Assessment of glomerular filtration rate with dynamic computed tomography in normal Beagle dogs

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The objective of our study was to determine individual and global glomerular filtration rates (GFRs) using dynamic renal computed tomography (CT) in Beagle dogs. Twenty-four healthy Beagle dogs were included in the experiment. Anesthesia was induced in all dogs by using propofol and isoflurane prior to CT examination. A single slice of the kidney was sequentially scanned after a bolus intravenous injection of contrast material (iohexol, 1 mL/kg, 300 mgI/mL). Time attenuation curves were created and contrast clearance per unit volume was calculated using a Patlak plot analysis. The CT-GFR was then determined based on the conversion of contrast clearance per unit volume to contrast clearance per body weight. At the renal hilum, CT-GFR values per unit renal volume (mL/min/mL) of the right and left kidneys were 0.69 ± 0.04 and 0.57 ± 0.05, respectively. No significant differences were found between the weight-adjusted CT-GFRs in either kidney at the same renal hilum (p = 0.747). The average global GFR was 4.21 ± 0.25 mL/min/kg and the whole kidney GFR was 33.43 ± 9.20 mL/min. CT-GFR techniques could be a practical way to separately measure GFR in each kidney for clinical and research purposes.

Keywords: computed tomography, dog, glomerular filtration rate

Introduction

The glomerular filtration rate (GFR) is an important indicator of renal function, monitoring progression of kidney disease, and the best way to determine an early diagnosis of subclinical renal function [33]. When there is a need to accurately determine GFR, such as when planning chemotherapy strategies with nephrotoxic agents or staging chronic renal disease in preparation for renal replacement, it may be necessary to use direct and accurate methods to measure GFR [19]. In current practice, there has been a general shift from purely anatomical imaging to a combined structural and functional approach. For example, functional computed tomography (CT) imaging of a main organ through dynamic CT scans using contrast media has been reported [8,28]. Other reports have indicated that GFR can be evaluated through advances in CT technology and application of a specific kinetic model [7,8,24]. In addition, GFR is determined by measuring the plasma clearance of a GFR marker that may be an endogenous metabolic product (e.g. urea or creatinine) or an exogenously administered substance [3,27]. Inulin, a 5.2 kDa polymer of fructose, is regarded as a gold standard substance for GFR determination [23]. However, inulin-based determination is a time-consuming chemical analysis and clinical availability may be limited [11]. Since the advent of using inulin for measuring GFR, new methods have been studied. There is an increasing interest in the use of iodinated contrast medium, such as iohexol, as a new alternative marker for estimating GFR in humans and animals [1,3,20]. Recently, it has been possible to simply and rapidly
measure GFR using dynamic CT with a Patlak plot analysis in human and veterinary medicine [1,8,20,28]. Blood clearance per unit renal volume is generally about 0.4–0.7 mL/min/mL in humans [9,28]. CT-GFR studies have been used to evaluate various diseases affecting renal function [29,30]. However, there are few published reports on the use of CT-GFR in normal dogs including the use of dynamic CT with a Patlak plot to measure CT-GFR in normal dogs and pigs [1,20]. There is also a lack of published reference data on CT-GFR values measured by functional CT in dogs. The purpose of this study was therefore to determine individual and global CT-GFR. We suggest the use of a CT-GFR technique combined triphasic renal imaging by presenting physiologic parameters obtained through aortic and renal time attenuation curves in clinically healthy Beagles.

Materials and Methods

Experimental animals
The procedures performed in the present study were approved by the Institute of Laboratory Animal Resources (ILAR) at Seoul National University, Korea. Sixteen intact male and 8 intact female Beagles 1- to 4-years-old (average age, 1.96 ± 1.00 years) and weighing 5.5 to 11.7 kg (average weight, 8.06 ± 1.53 kg) were used for the study. The dogs were housed individually in ILAR-approved facilities, fed a commercial diet (Jerony; Che-il Jedang, Korea) twice a day, and given water ad libitum.

All dogs were determined to be clinically normal based on physical examination, complete blood counts (CBCs), biochemical and urinalysis profiles, and heartworm antigen test results (Snap; IDEXX Laboratories, USA). Serum biochemical analyses, including ones that measured sodium, potassium, chloride, calcium, phosphorous, total protein, creatinine kinase, blood urea nitrogen (BUN), creatinine, albumin, glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gammaglutamyl transpeptidase, amylase, and cholesterol, were performed. Using an ultrasound-guided technique, urine was collected from all dogs for urinalysis which included specific gravity measurement by a refractometer (Reichert Vet 360; Reichert, USA), routine dipstick tests (Combostick; YD Diagnostics, Korea), and sediment and cytologic examinations. General diagnostic imaging techniques using thoracic and abdominal radiography, abdominal ultrasonographic, and echocardiographic examinations were performed on all dogs.

Animal preparation and anesthesia
The animals were fasted for approximately 12 h before anesthesia. CBC was performed to determine hematocrit (HCT) levels before anesthesia. Twenty-two-gauge IV catheters (Becton-Dickinson Korea, Korea) were placed in the bilateral cephalic veins for propofol (Provive; Myungmoon Pharm, Korea) and iohexol (Omnipaque; GE Healthcare, USA) administration. No other medications were given before anesthesia induction. After inducing anesthesia with propofol (6 mg/kg, IV administration), the trachea was intubated. Anesthesia was maintained with isoflurane (Forane; Choongwae Pharm, Korea) and oxygen. The oxygen flow rate was 1 L/min, and a 1.5 to 2.0 minimum alveolar concentration of isoflurane was maintained during the CT-GFR study. Heart rate, respiratory rate, and carbon dioxide levels were monitored continuously during anesthesia. Blood pressure was measured directly or indirectly; arterial pressure was directly measured at the dorsal pedal artery or femoral artery. Indirect systolic arterial pressure was determined using a Doppler-based technique (Vet-Dop Doppler; Vmed Technology, USA). Total time spent for CT-GFR assessment was approximately 30 min from the induction of anesthesia until the conclusion of the postcontrast helical scan. The CT-GFR study was performed during a single-slice dynamic scan for 2 min after 15 to 20 min following isoflurane-induced anesthesia.

CT examination
The dogs were placed in a dorsal recumbent position on the CT table, and a CT power injector (LF CT 9000 ADV; Liebel-Flarsheim, USA) was connected to a cephalic venous cannula to control the injection rate of the contrast medium, iohexol. CT was performed with a GE CT/e (General Electric Medical System, Japan), a single-detector CT scanner. The image acquisition parameters included a helical acquisition and matrix of 512 × 512, and a 25 cm display field of view.

The general renal CT protocols included three steps: baseline precontrast imaging, single-slice dynamic imaging, and postcontrast imaging. To minimize motion artifacts, obtain excellent image quality, and achieve optimal results, all scans were performed following hyperventilation to induce apnea. Initial precontrast examination of both kidneys and the abdominal aorta was performed using a helical mode with 120 kVp, 50 mA, a 3 mm slice thickness, and a 1.3 pitch. Using this procedure, the exact location of the entire kidney was identified and the region for the dynamic scan was determined. Single-slice dynamic CT was concurrently initiated with the beginning of contrast medium injection by using an automated power-injector and related software; iohexol (300 mgI/mL) was also administered at a low dosage of 300 mg/kg at the rate of 3 mL/sec. Dynamic CT was performed in one region (1 mm slice thickness) of the renal hilum of the kidney every 1.5 sec for 2 min. Following dynamic CT acquisition, both kidneys were again scanned entirely to calculate the renal volume using the same scan parameters as the initial unenhanced CT scan.
**CT-GFR with a Patlak plot analysis**

The Patlak plot analysis is a popular tool for estimating blood-to-tissue transfer constants from multiple time uptake data [18].

The basic concept of the Patlak plot is that the amount of contrast media in the nephron is proportional to the integrated concentration of the contrast media in the aorta during the 2 min dynamic CT scan after contrast media administration [8,28]. \( Q(t) \) is the contrast mass at time \( t \) in the circulation, \( B(t) \) is the blood concentration at time \( t \), and \( \alpha \) represents the GFR. The mass transferred out of the blood into the renal tubules by time \( t \) will therefore be

\[
Q(t) = \alpha \int_0^t b(t) \, dt.
\]

If this formula is divided by \( V \), the volume of the region of interest (ROI) under consideration, we obtain

\[
\frac{Q(t)}{V} = \frac{\alpha}{V} \int_0^t b(t) \, dt.
\]

This represents the concentration at any time \( t \) relative to the total concentration in the ROI filtered contrast. For example, \( C(t) \) represents the total amount of iodine in a given volume, \( V \); therefore, \( C(t) = V \times c(t) \). In this equation, \( C(t) \) is the sum of iodine in the renal blood volume \( B(t) \) and in the renal glomerular filtrates \( Q(t) \). Therefore, when \( C(t) = B(t) + Q(t) \) is divided by \( V \), it becomes

\[
c(t) = \frac{Q(t)}{V} = \frac{B(t)}{V} + \frac{Q(t)}{V}.
\]

If it is substituted with

\[
\frac{Q(t)}{V} = \frac{\alpha}{V} \int_0^t b(t) \, dt,
\]

it becomes

\[
c(t) = \frac{B(t)}{V} + \frac{\alpha}{V} \int_0^t b(t) \, dt.
\]

\( B(t) \) is \( V_b b(t) \), so when substituted with \( \frac{B(t)}{V} \), it becomes

\[
\frac{c(t)}{b(t)} = \frac{V_b}{V} + \frac{\alpha}{V} \int_0^t b(t) \, dt.
\]

The CT value from which the background has been subtracted is then substituted for the concentrations in these equations. Components \( c(t) \) and \( b(t) \) are the CT value of the renal ROI and the aorta minus the baseline. \( \frac{V_b}{V} \) is the volume of the contrast media remaining in the blood at a given time, fractional vascular volume (% fvv). The Patlak plot will be linear with a slope of \( \frac{\alpha}{V} \), which is the whole blood clearance rate per unit volume (mL/min/mL), and must be corrected by the HCT values to obtain the plasma clearance GFR [Slope \( \times \) (1 – HCT)]. Since plasma clearance is usually reported in mL/min/kg, the results were first converted from contrast clearance per unit volume (mL/min/mL) to contrast clearance (mL/min) by multiplying by the kidney volume. Next, the contrast clearance (mL/min) was divided by the weight of the dog in kilograms to allow comparison of different GFR values in mL/min/kg units [24,30].

**Image analysis**

The CT-GFR of a single-kidney measured by CT was estimated using a Patlak plot [28]. For this procedure, aortic and renal parenchymal attenuation curves and Hounsfield unit (HU) values of the ROIs were acquired. A circular aortic ROI was located inside the aortic lumen at the level of the renal hilum using the manufacturer’s CT functional software (Fig. 1). The unenhanced density of the aorta was calculated as the mean of three density measurements at the same enhanced aortic level in the renal hilum. The mean HU value within the aortic ROI before contrast medium administration was subtracted from each value after contrast medium administration, thus providing a corrected aorta HU value. The corrected aorta HU values reflected attenuation changes in the 2 min uptake of the contrast media.

Similarly, ROIs were drawn around the left and right kidneys (Fig. 1). The borders of the ROIs were drawn as close to the periphery of the renal parenchyma as possible, thus excluding main vessels and fatty tissue. The mean precontrast and postcontrast HU values were evaluated at a location adjacent to the site where the aorta was measured. The corrected HU values of the renal parenchyma, from which the precontrast HU value was subtracted from the postcontrast HU, were then analyzed. For the Patlak plot analysis, an in-house program based on IDL 6.4 development software (IDL 6.4; Interactive Display Language, USA) was used.

Experimental animals were divided into two groups based on ROI location. In group 1, the CT-GFR was measured at the renal hilum of the right kidney while the ROI in group 2 was in the left kidney. CT-GFRs along with other quantitative and functional parameters of each kidney were determined. Significant correlations among the functional parameters between the right and left kidney were then assessed. The following physiologic parameters were evaluated: baseline and postcontrast HU values in the

**Fig. 1.** Dynamic CT images centered in the left renal hilum obtained at maximal aortic enhancement with iohexol. The black circle indicates the aorta, the black line indicates the left kidney, and the dotted line indicates the right kidney. Regions of interest (ROI) are drawn around the aorta as well as left and right kidneys. Vessels and fatty tissue are excluded from the ROIs. LK: left kidney, RK: right kidney, AO: aorta.
Jinhwa Chang et al.

Table 1. Precontrast and postcontrast Hounsfield unit values along with time-to-peak enhancement of the renal and aortic regions of interests

|                  | Right kidney hilum (n = 14) | Left kidney hilum (n = 10) | p-value |
|------------------|-----------------------------|---------------------------|---------|
| PreAo            | 34.61 ± 3.94 (26.80 ~ 40.20) | 32.56 ± 4.81 (24.80 ~ 39.90) | 0.364   |
| PreKd            | 38.20 ± 5.67 (29.80 ~ 54.80) | 38.85 ± 9.24 (31.40 ~ 57.70) | 0.348   |
| PostAo           | 219.68 ± 63.19 (105.40 ~ 337.80) | 218.11 ± 72.22 (89.19 ~ 352.20) | 0.875   |
| PostKd           | 129.57 ± 18.39 (109.40 ~ 174.70) | 116.99 ± 31.50 (74.40 ~ 174.60) | 0.192   |
| Aopt             | 13.29 ± 2.75 (10.50 ~ 21.00) | 13.20 ± 1.84 (9.00 ~ 15.00) | 0.668   |

PreAo: precontrast aortic attenuation, PreKd: precontrast renal attenuation, PostAo: postcontrast aortic peak attenuation, PostKd: postcontrast renal peak attenuation, Aopt: time-to-peak enhancement of the aorta (sec). All data are expressed as the mean ± SD (range).

Fig. 2. Time attenuation curves (TACs) showing iohexol concentrations in the aortic blood (A) and left kidney (B) of a dog. The threshold (arrow) is the background Hounsfield unit (HU) value of the aortic (A) and renal (B) ROIs. The initial postcontrast aortic and renal peak enhancements and their times are shown (cross mark).

Fig. 3. Patlak plots of the right (A) and left (B) kidneys of a Beagle dog. The slope represents the blood clearance (mL/min/unit volume), and the y-intercept indicates the fractional vascular volume (%). Components c(t) and b(t) are the CT values from which the baseline has been subtracted of the renal ROI and the aorta.

Measurement of renal volume
Renal volume was calculated by measuring the cross-sectional area (cm²) of an ROI drawn on each kidney in each CT slice. Renal volume was determined during the postcontrast helical scan. Image window width and level were set at 80 and 25 HU, respectively, for ROI determination [1]. Each of the slice areas were summed and multiplied by slice thickness (mm) to yield the renal volume (mL) [14,25].

Statistical analysis
Statistical analysis was performed using SPSS software (ver 17.0; SPSS, USA). Because of the small sample sizes, Mann-Whitney U and Wilcoxon signed rank tests were used to compare the physiologic parameters for the right and left kidneys. Functional parameters and CT-GFR of both kidneys were expressed as the mean ± SD. For all statistical analyses, p-values were considered significant when < 0.05.

Results
The precontrast HU values of the aorta and those of the right and left renal parenchyma were 33.75 ± 4.35, 38.20 ± 5.67, and 38.85 ± 9.24 HU, respectively (Table 1). Peak aortic enhancement occurred between 9.5 and 16 sec (13.29 ± 2.75) after iohexol injection (Table 1, Fig. 2A). During this time, the vascular phase was detected and the renal vasculature was evaluated. The aortic TAC also showed a second, lower peak at 25 ~ 36 sec. The initial peak of renal parenchymal enhancement occurred at 15 ~ 21 sec (average, 18.32 ± 3.39 sec; Table 1, Fig. 2B). This graph showed an overall gradual increase in renal parenchymal HU values following the initial enhancement peak until the end of data acquisition at 120 sec with small undulations in the renal TAC (Fig. 2B).

The slopes of the Patlak graph (Fig. 3) of the right and left kidneys were 0.69 ± 0.04 and 0.57 ± 0.05 mL/min/kg of volume, respectively. The CT-GFR values (mL/min/kg) of
The right and left kidney were 2.19 ± 0.17 and 2.28 ± 0.17, respectively. There were no statistically significant differences between these values (Table 2). The average global GFR, which is the sum of the GFR of both kidneys, was 4.21 ± 0.25 mL/min/kg while the whole kidney GFR was 33.43 ± 9.20 mL/min.

**Discussion**

For the present study, a single-slice dynamic CT technique, Patlak plot analysis, and a low dose of contrast medium with a propofol-isoflurane anesthetic protocol were used. We chose propofol for our study to induce anesthesia in the young healthy dogs undergoing CT-GFR because of ability of this drug to cause smooth and rapid induction and uncomplicated recovery [4]. Mean CT-GFR values of the right and left kidney were 2.19 ± 0.17 mL/min/kg and 2.28 ± 0.17 mL/min/kg, respectively. The average global GFR was 4.21 ± 0.25 mL/min/kg in the 24 clinically healthy Beagles. The CT-GFR technique used in this study may be extremely useful for assessing GFR in each kidney separately in specific clinical setting, such as prior to performing uninephrectomy in patients for testing the function of the remaining kidney and the potential risk of post-surgery kidney failure, unlike plasma or urinary clearance methods. In the study by O’Dell-Anderson et al. [20], the average global GFR was found to be 2.57 ± 0.33 mL/min/kg using functional CT, 4.06 ± 0.37 mL/min/kg using plasma iohexol clearance, and 4.05 ± 1.10 mL/min/kg using renal scintigraphy in eight healthy intact male dogs weighing between 14.6 and 16.5 kg. Other studies determined that the mean global GFR was 2.9 ± 0.3 mL/min/kg using plasma iohexol clearance in six healthy Beagles [17] and 3.46 ± 0.52 mL/min/kg using $^{99m}$Tc-DTPA scintigraphy in 10 healthy Beagles [15]. When comparing the present CT-GFR results to those from other GFR methods, we obtained considerably higher values. This may be explained by differences by body weight, gender, and age of the experimental animals or a potential effect associated with the investigator.

Information from triphasic renal imaging could be obtained through the time attenuation curves of the aorta and renal parenchyma obtained during single-slice dynamic scanning. Triphasic renal imaging consists of the precontrast scan along with corticomedullary and nephrographic phases [5,16,26]. In present study, the corticomedullary phase was scanned during the initial cortical peak time ranging from 15 to 21 sec. The nephrographic phase and diffuse enhancement of general renal parenchyma could be obtained after approximately 40 to 50 sec when reaching the contrast media in the renal pelvis. Time-to-peak enhancement of the aorta could be also applied when performing renal angiography; by doing this, excellent visualization of the aorta and its branches is acquired [21]. Triphasic renal CT including a vascular phase is a valuable method for detecting and characterizing lesions, anatomic examination of potential kidney transplant donors, and preoperative planning for urologic surgery [6,13,32].

By performing a Patlak plot analysis during CT examination, rapid and simple GFR determination is possible within at least the first 2 min following tracer injection [2]. In particular, the best window of time for GFR calculation is 40 – 110 sec following aortic rise [12,31]. Our study showed that multiple time data by dynamic CT can be obtained from only one section level. This could present a drawback for cases in which a solid organ may show functional inhomogeneity or in patients with renal disease that is unevenly distributed.

A low dose of iohexol acts in a manner pharmacokinetically similar to inulin during functional CT scanning [10]. Such a low dose of contrast medium (1 mL/kg) allows the calculation of GFR while limiting the risk of contrast medium-induced nephropathy [22]. In our preliminary study, it was possible to evaluate renal function with a dose of 0.75 mL/kg, but it was difficult to judge the renal margin to measure renal volume during the immediate postcontrast helical scan. An even lower dose of contrast medium (0.5 mL/kg) created noise on the TAC curves and the correlation coefficients from the Patlak plot were relatively low. Part of the tracer-use concept indicates that the mass of the chemical administered is so small that it does not

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**Table 2. Results of Patlak plot analysis and computed tomography-glomerular filtration rate (GFR) values of the right and left kidneys**

|                  | Right kidney hilum | Left kidney hilum | $p$-value |
|------------------|--------------------|-------------------|-----------|
| Slope (mL/min/mL) | 0.69 ± 0.04 (0.30 – 0.94) | 0.57 ± 0.05 (0.33 – 0.84) | 0.069     |
| Intercept (%)     | 0.38 ± 0.02 (0.20 – 0.63) | 0.38 ± 0.03 (0.19 – 0.50) | 0.725     |
| GFR 1 (mL/min)    | 18.28 ± 1.38 (9.79 – 30.41) | 16.67 ± 1.24 (9.82 – 22.12) | 0.520     |
| GFR 2 (mL/min/kg) | 2.19 ± 0.17 (0.95 – 3.39) | 2.28 ± 0.17 (1.31 – 3.31) | 0.747     |
| RV (mL)           | 26.61 ± 5.14 (21.32 – 37.24) | 29.65 ± 5.46 (25.36 – 43.31) | 0.074     |

RV: estimated renal volume. All data are expressed as the mean ± SD (range).
itself affect the function of the organ system being studied [19]. Therefore, the dose used in our study was chosen on the basis of preliminary CT-GFR examinations [20].

One drawback of our study was that the accuracy of our technique was not compared to a gold standard method, but it was already considered to be a simple alternative to GFR measurement for clinical and research purposes. Erratic breath may have also caused respiratory misregistration problems and affected CT number measurements. Additionally, the radiation burden of the patient may be significant when taking repeated CT images.

Despite these limitations associated with functional CT techniques using the Patlak plot, we recommend the use of functional CT-GFR and triphasic renal scan based on the results of our study. We were able to obtain scout, baseline, and single-slice dynamic scans using contrast media (1 mL/kg), and two postcontrast scans including corticomedullary and nephrographic phases using additional contrast media (2 mL/kg). This technique can simultaneously provide detailed functional and morphological information and is practical for application in veterinary medicine. Further investigations are required to validate our findings, including ones examining differences associated with age or breed-related GFR, and the application of CT-GFR for patients with various diseases.

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