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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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 reports5,6 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.12–14 The

P

Abbreviations

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

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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. This was done by comparing the TPAE and TIRVE for each dog. 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 peak contrast medium enhancement of the renal vein was detected. The TIRVE was measured by placing 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. The region of interest (total area of 400 to 500 mm²) was placed over the renal cortex in the CT perfusion blood volume map image for each dog. 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 peak contrast medium enhancement of the renal vein was detected. The TIRVE was measured by placing 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.

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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-

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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.\textsuperscript{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 through 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.\textsuperscript{11,16,17,a}

The TPVE 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.\textsuperscript{18} Therefore, a long duration of contrast medium injection may result in a delay in the TPVE until after venous outflow of the contrast medium has occurred. In a previous study\textsuperscript{11,16,17,a} 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 TPVE was shorter than the TPVE at an injection rate < 6 mL/s, whereas the TPVE occurred before the TPVE 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 TPVE, 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 TPVE mainly determined by the time to contrast medium arrival at the target organ.\textsuperscript{16} In dogs, changes in the contrast medium injection rate have no significant impact on TPVE when small doses of contrast medium (< 2 mL/kg) are used.\textsuperscript{19} The effect of the injection rate on TPVE should be negligible in small dogs owing to the small volume of contrast medium needed and resultant short injection period.\textsuperscript{20} In the present

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**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.

<table>
<thead>
<tr>
<th>Injection rate (mL/s)</th>
<th>TPAE (s)</th>
<th>TIRVE (s)</th>
<th>TIRVE – TPAE (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>22.0 (18.0–22.8)</td>
<td>23.6 (21.0–26.0)</td>
<td>3.0 (0.9–4.0)</td>
</tr>
<tr>
<td>3.0</td>
<td>21.0 (19.0–23.0)</td>
<td>23.0 (19.0–27.0)</td>
<td>3.0 (0.0–4.0)</td>
</tr>
<tr>
<td>4.5</td>
<td>21.0 (18.0–23.0)</td>
<td>23.0 (18.0–26.0)</td>
<td>2.0 (0.0–5.0)</td>
</tr>
</tbody>
</table>

**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.

<table>
<thead>
<tr>
<th>Injection rate (mL/s)</th>
<th>Blood flow (mL/100 mL/min)</th>
<th>Blood volume (mL/1,000 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>308.3 (295.8–326.0)</td>
<td>396.0 (394.7–476.1)</td>
</tr>
<tr>
<td>3.0</td>
<td>276.4 (255.6–311.4)</td>
<td>407.6 (376.0–456.1)</td>
</tr>
<tr>
<td>4.5</td>
<td>284.1 (246.2–312.1)</td>
<td>446.6 (384.2–494.4)</td>
</tr>
</tbody>
</table>

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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...
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 study21 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 study5 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 study22 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 reported21 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.

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The authors declare that there were no conflicts of interest.

Footnotes

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