SD [range]	63.1±13.5[43-82]	64.6±13.9 [43-90]
<b>Height [cm]:</b> Mean±SD [range]	165.1±8.3 [149.2-180.7]	164.2±8.7 [149.3-176.0]
<b>Weight [kg]:</b> Mean±SD [range]	61.5±11.6 [36.0-80.1]	62.2±11.3 [36.7-76.0]
<b>BMI [kg/m<sup>2</sup>]:</b> Mean±SD [range]	22.5±3.5 [16.2-29.6]	23.0±3.8 [16.3-31.2]
<b>Tumor location, n (%)</b>		
Ascending colon	3 (20.0)	4 (26.7)
Transverse colon	0 (0.0)	1 (6.7)
Descending colon	0 (0.0)	0 (0.0)
Sigmoid colon	4 (26.7)	7 (46.7)
Rectum	8 (53.3)	3 (20.0)
<b>Macroscopic type, n (%)</b>		
Type 0: Superficial	2 (13.3)	4 (26.7)
Type 1: Raised mass	2 (13.3)	2 (13.3)
Type 2: Ulcer, localized	8 (53.3)	6 (40.0)
Type 3: Ulcer, infiltrated	1 (6.6)	1 (6.6)
Type 4: Diffuse infiltration	0 (0.0)	0 (0.0)
Type 5: Unclassifiable	0 (0.0)	0 (0.0)
Details unknown	2 (13.3)	2 (13.3)
<b>Stage, n (%)</b>		
I	4 (26.7)	8 (53.3)
II	4 (26.7)	1 (6.6)
III	3 (20.0)	2 (13.3)
IV	2 (13.3)	3 (20.0)
Details unknown	2 (13.3)	1 (6.6)

There were no significant differences in sex, age, height, weight, body mass index (BMI), and tumor location between the 3D-CTA and 3D-CTA with CTC groups. Age, height, weight, and BMI were analyzed at a significance level of 0.05 using the Mann-Whitney U test. Sex and tumor location were statistically analyzed at a significance level of 0.05 using Fisher's exact test. 3D-CTA – three-dimensional computed tomographic angiography; 3D-CTA with CTC – three-dimensional computed tomographic angiography with computed tomographic colonography; SD – standard deviation.

to distinguish residues from lesions. Patients who underwent 3D-CTA with CTC lay on the bed in the lateral decubitus position prior to CT imaging, and a flexible rubber catheter with an attachment for a CO<sub>2</sub> gas insufflator was inserted. Using a CO<sub>2</sub> gas supply device, intestinal dilation with CO<sub>2</sub> was performed, and a total of 1.5 to 2.0 L CO<sub>2</sub> gas was supplied to the patient. Then, a CT scan was performed with the patients in both supine and prone positions. Volume data for all phases of imaging were transferred to a Ziostation2. 3D-CTA with CTC images of the mesenteric artery, portal vein, and mesenteric vein were reconstructed from volume data.

### Image Evaluation and Analysis

Three board-certified radiologists evaluated the images taken with and without CO<sub>2</sub>. Delineative imaging quality was assessed for the following structures in the arterial phase: superior mesenteric artery (SMA), middle colic artery (MCA), right colonic artery (RCA), ileocolic artery (ICA), small intestinal artery (SIA), inferior mesenteric artery (IMA), left colonic artery (LCA), sigmoidal artery (SA), and superior rectal artery (SRA) (Figure 1). The following were assessed in the portal phase: the superior mesenteric vein (SMV), middle colonic vein (MCV), right colonic vein (RCV), ileocolic vein (ICV), inferior mesenteric vein (IMV), left colonic vein (LCV), sigmoidal vein (SV), and superior rectal vein (SRV) (Figure 2).

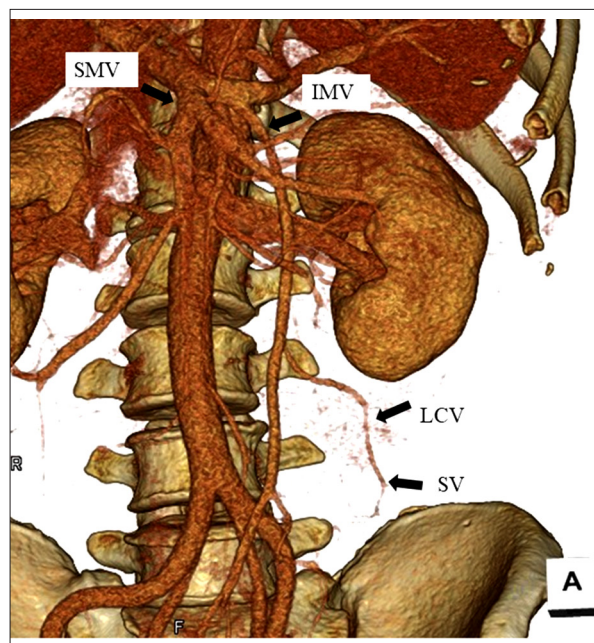


**Figure 1.** Visual evaluation of arterial blood vessels using three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC). 3D-CTA with CTC in a 63-year-old man with ascending colon cancer. Arrows indicate each vessel for image evaluations. The average CT values and average scores according to a 7-point scale from 0 to 6 in ascending order of visibility were as follows: superior mesenteric artery (SMA), CT value 418 Hounsfield unit [HU], 6 points; middle colic artery (MCA), 369.2 HU, 5 points; right colonic artery (RCA), 353.0 HU, 5 points; and ileocolic artery (ICA), 355.6 HU, 4.7 points.

The radiologists independently and blindly evaluated images using the window width. Window level settings were fixed left, and magnification and rotation were adjusted according to the personal preference of the radiologists. The CT value was assessed using 5 ROI for the delineation of the structures, and the average was calculated. Delineative quality was rated using a 7-point scale from 0 to 6, where the values represented the following: 0, blood vessels were not visually recognized; 1, about 1/3 of blood vessels were slightly visible; 2, about 1/3 of blood vessels were clearly visible; 3, about 2/3 of blood vessels were visible; 4, the peripheral side of the blood vessel was slightly visible; 5, the peripheral side of the blood vessel was clearly visible; and 6, the branch on the peripheral side of the blood vessel was clearly visible.

### Ethical Considerations

This study was reviewed and approved by the Juntendo University Hospital Ethics Committee (Institutional Review

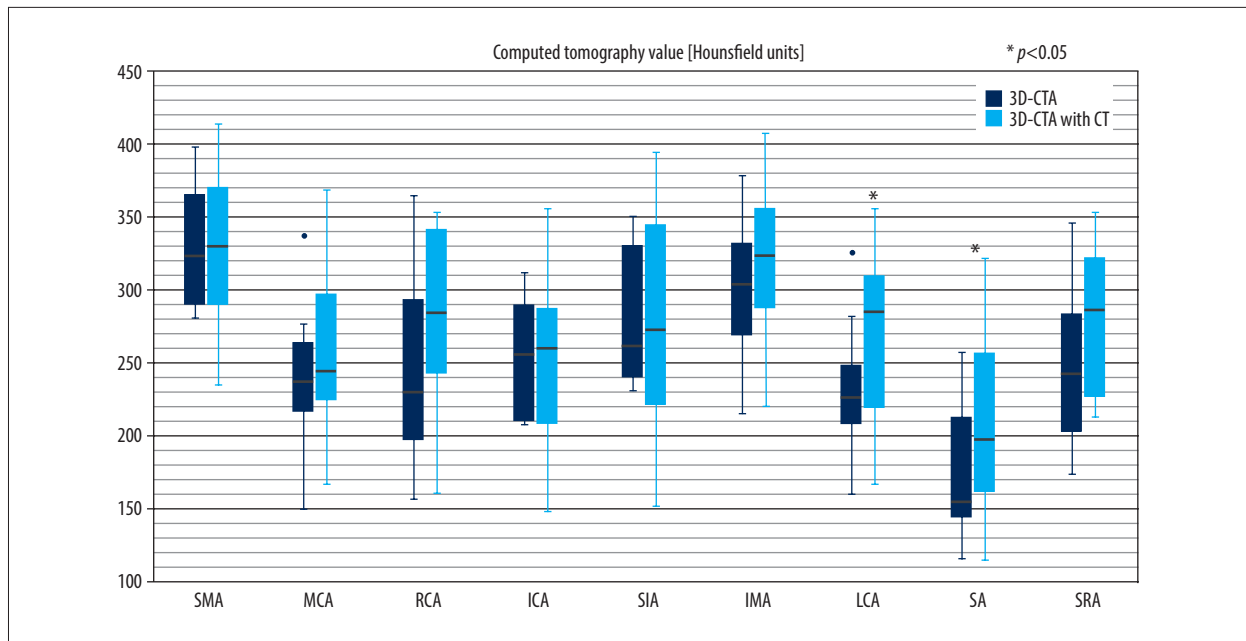


**Figure 2.** Visual evaluation of portal blood vessels by three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC). 3D-CTA with CTC in a 51-year-old man with sigmoid colon cancer. Arrows indicate vessels for image evaluations. The average CT values and average scores according to the 7-point scale from 0 to 6 according to visibility were, respectively, as follows: superior mesenteric vein (SMV), CT value 211.6 Hounsfield units [HU], 5.3 points; inferior mesenteric vein (IMV), 253.0 HU, 5.7 points; left colonic vein (LCV), 220.0 HU, 3.3 points; and sigmoidal vein (SV), 207.4 HU, 3.3 points.

Board No. 20-278). The principles of the Helsinki Declaration of 2013 were followed.

### Statistical Analysis

For statistical analysis, statistical software 'EZR' (Easy R, Ver. 1.33) was used. *P* values of <0.05 indicated a statistically significant difference. Statistical analysis was performed on averages of measured CT values and scores of the visual evaluation. The Shapiro-Wilk normality test was used to assess normal distribution for all continuous variables. A Mann-Whitney *U* test was used for statistical evaluation. For categorical data, we used Fisher's exact test because more than 20% of expected cells were found to be <5.



**Figure 3.** Values obtained by three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC) and 3D computed tomographic angiography (CTA) for the arterial phase. The average CT values for 3D-CTA with CTC were significantly superior to those with 3D-CTA in left colonic artery (LCA) (3D-CTA, 228.5±44.4 Hounsfield unit [HU]; 3D-CTA with CTC, 269.7±56.2 HU;  $P=0.045$ ) and sigmoidal artery (SA) (3D-CTA, 170.2±44.1 HU; 3D-CTA with CTC, 209.8±60.4 HU;  $P=0.034$ ). Statistical analyses were performed at a significance level of 0.05 by using the Mann-Whitney U test.

## Results

### Patient Characteristics

**Table 1** is a summary of patient characteristics. Patients were divided into 2 groups: 3D-CTA patients (10 men and 5 women; average age, 63.1±13.5 years; average height, 165.1±8.3 cm; average weight, 61.5±11.6 kg; average body mass index (BMI), 22.5±3.5 kg/m<sup>2</sup>) and 3D-CTA with CTC patients (11 men and 4 women; average age, 64.6±13.9 years; average height, 164.2±8.7 cm; average weight, 62.2±11.3 kg; average BMI, 23.0±3.8 kg/m<sup>2</sup>). There were no significant differences in age, sex, height, weight, BMI, and tumor location between the 2 groups.

### Image Evaluations

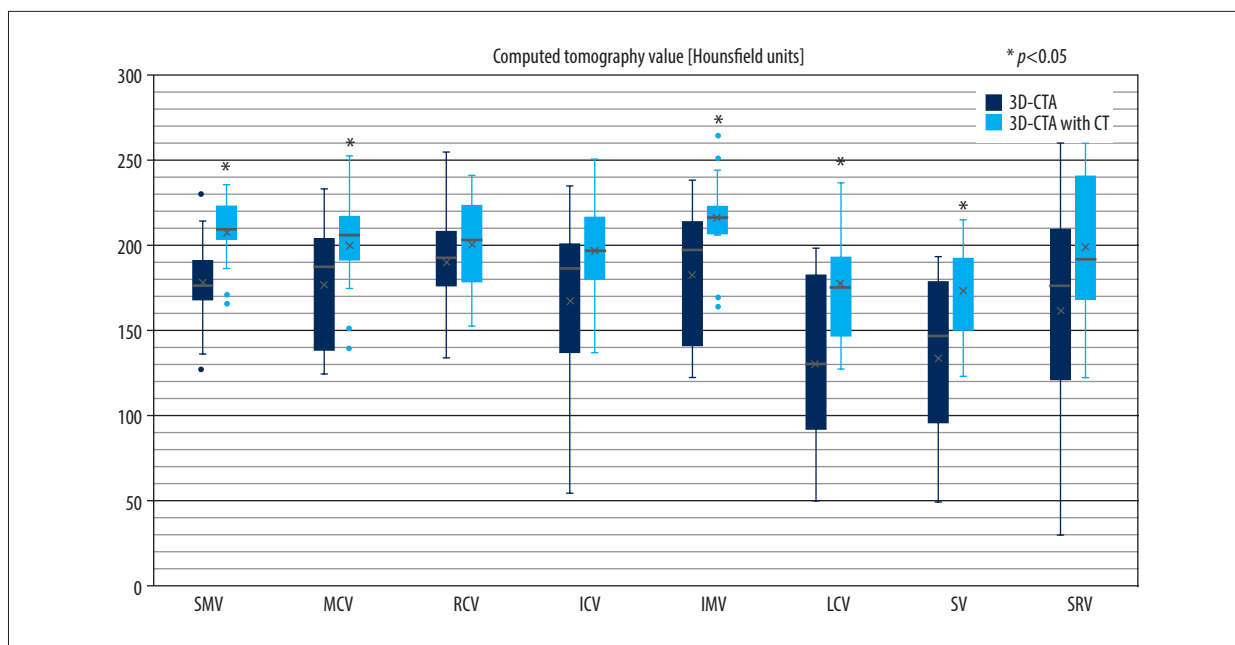
**Figure 3** summarizes the CT values for the arterial phase. CT values for the LCA and SA in the 3D-CTA with CTC group were significantly superior to those for the 3D-CTA group and were as follows in the 2 groups: LCA (3D-CTA, 228.5±44.4 HU; 3D-CTA with CTC, 269.7±56.2 HU;  $P=0.045$ ) and SA (3D-CTA, 170.2±44.1 HU; 3D-CTA with CTC, 209.8±60.4 HU;  $P=0.034$ ). **Figure 4** summarizes the CT values for the portal phase, which were significantly higher for 3D-CTA with CTC for the SMV (3D-CTA, 178.9±26.1 HU; 3D-CTA with CTC, 208.2±19.9 HU;  $P=0.003$ ), MCV (3D-CTA, 177.6±34.6 HU; 3D-CTA with CTC, 200.4±27.9

HU;  $P=0.036$ ); IMV (3D-CTA, 183.3±38.0 HU; 3D-CTA with CTC, 216.9±26.3 HU;  $P=0.019$ ), LCV (3D-CTA, 130.7±52.4 HU; 3D-CTA with CTC, 178.3±31.6 HU;  $P=0.024$ ), and SV (3D-CTA, 134.6±50.9 HU; 3D-CTA with CTC, 174.5±27.3 HU;  $P=0.046$ ).

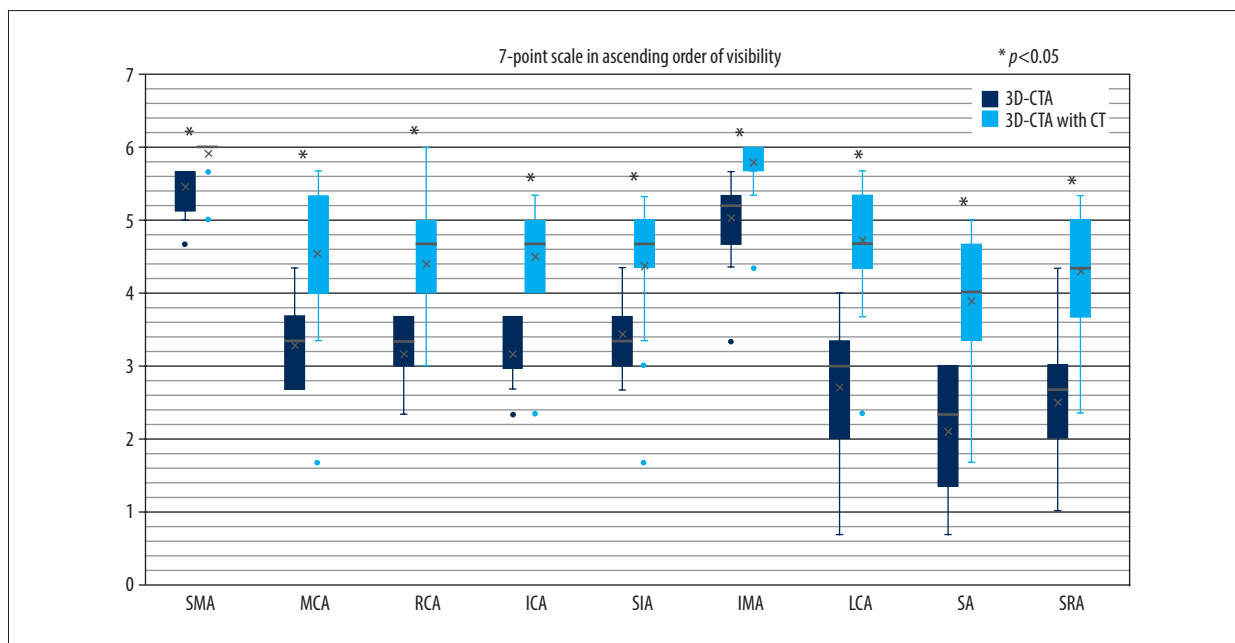
**Figure 5** summarizes evaluations of delineative quality of images of the arterial phase according to the 7-point scale. Image quality of 3D-CTA with CTC were significantly superior to that of 3D-CTA for all structures ( $P<0.001$ ). Quality of images according to the 7-point scale for the portal phase in the 3D-CTA with CTC group was significantly superior to that in the 3D-CTA group for the following structures: MCV ( $P=0.049$ ), ICV ( $P=0.049$ ), IMV ( $P=0.001$ ), LCV ( $P<0.001$ ), SV ( $P=0.003$ ), and SRV ( $P<0.001$ ) (**Figure 6**).

## Discussion

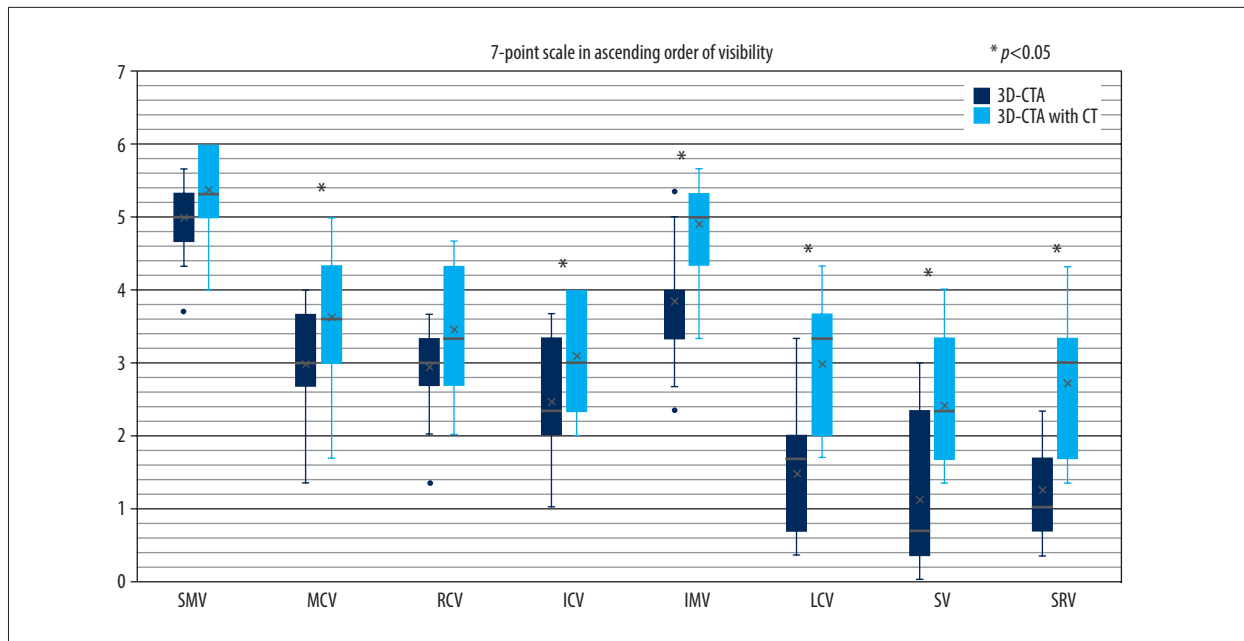
Our findings showed that CO<sub>2</sub> gas infusion in CTC improved peripheral vascular visualization. CO<sub>2</sub>-enriched water induces peripheral vasodilatation, which increases cutaneous blood flow [7,9]. Increases in blood flow of the mesenteric artery during intraluminal CO<sub>2</sub> insufflation into the canine colon were demonstrated by Brandt et al [12]. The exact mechanism and impact of CO<sub>2</sub> insufflation on colonic blood flow is not yet completely clear. There have been reports that the vasodilative



**Figure 4.** Values obtained by three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC) and 3D computed tomographic angiography (CTA) for the portal phase. The CT values according to 3D-CTA with CTC were significantly superior than those of 3D-CTA for the superior mesenteric vein (SMV) (3D-CTA, 178.9±26.1 Hounsfield unit [HU]; 3D-CTA with CTC, 208.2±19.9 HU;  $P=0.003$ ), middle colonic vein (MCV) (3D-CTA, 177.6±34.6 HU; 3D-CTA with CTC, 200.4±27.9 HU;  $P=0.036$ ), inferior mesenteric vein (IMV) (3D-CTA, 183.3±38.0 HU; 3D-CTA with CTC, 216.9±26.3 HU;  $P=0.019$ ), left colonic vein (LCV) (3D-CTA, 130.7±52.4 HU; 3D-CTA with CTC, 178.3±31.6 HU;  $P=0.024$ ), and sigmoidal vein (SV) (3D-CTA, 134.6±50.9 HU; 3D-CTA with CTC, 174.5±27.3 HU;  $P=0.046$ ). Statistical analyses were performed at a significance level of 0.05 by using the Mann-Whitney U test.



**Figure 5.** Evaluation of visibility according to 7-point scale in ascending order of visibility in the arterial phase. Scores obtained by three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC) indicated significantly superior image quality than those obtained by 3D computed tomographic angiography (CTA) for all structures ( $P<0.001$ ). Statistical analyses were performed at a significance level of 0.05 by using the Mann-Whitney U test



**Figure 6.** Evaluation of visibility according to 7-point scale in ascending order of visibility in the portal phase. Scores obtained by three-dimensional (3D) computed tomographic angiography with computed tomographic colonography (3D-CTA with CTC) indicated significantly superior image quality than those obtained by 3D-computed tomographic angiography (CTA) for the middle colonic vein (MCV),  $P=0.049$ ; ileocolic vein (ICV),  $P=0.049$ ; inferior mesenteric vein (IMV),  $P=0.001$ ; left colonic vein (LCV),  $P<0.001$ ; sigmoidal vein (SV),  $P=0.003$ ; and superior rectal vein (SRV),  $P<0.001$ . Statistical analyses were performed at a significance level of 0.05 by using the Mann-Whitney U test.

effect of CO<sub>2</sub> was due to nitric oxide (NO), the K<sup>+</sup> channel, the adenosine triphosphate (ATP)-sensitive K<sup>+</sup> channel of vascular smooth muscle cells, or heme oxygenases, which consist of the inducible isozyme heme oxygenase-1 and the constitutive enzyme heme oxygenase-2 [10,13,14]. Yasumasa et al [15] reported that CO<sub>2</sub> has vasodilative effects on colonic microvessels with insufflation at low pressure and that CO<sub>2</sub> has direct vasodilative activity in the rat colon. They also showed negligible systemic hemodynamic effects of CO<sub>2</sub> on heart rate, mean arterial pressure, and respiratory rate.

We hypothesized that the vasodilatory mechanism of the CO<sub>2</sub> that is used in CTC affects blood flow and would give a CT device the capability to show details at the vascular bifurcation level.

Regarding visual assessments, the CT value of 3D-CTA with CTC was higher than that without CTC for the LCA, SA, SMV, MCV, IMV, LCV, and SV. Results of the 7-point scale for delineative quality showed that delineation of all of the arterial systems and the MCV, ICV, IMV, LCV, SV, and SRV was better with than without CTC. This result indicated that there are marked differences between the image qualities of 3D-CTA and 3D-CTA with CTC, especially for the LCA, SA, MCV, IMV, LCV, and SV. Blood vessels that were particularly well visualized were in the inferior mesenteric arteriovenous system. These feed only the large intestine, so the blood vessels of the superior mesenteric arteriovenous system

branch into the spleen as well as the colon and the effect of CO<sub>2</sub> from the large intestine would be less than that of the inferior colonic arteriovenous system. In such cases, CO<sub>2</sub> could contribute to the promotion of venous perfusion. The significant depiction of the blood vessels feeding the left hemicolon showed that the intestinal dilatation due to CO<sub>2</sub> insertion began in the lower colon, making exposure to CO<sub>2</sub> longer than in the upper colon.

In treating colon cancer, a complete understanding of the vascular anatomy is crucial for swollen lymph node dissection and vascular resection. 3D-CTA with CTC was reported to be useful for understanding mesenteric arterial and venous anatomy, the colon, and swollen lymph nodes. This modality is helpful for not only manipulation of the tumor vasculature, but also to prevent intraoperative vascular injury and to aid in dissection of swollen lymph nodes [4,5,6].

In this present study, we succeeded in describing the inferior colonic arteriovenous system, especially the LCA, SA, MCV, IMV, LCV, and SV. These findings would be useful to determine the branching patterns for treatment of sigmoid and rectal colon cancers. In particular, determination of branching patterns of the SAs is indispensable for resection of cancer in the sigmoid colon and rectum. The SA are selectively resected in sigmoid colon cancer, and the SRA and LCA are preserved, when possible, during dissection of the D2 lymph nodes. In rectal

cancer, the SRA is selectively resected, and, when feasible, the SA and LCA are preserved in D2 dissection to ensure a sufficient blood supply to the anastomosis. Determining whether the SA branches arise from the LCA or SRA is crucial in colon cancer surgery [6].

The small number of participants and that the study was performed in a single institution were limitations of this study, but we feel that these issues did not affect technical feasibility. More cases should be studied in the future. A further limitation was that we did not use low tube voltage imaging or dual energy imaging to improve the contrast effect. The impact of such usage should be addressed in the future.

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## Conclusions

In conclusion, our results showed that CO<sub>2</sub> gas increased blood flow in major blood vessels in the abdominal cavity, resulting in higher image quality. Also, CT values by 3D-CTC with CTA were superior to those by 3D-CTC, especially for the inferior colonic arteriovenous system. 3D-CTA with CTC would be useful to evaluate those vessels and help in preparation for laparoscopic surgery.

## Conflicts of Interest

None.