Effect of contrast medium injection rate on computed tomography–derived renal perfusion estimates obtained with the maximum slope method in healthy Beagles

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Received January 30, 2018.
Accepted May 21, 2018.

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OBJECTIVE
To evaluate the effect of contrast medium injection rate on CT-derived renal perfusion estimates obtained with the maximum slope method in healthy small dogs.

ANIMALS
6 healthy sexually intact male purpose-bred Beagles.

PROCEDURES
All dogs underwent CT perfusion analysis 3 times in a crossover design, receiving a different contrast medium injection rate (1.5, 3.0, and 4.5 mL/s) each time, with a 1-week interval between imaging sessions. All CT images were obtained at the level of the left renal hilus. The time to peak aortic enhancement (TPAE) and time to initial renal venous enhancement (TIRVE) were measured from time-attenuation curves. The renal CT perfusion estimates (blood flow and blood volume) were estimated by use of the maximum slope method, which assumes no venous outflow of contrast medium during CT perfusion analysis.

RESULTS
The TPAE occurred at or before the TIRVE at all injection rates. Median values of estimated blood flow and blood volume did not differ significantly among injection rates.

CONCLUSIONS AND CLINICAL RELEVANCE
Results suggested that the assumption of no venous outflow of contrast medium during renal CT perfusion analysis with the maximum slope method was satisfied for all 3 contrast medium injection rates in the evaluated dogs. A low injection rate may be more practical than higher injection rates that require large catheters for CT perfusion analysis in small dogs such as Beagles. (*Am J Vet Res* 2019;80:168–173)

Perfusion measurement is routinely used in human patients to diagnose, stage, and assess the prognosis and therapeutic response associated with conditions such as obstructive or stenotic lesions and vascular deformities.[1–3] Various noninvasive perfusion imaging modalities have been developed to estimate variables such as tissue blood flow and the exchange of fluids between the blood and extravascular space.[4] Among these modalities, CT perfusion analysis offers several advantages to human patients, including wide availability, short imaging time, and the positive correlation between the tissue contrast medium concentration and CT-based estimates of tissue perfusion.

Veterinary reports[5,6] have described the use of CT perfusion analysis to estimate pancreatic and hepatic perfusion in dogs, including those with and without portal vascular anomalies and with hepatic fibrosis. To the authors' knowledge, there are no published reports of renal CT perfusion analysis in dogs. However, given the demonstrated utility of renal CT perfusion analysis in humans,[7–10] this modality could be useful in veterinary patients for applications such as evaluating glomerular filtration rate and tissue viability following renal transplantation, grading and assessing the therapeutic response of renal tumors, and evaluating renal arterial stenosis and ureteral obstruction.

Estimates of tissue perfusion by CT perfusion analysis are based on temporal changes in tissue enhancement attributable to circulation of contrast medium.[4] Analytic approaches for computing these estimates include compartmental, deconvolution, and maximum slope methods, of which the maximum slope method is the most widely used in human clinical practice.[11] The maximum slope method is a single-compartment model based on the assumption that there is no venous outflow or recycling of the contrast medium during perfusion analysis.[12,a] The

ABBREVIATIONS
TIRVE Time to initial renal venous enhancement
TPAE Time to peak aortic enhancement

single-compartment model requires that the contrast medium achieve peak arterial enhancement before venous outflow of that medium occurs.[12] The assumption of no venous outflow of contrast medium depends on a short scanning time, typically until peak tissue enhancement is achieved, which also reduces the chance of motion artifacts.

Because the contrast medium takes only a few seconds to circulate from the injection site to the target tissues, a short injection duration is recommended to minimize underestimation of perfusion measures.[11] Recommendations from studies[13,14,a] involving humans include using an injection duration < 4 to 6 seconds and a contrast medium injection rate > 5 mL/s when performing cerebral CT perfusion analysis with the maximum slope method.

There are several factors to consider when performing CT perfusion analysis with the maximum slope method in veterinary patients. The use of large catheters to achieve high injection rates may be contraindicated in some patients, such as small dogs or cats, or those that are emaciated or have fragile veins (eg, cancer patients). High injection rates can also result in a shorter time to peak enhancement, making accurate image timing difficult because of the decreased temporal window.[15] Because the contrast medium dose is based on body weight, the volume required for small patients may permit a low injection rate that still results in a sufficiently short injection duration for CT perfusion analysis with the maximum slope method. The purpose of the study reported here was to evaluate different contrast medium injection rates in small dogs to determine whether a low injection rate would meet the assumption of the maximum slope method for CT perfusion analysis in this population.

Materials and Methods

Animals

All study procedures were approved by the Institutional Animal Care and Use Committee of Chonnam National University. Six sexually intact male purpose-bred Beagles were obtained from a commercial supplier. The dogs were housed individually in cages and provided with commercial dry food and water ad libitum. Median age of the dogs was 3 years (range, 2 to 4 years), and median body weight was 9 kg (range, 8.6 to 11 kg). All dogs were deemed healthy at the start of study, with no signs of dehydration, on the basis of physical examination, hematologic assessment, serum biochemical assay, Doppler ultrasonic blood pressure measurement at the dorsal pedal artery, thoracic and abdominal radiography, abdominal ultrasonography, and echocardiography, which included B-mode, M-mode, and color Doppler and spectral Doppler ultrasonography.

CT imaging

For each dog, food was withheld for 24 hours prior to induction of anesthesia for CT imaging. Physical examination, including heart rate and blood pressure measurements, was repeated for all dogs immediately prior to induction. A 20-gauge catheter was placed in the cephalic vein. Anesthesia was induced through IM injection of a combination of zolazepam hydrochloride–tiletamine hydrochloride[b] (0.75 mg/kg) and medetomidine hydrochloride[c] (0.03 mg/kg). An endotracheal tube was placed, and the dog was connected to a rebreathing circuit. Anesthesia was maintained with isoflurane[d] (1% to 2%) and oxygen (1 L/min).

All dogs underwent CT perfusion analysis 3 times in a crossover design, receiving a different contrast medium injection rate (1.5, 3.0, and 4.5 mL/s) each time, with a 1-week interval between imaging sessions. The order in which the dogs received the injection rates was determined by randomization. All CT images were obtained at the level of the left renal hilus with the dogs in sternal recumbency by use of a helical 16-row multidetector CT scanner.[e] First, precontrast CT imaging was performed with the following settings: slice thickness = 1 mm; pitch = 0.8; rotation time = 600 milliseconds; tube voltage = 120 kV; and tube current = 120 mA. Immediately before injection of the contrast medium, apnea was induced in each dog by the use of manual hyperventilation. Iohexol[f] (300 mg of iodine/kg [1 mL of iohexol/kg], IV) was then administered by use of a power injector.[g] Ten seconds after initiation of contrast medium injection, CT perfusion imaging was performed with 4.8-mm collimation (4 slices × 1.2 mm), a tube voltage of 120 kV, and a tube current of 80 mA. The CT perfusion images were obtained continuously for 40 seconds at 1-second intervals during the period of induced apnea with an adaptive smoothing filter, slice thickness of 4.8 mm, window width of 400 HU, and window level of 100 HU.

Image analysis

The TPAE was defined as the interval between the time of initiation of contrast medium injection and the time at which peak contrast medium enhancement of the aorta at the level of the left renal artery occurred, and the TIRVE was defined as the interval between the time of initiation of contrast medium injection and the time at which enhancement of the renal vein increased by 15 HU, compared with the previous slice. To measure the TPAE and TIRVE, time-attenuation curves were drawn by use of a CT software program,[h] with placement of regions of interest over the aorta at the level of the left renal artery and over the left renal vein **(Figure 1)**. The difference between the TPAE and TIRVE was then calculated to evaluate whether peak arterial enhancement occurred before contrast medium was detected in the renal vein.

Each CT image was analyzed with the maximum slope method by use of commercially available CT perfusion software.[i] The region of interest (total area of 400 to 550 mm^2) was placed over the renal cortex in the CT perfusion blood volume map image for es-

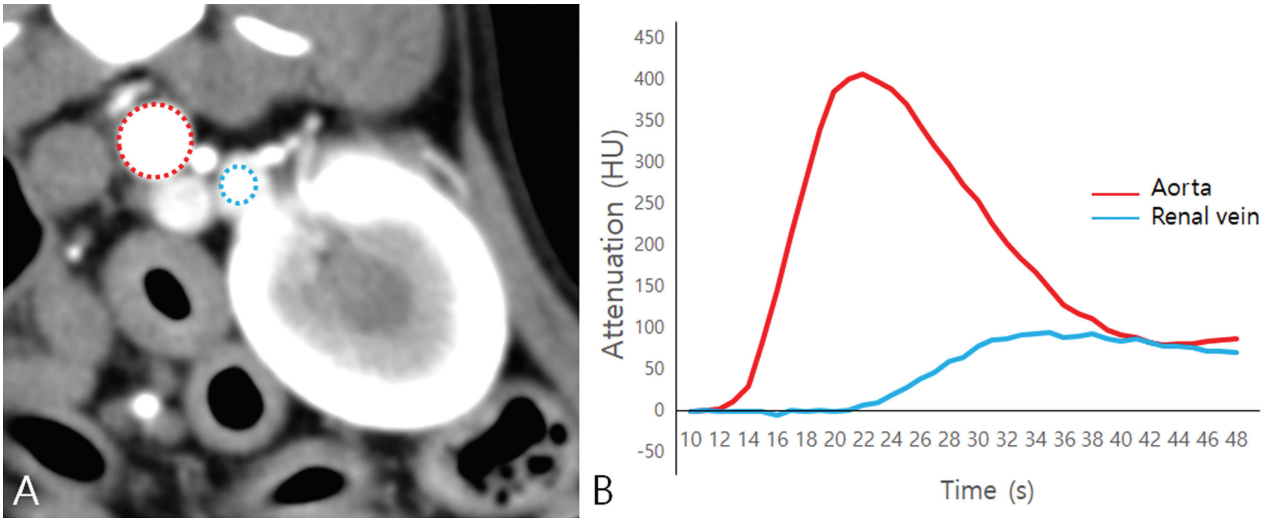

Figure 1—Representative transverse CT perfusion image of the hilar region of the left kidney of a healthy young adult Beagle showing the placement of the regions of interest over the aorta at the level of the left renal artery (red circle) and renal vein (blue circle; A) and time-attenuation curves (B) showing the degree of contrast enhancement of the aorta (red line) and renal vein (blue line) after initiation of contrast medium injection. The first postcontrast CT image was obtained 10 seconds after initiation of the contrast medium injection. The time-attenuation curves show that the TPAE (at 23 seconds) occurred before the TIRVE (at 25 seconds), indicating no venous outflow of contrast medium during CT perfusion analysis.

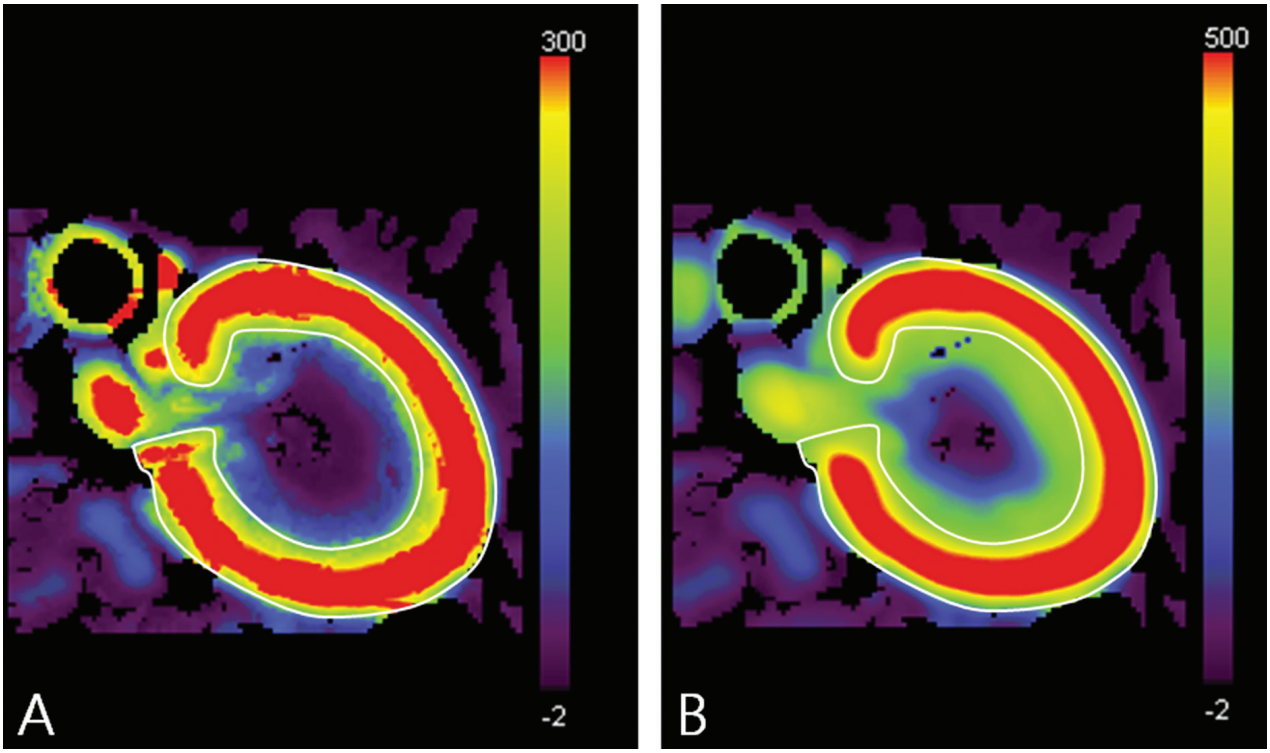

Figure 2—Transverse CT perfusion blood volume map images of the renal cortex of a healthy young adult Beagle obtained at a contrast medium injection rate of 1.5 mL/s showing measurement of blood flow (A) and blood volume (B). The region of interest was placed over the renal cortex (white line) for these measurements. The colored vertical scale bars represent the corresponding values for blood flow (mL/100 mL/min) and blood volume (mL/1,000 mL).

timation of blood flow and blood volume **(Figure 2)**. Perfusion analysis was performed 3 times for each CT perfusion image, and median values of the blood flow and blood volume estimates for each dog were calculated for each injection rate for use in the statistical analysis.

Statistical analysis

The Friedman test and Wilcoxon signed rank test were used to evaluate the effect of injection rate on TPAE, TIRVE, and blood flow and blood volume estimates derived from CT perfusion analysis with the maximum slope method. Values of $P \leq 0.05$ were con-

Table 1—Median (range) values of renal hemodynamic indices at 3 contrast medium injection rates for 6 healthy young adult male purpose-bred Beagles as obtained through CT imaging.

Injection rate (mL/s)	TPAE (s)	TIRVE (s)	TIRVE – TPAE (s)
1.5	22.0 (18.0–22.8)	23.6 (21.0–26.0)	3.0 (0.9–4.0)
3.0	21.0 (19.0–23.0)	23.0 (19.0–27.0)	3.0 (0.0–4.0)
4.5	21.0 (18.0–23.0)	23.0 (18.0–26.0)	2.0 (0.0–5.0)

Table 2—Median (range) renal perfusion estimates at 3 contrast medium injection rates for the dogs in Table 1 as derived through CT perfusion analysis with the maximum slope method.

Injection rate (mL/s)	Blood flow (mL/100 mL/min)	Blood volume (mL/1,000 mL)
1.5	308.3 (295.8–332.6)	396.0 (394.7–476.1)
3.0	276.4 (255.6–311.4)	407.6 (376.0–456.1)
4.5	284.1 (246.2–312.1)	446.6 (384.2–494.4)

sidered significant. Statistical analysis was performed with commercially available software.[j]

Results

Median systolic arterial blood pressure measured immediately before the start of CT imaging was 140.5 mm Hg (range, 92 to 162 mm Hg), and median heart rate was 49 beats/min (range, 32 to 60 beats/min). No complications were noted during the CT imaging sessions. Median duration of contrast medium injection at each injection rate was as follows: 6 seconds (range, 5.3 to 7.3 seconds) at 1.5 mL/s, 3 seconds (range, 2.7 to 3.7 seconds) at 3.0 mL/s, and 2 seconds (range, 1.8 to 2.4 seconds) at 4.5 mL/s.

Median values for renal hemodynamic indices (TPAE and TIRVE) did not differ significantly among the 3 contrast medium injection rates **(Table 1)**. In addition, the difference between the TIRVE and TPAE was zero or positive for all CT perfusion analyses, indicating that peak aortic enhancement was achieved at or before occurrence of venous outflow of contrast medium. The median blood flow and blood volume values derived from CT perfusion analysis with the maximum slope method did not differ significantly among the 3 contrast medium injection rates **(Table 2)**.

Discussion

The results of the present study indicated that a low rate of contrast medium injection (1.5 mL/s) satisfied the assumption of the maximum slope method (ie, no venous outflow of contrast medium) for CT perfusion analysis in small dogs, as evidenced by the absence of negative values for the difference between the TIRVE and TPAE. In addition, the median values for blood flow and blood volume derived from CT perfusion analysis did not differ significantly among the 3 injection rates.

The maximum slope method is based on the Fick principle, which assumes that contrast medium accumulation in the target organ is equal to the difference in contrast medium concentration between arterial inflow and venous outflow for that organ.[12] Assuming no venous outflow of contrast medium during perfusion analysis, the maximum slope method estimates tissue perfusion on the basis of the maximum slope of increasing tissue enhancement by contrast medium on time-attenuation curves and peak aortic enhancement. To satisfy that assumption, the venous contrast medium concentration, as inferred though attenuation (HU) values, should be zero when arterial enhancement peaks. Accordingly, a short injection duration (ie, high contrast medium injection rate) is recommended in humans undergoing CT perfusion analysis.[11,16,17,a]

The TPAE is directly related to the contrast medium injection duration and is calculated as the sum of the injection duration plus the time to contrast medium arrival at the target organ after injection.[18] Therefore, a long duration of contrast medium injection may result in a delay in the TPAE until after venous outflow of the contrast medium has occurred. In a previous study[11] comparing 2 contrast medium injection rates in human patients that underwent cerebral CT perfusion analysis with the maximum slope method following injection of 50 mL of contrast medium, the TIRVE was shorter than the TPAE at an injection rate < 6 mL/s, whereas the TPAE occurred before the TIRVE at an injection rate of 7.5 mL/s. Although a lower injection rate in the present study resulted in a longer injection duration, this had no significant effect on the TPAE, and all 3 injection rates satisfied the aforementioned assumption of the maximum slope method.

In humans, the effect of injection duration is limited when the duration is < 15 seconds, with the TPAE mainly determined by the time to contrast medium arrival at the target organ.[16] In dogs, changes in the contrast medium injection rate have no significant impact on TPAE when small doses of contrast medium (< 2 mL/kg) are used.[19] The effect of the injection rate on TPAE should be negligible in small dogs owing to the small volume of contrast medium needed and resultant short injection period.[20] In the present

study, the longest contrast medium injection duration was 7.3 seconds at an injection rate of 1.5 mL/s. This short injection duration likely contributed to the similar TPAE for the 3 injection rates.

The perfusion values calculated by use of CT perfusion analysis with the maximum slope method can be underestimated at low contrast medium injection rates.[11,17] Cerebral CT perfusion analysis in humans revealed significantly higher blood flow estimates at a contrast medium injection rate of 7.5 mL/s, compared with estimates obtained with injection rates of 4.5 and 6.0 mL/s.[11] In a previous study[21] comparing renal blood flow estimates derived from CT perfusion analysis with blood flow directly measured in pigs by use of a flow probe attached to the renal artery, a longer contrast medium injection duration (11.5 seconds) led to underestimation of true perfusion values by 8%, whereas a shorter contrast medium injection duration (3.8 seconds) led to overestimation of true perfusion values by 1%. However, the different injection rates used in the small dogs of the present study yielded no significant difference in the blood flow and blood volume estimates derived from CT perfusion analysis. This lack of a difference was likely due to the relatively short injection duration (≤ 7.3 seconds) and the lack of venous outflow of contrast medium during the CT perfusion analysis at all injection rates.

In the study reported here, a contrast medium dose of 1 mL/kg was sufficient for CT perfusion analysis. Although, to the authors' knowledge, there have been no previous studies of renal CT perfusion analysis with the maximum slope method in dogs, a contrast medium dose of 0.5 mL/kg was used in another study[5] to estimate hepatic, gastric, and pancreatic perfusion in dogs. An insufficient dose of contrast medium can lead to inadequate enhancement of the aorta and target organ, whereas an unnecessarily large dose can lead to a long injection duration and underestimation of perfusion estimates. In a study[22] involving humans, a contrast medium dose of 0.8 mL/kg was sufficient for analyzing renal perfusion.

The present study had several limitations. First, CT perfusion analysis can yield only estimates. To obtain true renal perfusion values, other methods, such as the use of a flow probe (considered the gold standard for perfusion measurement), would have been required. However, in the present study, CT perfusion analysis with the maximum slope method yielded estimates that correlated closely with previously reported[21] perfusion values obtained through flow probing in pigs. Therefore, we assume that the perfusion estimates we obtained in the present study would not differ meaningfully from the true perfusion values. Second, because CT imaging was performed at 1-week intervals, renal perfusion could have fluctuated between imaging sessions. To minimize this potential bias, we used a standardized anesthesia protocol and verified similar blood pressure measurements among study dogs when performing CT perfusion analysis. Third, cardiac output and circulation volume were not measured in this study. Although these factors could affect the TPAE and TIRVE, in the present study, we mainly focused on whether the difference between TPRVE and TPAE was positive. No significant difference in TPAE was found among groups with different injection rates; this finding was likely due to the low heart rate induced by the use of medetomidine for anesthetic induction. The TPAE can be affected by the injection rate when sufficient cardiac output and heart rate are maintained during anesthesia. Finally, dogs used in this study were small and had a narrow range in body weights. Because body weight can influence injection duration, further research is necessary to evaluate the effect of injection duration on perfusion estimates obtained through CT perfusion analysis with the maximum slope method in medium-sized and large dogs.

In conclusion, the results of the present study indicated that a low contrast medium injection rate of 1.5 mL/s satisfies the assumption of no venous outflow of contrast medium for CT perfusion analysis with the maximum slope method and yields perfusion estimates similar to those obtained at the higher injection rates of 3.0 and 4.5 mL/s. Therefore, we propose that a low injection rate of 1.5 mL/s can be used for CT perfusion analysis with the maximum slope method in small dogs; this rate may provide clinicians with the option of selecting smaller catheter sizes when medically indicated.

Acknowledgments

Supported by the Animal Medical Institute of Chonnam National University and the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT, and Future Planning (grant No. 2018R1A2B6006775).

The authors declare that there were no conflicts of interest.

Footnotes

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c. Domitor (1 mg of medetomidine/mL), Orion Corp, Espoo, Finland.
d. Terrell, Piramal Critical Care, Bethlehem, Pa.
e. Siemens Emotion 16, Siemens, Forchheim, Germany.
f. Omnipaque 300, GE Healthcare, Oslo, Norway.
g. Medrad Vistron CT injection system, Medrad, Warrendale, Pa.
h. Syngo Dynamic Evaluation, Siemens, Forchheim, Germany.
i. Syngo Body Perfusion CT, Siemens, Forchheim, Germany.
j. SPSS Statistics, version 20, IBM Corp, New York, NY.

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