

Effect of different contrast medium injection protocols for analysis of hepatic computed tomography perfusion in healthy dogs

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OBJECTIVE

To evaluate the hepatic CT perfusion (CTP) for determining the appropriate protocol for the dual-input maximum-slope model in dogs.

ANIMALS

5 healthy dogs.

PROCEDURES

Each dog underwent CTP with different contrast medium administration protocols. Combinations of three different injected doses of iohexol (450, 600, and 750 mg/kg) and injection durations (5, 10, and 15 seconds) were used. The CT values at the aorta, portal vein, and hepatic parenchyma were measured to create a time-density curve, and CTP parameters were measured simultaneously on each hepatic lobe using a 320-row multidetector CT scanner.

RESULTS

The maximum peak enhancement at the aorta, portal vein, and hepatic parenchyma was greater with the 750-mg/kg dose than with the 450-mg/kg dose. With an injection duration of 15 seconds, the aortic enhancement peak was less, and the arrival time at the aortic enhancement peak was longer compared to that with a 5-second injection duration. The CTP parameters in the caudate process of the caudate lobe and left lateral lobe differed with different injection durations. The CTP parameters in the caudate process of the caudate lobe, left lateral lobe, and right lateral lobe differed with varying injected doses.

CLINICAL RELEVANCE

Our study demonstrated that rapid administration of the contrast medium was required for quantitative analysis of hepatic CTP in healthy dogs. The CTP parameters differed with respect to the contrast medium administration protocol, and it was necessary to administer the contrast medium within a fixed duration and at a fixed dose to evaluate CTP correctly.

CT perfusion (CTP) is a functional imaging technique that reveals blood flow in the smallest vessels, particularly in the capillaries. CTP is evaluated based on contrast enhancement changes of the targeted tissues and organs after the IV administration of iodinated contrast medium.¹ The contrast enhancement in the region of interest (ROI) is measured as HU, and the change in HU over time is illustrated as a time-density curve (TDC). In humans, previous studies^{2,3} on CTP have demonstrated that parameters derived from the TDC facilitate the detection of hepatic cirrhosis and tumors, predict the severity of hepatic diseases, estimate the prognosis of hepatic tumors, and aid in assessing the therapeutic effects of various treatment regimens for hepatic tumors.

In human medicine, there are several kinetic models for the CTP protocol.^{2,4,5} The dual-input maximum-slope (DIMS) model is one of the kinetic models and it estimates blood flow in the aorta and portal vein. Fitting the DIMS model requires both a clear peak formation of the arterial TDC and a clear separation between the aorta and portal peaks. Therefore, the contrast medium should be administered rapidly, within 10 seconds in humans.^{4,6,7} To our knowledge, a few reports^{8,9} have revealed arterial, portal, and hepatic parenchymal TDCs in dogs; however, each TDC has not yet been analyzed according to the DIMS model, and the parameters derived from each TDC have not been evaluated. Therefore, CTP analysis may be helpful in the canine clinical setting as in the human clinical setting. However, a suitable protocol

of contrast medium administration is still unclear for fitting the DIMS model in canine hepatic CTP.

CTP requires the dynamic image acquisition of a fixed volume over time. Recently, the development of a 320-row multidetector CT (MDCT) scanner has enabled the capture of images with a 16-cm width in one scanner rotation. Furthermore, the fewer numbers of detectors in MDCT are the smaller tissue volume, which can be analyzed. Thus, 320-row MDCT allows CTP analysis with a width of 16 cm, making it possible to cover the entire liver in most dogs. A previous study¹⁰ has shown CTP variables measured using single-row detector CT in healthy dogs; however, CTP was analyzed with one axial slice image. Therefore, hepatic CTP has yet to be analyzed in each lobe. Mogenicato et al¹¹ have reported that many tributaries of portal veins primarily supply the right lateral lobe and caudate process of the caudate lobe, and, secondarily, the left lateral lobe, left medial lobe, and quadrate lobe. Therefore, we hypothesized that the parameters derived from hepatic CTP would reveal different values in different lobes.

This study aimed to evaluate hepatic CTP to determine the appropriate protocol for the DIMS model specifically in dogs. We investigated different injection doses and speeds of contrast medium to verify TDC parameters in the aorta, portal vein, and hepatic lobes.

Materials and Methods

Animals

Five healthy Beagles (sexually intact females, 1 year old, 9.2–10.6 kg) were used. All procedures involving the dogs were performed according to the Guidelines for Proper Conduct of Animal Experiments (Science Council of Japan) and were approved by the Nihon University Animal Care and Use Committee (Accession No. AP16B003). For all dogs, the results of a clinical physical examination, CBC, serum biochemical analysis, thoracic and abdominal radiographic examination, and abdominal ultrasound examination were assessed, and there were no abnormalities.

CT procedures

In all dogs, a 22- or 18-gauge catheter was placed in the cephalic vein. Each dog was premedicated with butorphanol tartrate (0.2 mg/kg, IV), and endotracheal intubation was performed after induction with propofol. General anesthesia was maintained by mechanical ventilation with isoflurane (1.5% to 2%) and oxygen (2 L/min). For all dogs, anesthesia was continued for at least 30 minutes before CT was performed. All dogs were positioned in ventral recumbency, and all scans were obtained using a 320-row MDCT scanner (Aquilion One; Canon Medical Systems Co). Iohexol (300 mg/mL) (Ioverin 300; Teva Pharma Japan Inc) was administered via a catheter placed in the cephalic vein with a power injector (Auto Enhance A-60; Nemoto Kyorindo Co), and 5 CT scans were performed on different days using the crossover method with a different contrast medium injection protocol. The 450-, 600-, or

750-mg iohexol/kg dose of contrast medium was administered over 10 seconds, and the 600-mg/kg dose was administered over 5 or 15 seconds. A temporal scan of the same location (volume scan) was performed. One scan covered the area from the diaphragm to the caudal side within 16 cm (about the left kidney). The scans were initiated at the same time the contrast medium was injected. The scan was performed intermittently 41 times in 1 minute (the rotation time was 0.5 second and the interval time was 1.0 second). The scan was performed with expiratory breath-hold, and CT scans were reconstructed with smoothing but without beam-hardening correction. The other scanning parameters were as follows: slice thickness, 0.5 mm; reconstruction interval, 0.5 mm; x-ray tube potential, 100 kV; and x-ray tube current, 100 mA.

Time-density curve analysis

The TDC was generated by one veterinarian (TA). Before TDC analysis, body registration was performed to correct motion between the dynamic volumes using a software program (Body Registration; Canon Medical Systems Co). The contrast value was recorded in HU, and all scans were measured at the aorta (T13 region), main portal vein (between the junction of the gastroduodenal vein and the bifurcation of the portal right branch), and hepatic parenchyma to create a TDC. The ROI was placed manually and sized at approximately 70% to 80% of the sectional area of the vessel. For the hepatic parenchyma, the ROI was as large as possible while avoiding the vessels on CT scans. The contrast value of the hepatic parenchyma was determined by averaging the contrast value of all hepatic lobes (ie, right lateral lobe, caudate process of the caudate lobe, right medial lobe, quadrate lobe, papillary process of the caudate lobe, left medial lobe, left lateral lobe). The parameters were determined from the TDC as follows: arrival time at the aortic enhancement appearance (T-AEA, measured in seconds), aortic enhancement peak (AEP, measured in HU), arrival time at the aortic enhancement peak (T-AEP, measured in seconds), arrival time at the portal venous enhancement appearance (T-PEA, measured in second), portal venous enhancement peak (PEP, measured in HU), arrival time at the portal venous enhancement peak (T-PEP, measured in seconds), arrival time at the hepatic parenchymal enhancement appearance (T-HEA, measured in seconds), hepatic parenchymal enhancement peak (HEP, measured in HU), and arrival time at the hepatic parenchymal enhancement peak (T-HEP, measured in seconds).

Computed tomography perfusion analysis

CTP analysis was performed by a veterinarian (TA). Before the CTP analysis, body registration was performed using a software program (Body Registration; Canon Medical Systems Co). CTP analysis was performed using the body perfusion software available on the CT scanner (Body Perfusion; Canon Medical Systems Co), and the DIMS model was used for

hepatic CTP analysis. In each hepatic lobe, hepatic arterial blood flow (HAF, measured in milliliters per minute per 100 mL) and portal venous blood flow (PVF, measured in milliliters per minute per 100 mL) were measured, and the hepatic perfusion index (HPI, measured as a percentage) was calculated as follows: $HAF/(HAF + PVF) \times 100$. To measure each parameter, the circular ROI was placed manually as large as possible while still excluding blood vessels. All measurements were performed 5 times for 1 hepatic lobe, and the average was used for data analysis.

Data analysis

All data are presented as median (range). Statistical tests were performed using commercially available statistical software (GraphPad Prism version 6.0 for Macintosh; Graph Pad Software Inc). Comparisons were performed of TDC parameters or CTP values among the 450-, 600-, and 750-mg/kg injected doses and among the 5-, 10-, and 15-second injection durations of the contrast medium. $P < 0.05$ was considered statistically significant.

Results

Time-density curve analysis

The TDC parameters for the 10-second injection duration of the contrast medium doses of 450, 600, and 750 mg iohexol/kg were summarized (**Table 1**). An increased volume of contrast medium led to an upward shift in arterial, portal, and hepatic parenchymal TDCs. The AEP for the 450-mg/kg injected dose was 683.0 HU (602.9 to 775.8 HU), which was significantly less than the HU from the injected dose of 750 mg/kg (1,178.4 HU [802.6 to 1039.7 HU], $P = 0.005$). Similarly, the PEP and the HEP for the 450-mg/kg dose were significantly less than those measured in the 750-mg/kg protocol (201.0 HU [179.7 to 229.2 HU] vs. 324.3 HU [248.5 to 305.6 HU], $P = 0.013$ and 130.0 HU [128.3 to 140.5 HU] vs. 173.3 HU

[163.4 to 194.9 HU], $P = 0.005$, respectively). The other parameters—T-AEP, T-AEA, T-PEP, T-PEA, T-HEP, and T-HEA—did not differ significantly with respect to contrast medium injection duration.

The TDC parameters for the injection durations of 5, 10, and 15 seconds at a contrast medium dose of 600 mg/kg were summarized (**Table 2**). An increased contrast median injection duration led to a downward and rightward shift of the arterial TDC. The median (range) T-AEP for the 5-second injection duration was 14.4 seconds (14.4 to 19.0 seconds), which was significantly shorter than for the 15-second injection duration (23.6 seconds [22.1 to 23.6 seconds], $P = 0.008$). The median AEP was significantly ($P = 0.005$) greater for the 5-second injection duration than for the 15-second injection duration (1,105.7 HU [947.0 to 1214.6 HU] and 732.6 HU [661.6 to 822.8 HU], respectively). The hepatic parenchymal TDC was shifted upward as the injection duration increased. The median T-HEA was 12.8 seconds (11.3 to 17.5 seconds) for the 5-second contrast medium injection duration, which was significantly ($P = 0.008$) shorter than the 15-second injection duration (22.1 seconds [20.6 to 25.2 seconds]). The median HEP in which the contrast medium injection duration was 5 seconds was 154.3 HU (138.9 to 162.3 HU), which was significantly ($P = 0.03$) less than the 15-second injection duration (163.2 HU [144.4 to 169.2 HU]). The other parameters, including T-AEA, PEP, T-PEP, T-PEA, and T-HEP, did not differ significantly with respect to the contrast medium injection duration.

Computed tomography perfusion analysis

Values of CTP variables were summarized (**Tables 3 and 4**). In comparing the doses of injected contrast medium, the median HAF in the caudate process of the caudate lobe was significantly ($P = 0.03$) greater with the 450-mg/kg dose than with the 600-mg/kg dose (31.5 mL/min/100 mL

Table 1—Median (range) time-density curve parameters for evaluation of hepatic computed tomography perfusion in 5 healthy dogs, by dose of injected contrast medium (iohexol)

Parameter	Iohexol, 450 mg/kg	Iohexol, 600 mg/kg	Iohexol, 750 mg/kg
Aorta			
AEP (HU)	683.0 (602.9–775.8) ^a	947.6 (802.6–1,039.7)	1,178.4 (802.6–1,039.7)
T-AEP (s)	17.5 (15.9–20.6)	19.0 (15.9–20.6)	19.0 (17.5–22.1)
T-AEA (s)	9.7 (8.2–12.8)	9.7 (6.6–11.3)	11.3 (8.2–12.8)
Portal vein			
PEP (HU)	201.0 (179.7–229.2) ^a	271.6 (248.5–305.6)	324.3 (248.5–305.6)
T-PEP (s)	31.4 (29.8–40.2)	34.5 (31.4–37.6)	32.9 (31.4–39.1)
T-PEA (s)	19.0 (17.5–20.6)	19.0 (17.5–22.1)	22.1 (17.5–26.7)
Hepatic parenchyma			
HEP (HU)	130.0 (128.3–140.5) ^a	156.1 (137.6–168.2)	173.3 (163.4–194.9)
T-HEP (s)	51.5 (43.7–57.6)	54.6 (48.4–56.1)	62.3 (42.2–62.3)
T-HEA (s)	12.8 (11.3–19.6)	17.5 (11.3–19.0)	19.0 (15.9–22.1)

AEP = aortic enhancement peak; HEP = hepatic parenchymal enhancement peak; PEP = portal venous enhancement peak; T-AEA = arrival time at the aortic enhancement appearance; T-AEP = arrival time at the aortic enhancement peak; T-HEA = arrival time at the hepatic parenchymal enhancement appearance; T-HEP = arrival time at the hepatic parenchymal enhancement peak; T-PEA = arrival time at the portal venous enhancement appearance; T-PEP = arrival time at the portal venous enhancement peak.

^aValue is significantly ($P < 0.05$) less than for the 750-mg/kg injected dose.

Table 2—Median (range) time–density curve parameters by contrast medium injection duration.

Parameter	5 s	10 s	15 s
Aorta			
AEP	1,105.7 (947.0–1,214.6) ^a	947.6 (802.6–1,039.7)	732.6 (661.6–822.8)
T-AEP	14.4 (14.4–19.0) ^a	19.0 (15.6–20.6)	23.6 (22.1–23.6)
T-AEA	8.2 (6.6–11.3)	9.7 (6.6–11.3)	9.7 (9.7–11.3)
Portal vein			
PEP	261.2 (207.4–282.6)	271.6 (248.5–305.6)	275.4 (222.1–348.4)
T-PEP	32.9 (26.7–42.2)	34.5 (31.4–37.6)	34.5 (32.9–48.4)
T-PEA	19.0 (14.4–22.1)	19.0 (17.5–22.1)	19.0 (17.5–20.6)
Hepatic parenchyma			
HEP	154.3 (138.9–162.3) ^a	156.1 (137.6–168.2)	163.2 (144.4–169.2)
T-HEP	56.1 (43.7–62.3)	54.6 (48.4–56.1)	56.1 (53.0–62.3)
T-HEA	12.8 (11.3–17.5) ^a	17.5 (11.3–19.0)	22.1 (20.6–25.2)

AEP = aortic enhancement peak; HEP = hepatic parenchymal enhancement peak; PEP = portal venous enhancement peak; T-AEA = arrival time at the aortic enhancement appearance; T-AEP = arrival time at the aortic enhancement peak; T-HEA = arrival time at the hepatic parenchymal enhancement appearance; T-HEP = arrival time at the hepatic parenchymal enhancement peak; T-PEA = arrival time at the portal venous enhancement appearance; T-PEP = arrival time at the portal venous enhancement peak.

^aValue is significantly ($P < 0.05$) different from that for the 15-second injection duration.

Table 3—Median (range) parameters of hepatic computed tomography perfusion in each lobe, by dose of injected contrast medium.

Parameter	Iohexol, 450 mg/kg	Iohexol, 600 mg/kg	Iohexol, 750 mg/kg
Hepatic arterial blood flow (mL/min/100 mL)			
Right lateral lobe	29.7 (22.6–55.1)	29.4 (13.2–33.3)	23.2 (14.1–37.6)
Caudate process of the caudate lobe	31.5 (24.9–43.5) ^a	15.0 (11.5–21.4)	21.7 (8.3–32.5)
Right medial lobe	34.8 (29.3–58.6)	30.5 (17.3–40.2)	27.3 (12.5–38.1)
Quadrate lobe	33.5 (24.3–57.7)	25.7 (18.6–31.8)	23.7 (13.1–41.3)
Papillary process of the caudate lobe	36.1 (28.7–84.2)	30.1 (24.2–33.0)	26.1 (17.2–48.0)
Left medial lobe	41.4 (25.9–88.7)	26.4 (22.7–34.1)	24.9 (16.0–29.0)
Left lateral lobe	27.4 (22.1–44.6)	26.0 (14.5–31.8)	24.6 (14.3–30.9)
Portal venous blood flow (mL/min/100 mL)			
Right lateral lobe	104.7 (85.2–123.8)	102.5 (95.5–129.7)	112.4 (95.2–135.1)
Caudate process of the caudate lobe	95.3 (80.0–104.2)	100.8 (87.3–104.5)	95.8 (66.0–109.8)
Right medial lobe	91.6 (70.6–123.1)	93.8 (84.6–155.8)	101.4 (72.0–134.1)
Quadrate lobe	92.5 (73.8–101.2)	97.3 (75.8–125.9)	90.2 (82.4–117.8)
Papillary process of the caudate lobe	92.1 (85.9–107.7)	91.8 (79.4–93.1)	84.0 (64.5–120.8)
Left medial lobe	107.0 (98.3–113.1)	103.1 (78.9–149.1)	90.8 (80.1–110.8)
Left lateral lobe	88.3 (82.1–100.5)	101.8 (87.1–114.6) ^b	75.3 (73.7–103.2)
Hepatic perfusion index (%)			
Right lateral lobe	21.0 (18.0–34.6) ^b	19.2 (11.6–23.8)	16.9 (12.5–24.1)
Caudate process of the caudate lobe	27.4 (20.6–33.4) ^a	12.5 (10.1–18.9)	19.5 (11.1–25.3)
Right medial lobe	24.4 (21.1–40.2)	22.1 (15.5–25.7)	20.0 (14.7–25.0)
Quadrate lobe	25.6 (21.0–41.0)	18.5 (15.5–25.3)	22.3 (12.2–29.4)
Papillary process of the caudate lobe	27.3 (21.1–49.8)	24.5 (20.4–29.4)	24.2 (20.1–28.3)
Left medial lobe	20.2 (18.1–29.6)	17.9 (14.2–30.3)	20.2 (16.7–23.6)
Left lateral lobe	25.3 (18.1–33.8)	20.7 (12.1–26.7)	21.0 (15.1–29.5)

^aValue is significantly ($P < 0.05$) greater than that for 600 mg/kg.

^bValue is significantly ($P < 0.05$) greater than that for 750 mg/kg.

[24.9 to 43.5 mL/min/100 mL] vs. 15.0 mL/min/100 mL [11.5 to 21.4 mL/min/100 mL], respectively). The median PVF was significantly ($P = 0.03$) greater in the left lateral lobe with an injected contrast medium dose of 600 mg/kg than with a 750-mg/kg dose (101.8 mL/min/100 mL [87.1 to 114.6 mL/min/100 mL] vs. 75.3 mL/min/100 mL [73.7 to 103.2 mL/min/100 mL], respectively). The median HPI in the right lateral lobe with the 450-mg/kg dose was significantly ($P = 0.03$) greater than that with the 750-mg/kg dose (21.0% [18.0 to 34.6%] vs. 16.9% [12.5 to 24.1%], respectively). The median HPI in the caudate process of the caudate lobe with the

450-mg/kg dose was significantly ($P = 0.03$) greater than that with the 750-mg/kg dose (27.4% [20.6 to 33.4%] vs. 12.5% [10.1 to 18.9%] respectively).

Concerning contrast medium injection duration, the median HAF in the caudate process of the caudate lobe for the 15-second injection duration was significantly ($P = 0.03$) greater than that for the 10-second injection duration (30.6 mL/min/100 mL [21.8 to 42.6 mL/min/100 mL] vs. 15.0 mL/min/100 mL [11.5 to 21.4 mL/min/100 mL], respectively). There were no significant differences in PVF with respect to the contrast medium injection duration. The median HPI in the caudate process of the

Table 4—Median (range) parameters of hepatic computed tomography perfusion in each lobe, by contrast medium injection duration.

Parameter	5 seconds	10 seconds	15 seconds
Hepatic arterial blood flow (mL/min/100mL)			
Right lateral lobe	22.6 (16.7–38.7)	29.4 (13.2–33.3)	30.4 (25.7–42.6)
Caudate process of the caudate lobe	19.2 (13.5–32.1)	15.0 (11.5–21.4) ^a	30.6 (21.8–42.6)
Right medial lobe	21.3 (21.0–35.7)	30.5 (17.3–40.2)	23.3 (10.9–30.3)
Quadrate lobe	29.0 (15.6–47.6)	25.7 (18.6–31.8)	29.3 (17.2–39.4)
Papillary process of the caudate lobe	27.6 (20.6–39.2)	30.1 (24.2–33.0)	34.4 (25.9–49.0)
Left medial lobe	22.7 (14.9–42.7)	26.4 (22.5–34.1)	37.3 (15.4–56.1)
Left lateral lobe	25.6 (17.0–30.5)	26.0 (14.5–31.8)	40.2 (13.6–49.2)
Portal venous blood flow (mL/min/100mL)			
Right lateral lobe	97.1 (83.3–157.1)	102.5 (95.9–129.7)	106.3 (82.1–121.3)
Caudate process of the caudate lobe	105.4 (68.2–126.0)	100.8 (87.3–104.5)	111.0 (56.7–120.7)
Right medial lobe	91.3 (70.3–128.8)	93.8 (84.6–155.8)	96.5 (66.8–122.2)
Quadrate lobe	96.4 (67.7–116.3)	97.3 (75.8–125.9)	96.2 (73.8–116.5)
Papillary process of the caudate lobe	77.6 (65.0–142.6)	91.8 (79.4–93.1)	105.5 (54.5–130.2)
Left medial lobe	95.9 (82.8–146.0)	103.1 (78.9–149.2)	105.6 (75.6–177.4)
Left lateral lobe	82.7 (69.4–132.4)	101.8 (87.1–114.6)	107.4 (83.7–158.0)
Hepatic perfusion index (%)			
Right lateral lobe	19.3 (14.7–23.6)	19.2 (11.6–23.8)	21.6 (19.4–31.1)
Caudate process of the caudate lobe	17.0 (15.3–21.3)	12.5 (10.1–18.9) ^a	25.0 (18.4–34.7)
Right medial lobe	19.7 (18.2–26.8)	22.1 (15.5–25.7)	19.5 (8.1–27.3)
Quadrate lobe	22.5 (13.6–31.2)	18.5 (15.5–25.3)	21.4 (16.5–28.4)
Papillary process of the caudate lobe	22.9 (20.9–32.3)	24.5 (20.4–29.4)	24.3 (19.6–39.0)
Left medial lobe	20.4 (12.8–24.0)	17.9 (14.2–30.3)	23.9 (16.9–28.4)
Left lateral lobe	21.7 (12.4–27.4)	20.7 (12.1–26.7) ^a	24.5 (14.1–28.6)

^aValue is significantly ($P < 0.05$) less than that for the 15-second injection duration.

caudate lobe (25.0% [18.7 to 47.7%] vs. 12.5% [10.0 to 21.9%], respectively; $P = 0.01$) and left lateral lobe (24.5% [14.1 to 28.6%] vs. 20.7% [12.1 to 26.7%]; $P = 0.03$) for the 15-second injection duration was significantly greater than values for the 10-second injection duration

Differences in the CTP parameters between the hepatic lobes were observed. The median HPI in the caudate process of the caudate lobe (27.4% [20.6 to 33.4%]) was significantly ($P = 0.006$) greater than that in the left medial lobe (20.2% [18.1 to 29.6%]) for the 10-second injection duration with the 450-mg/kg protocol. The median HPI in the papillary process of the caudate lobe (24.5% [20.4 to 26.7%]) was significantly ($P = 0.03$) greater than that in the caudate process of the caudate lobe (12.5% [10.1 to 18.9%]) for the 10-second injection duration with the 600-mg/kg protocol. The median PVF in right lateral lobe (112.4 mL/min/100 mL [95.2 to 135.1 mL/min/100 mL]) was significantly ($P = 0.03$) greater than in the left lateral lobe (75.3 mL/min/100 mL [73.7 to 103.2 mL/min/100 mL]), in which the dose of the injected contrast medium was 750 mg/kg for a 10-second injection duration.

Discussion

Our study characterized the TDC parameters of aortic, portal venous, and hepatic parenchymal variables in healthy dogs with respect to different contrast medium administration protocols. Our study suggested that the contrast medium injection duration influenced peak enhancement and arrival time to peak enhancement in the arterial TDC. Furthermore, the data suggested that the shorter the

contrast medium injection duration, the greater the maximum contrast enhancement and the shorter the arrival time to peak enhancement. These results are supported by the results of previous studies.^{8,12–15}

Our results also showed that the contrast medium injection duration did not affect portal venous TDC. To fit the DIMS model in CTP analysis, clear peak formation of arterial TDC and separation of aortic TDC and portal venous TDC are required.^{4,6,7} Therefore, our results suggested that a suitable TDC for the DIMS model was obtained by a shorter contrast medium injection duration. The specific requirements of the shorter contrast medium injection duration are still unclear, and thus further studies in a clinical setting are needed.

Our study showed that the dose of injected contrast medium did not influence the time axis direction of TDC, and a large amount of injected contrast medium resulted in high peak enhancement only in the aorta, portal vein, and hepatic parenchyma. Therefore, our results suggested that to separate the arterial TDC and portal venous TDC clearly in the HU axis, a smaller dose of injected contrast medium would be unsuitable for CTP analysis in dogs. However, this result is inconsistent with current human reports,^{2,4,5} which suggest that the dose of injected contrast medium should be reduced to avoid imaging noise or beam-hardening artifacts in tissues adjacent to large vessels and to obtain the required short contrast medium administration duration.⁵ Moreover, the rate of contrast medium injection was increased, and the contrast medium injection rate might exceed the safety range.¹⁶ A large bolus administration of contrast medium with a short duration has the potential risks of IV catheter rupture and

extravasation of contrast medium.¹⁶ So, it has been recommended that the maximum injection pressure not exceed 150 psi.¹⁶ When a 20-gauge catheter is placed, the contrast injection rate should not exceed 5 mL/s.¹⁶ When a 22-gauge is used, the maximum injection rate should be 3 mL/s.¹⁶

In the DIMS model, the arterial blood flow and PVF are calculated by separating the hepatic parenchymal TDC into the arterial phase and the portal venous phase in the time axis direction.⁷ Our results showed that the TDC variable in the time axis direction was affected by the contrast medium injection duration, but not by the dose of the injected contrast medium. Therefore, injection duration might be a priority over the dose of injected contrast medium for the contrast medium injection protocol in hepatic CTP in dogs. Further studies in a clinical setting are necessary to define a suitable dose of injected contrast medium in dogs. However, our study suggested that it might be important to deliver the maximum contrast medium dose that can be administered safely within the short injection duration.

Our study showed that the contrast medium injection protocol changed the hepatic CTP values in dogs. To our knowledge, there have been no reports on hepatic CTP variables with respect to the contrast medium administration protocol in dogs. Our study characterized the hepatic CTP values in several protocols and provided baseline data that may be useful in future studies comparing dogs with hepatic diseases. Our results indicated that the dose of injected contrast medium and contrast medium injection duration should be fixed between individuals for an appropriate evaluation of hepatic CTP.

We are unaware of any published reports on the quantitative measurement of hepatic blood flow in each hepatic lobe in dogs. In our study, a suitable contrast medium administration protocol for hepatic CTP analysis in dogs was not identified by directly comparing the CTP-derived hepatic blood flow and the standard method-derived hepatic blood flow (eg, ultrasonic transit-time technology). Although our study did not identify factors that altered the CTP parameters, a few possibilities were considered. Hepatic blood flow is regulated by hepatic artery pressure or hepatic venous pressure to maintain homeostasis,¹⁶ and contrast medium administration might cause an increase in arterial pressure or venous pressure.^{14,17} Therefore, we considered that the CTP values might have been influenced by changes in hemodynamics caused by the administration of the contrast medium. As another possibility, the greater concentration of contrast medium produces more prominent beam-hardening artifacts in tissues adjacent to large vessels, and the total iodine dose injected should range within approximately 12 to 18 g and be limited to a maximum of 0.5 to 0.8 mL/kg in human medicine.⁵ Therefore, we considered that the beam-hardening artifacts might influence the CTP values in adjacent tissue or large vessels under the shorter duration or larger doses of contrast medium injection. Although our results showed differences in CTP parameters among hepatic lobes,

these significant differences might have been caused by the changes in the CTP values for each hepatic lobe concerning the contrast medium administration protocols.

In conclusion, CTP analyses were feasible for all contrast medium administration protocols in the healthy dogs of our study. Our study characterized the TDC variables of the aorta, portal vein, and hepatic lobes using different contrast medium injection protocols. Our study demonstrated that rapid administration of the contrast medium was required for quantitative analysis of hepatic CTP. The CTP parameters differed with respect to the contrast medium administration protocol, and it was necessary to administer the contrast medium within a fixed duration and at a fixed dose to evaluate CTP correctly. These data may prove useful as baseline values in future studies or as standard bases in comparing data from dogs with hepatic diseases.

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