ผลของการให้สารน้ำต่อการวัดอัตราการกรองผ่านกลอเมอรูลัส (GFR) โดยวิธี Scintigraphy ในสุนัข

The Effect of Fluid Administration on Glomerular Filtration Rate (GFR) Measured by Scintigraphy in Dogs

นฤพนธ์ คำพา[1,2]
Naruepon Kampa[1,2]

บทคัดย่อ

มีการรายงานว่าสภาวะของน้ำในร่างกายส่งผลกระทบต่อค่า Glomerular Filtration Rate (GFR) ดังนั้นในมนุษย์ จึงมีการให้สารน้ำก่อนทำการตรวจวัด GFR อย่างไรก็ตามยังไม่มีรายงานการศึกษานี้ในสุนัข วัตถุประสงค์ของการศึกษานี้คือเพื่อทำการประเมินผลของการให้สารน้ำต่อค่า GFR ในสุนัขที่สงสัยว่าเป็นโรคไต การศึกษาครั้งนี้กระทำในสุนัข 8 ตัวที่สงสัยว่าเป็นโรคไต โดยมีสุนัขหนึ่งตัวได้รับการศึกษา 2 ครั้ง ในช่วงห่างกัน 6 เดือน ไตของสุนัขทุกตัวได้รับตรวจด้วยอุลตร้าซาวน์ การตรวจวัดค่า GFR ด้วย scintigraphy แบบมาตรฐานถูกใช้ในสุนัขทุกตัว หลังการตรวจ scintigraphy ครั้งแรก สุนัขได้รับสารน้ำ (Ringer-acetate) ขนาด 15 ml/kg ทางหลอดเลือดดำด้วยอัตรา 5-7 ml/min/kg โดยใช้เครื่องให้สารน้ำอัตโนมัติ หลังจากนั้นสุนัขได้รับการตรวจ scintigraphy ซ้ำอีกครั้งหนึ่ง ผลการศึกษาพบว่า ค่า GFR รวมของไตทั้งสองข้าง มีค่าสูงขึ้นอย่างมีนัยสำคัญ ภายหลังได้รับสารน้ำ ค่าเฉลี่ยของ GFR ในสภาวะปกติคือ 2.90 ml/min/kg และภายหลังได้รับสารน้ำคือ 3.22 ml/min/kg สุนัข 2 ตัวในการศึกษานี้อาจถูกวินิจฉัยว่ามีปัญหาเกี่ยวกับโรตไต อันเนื่องมาจากค่า GFR ต่ำในการวัดครั้งแรก ซึ่งภายหลังการได้รับสารน้ำแล้วค่า GFR ที่ได้จากการวัดครั้งที่สอง อยู่ในเกณฑ์ปกติ ดังนั้น จึงเป็นข้อแนะนำว่า สุนัขที่ได้รับการตรวจวัดค่า GFR โดยวิธี scintigraphy ควรจะต้องได้รับสารน้ำ เพื่อให้น้ำในร่างกาย มีสภาวะสมดุลเพียงพอเสมอ

คำสำคัญ: อัตราการกรองผ่านกลอเมอรูลัส scintigraphy สารน้ำ

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[1] ภาควิชาศัลยศาสตร์และวิทยาการสืบพันธุ์ คณะสัตวแพทยศาสตร์ มหาวิทยาลัยขอนแก่น จ.ขอนแก่น 40002
Department of Surgery and Theriogenology, Faculty of Veterinary Medicine, Khon Kaen University, Khon Kaen, 40002

[2] Division of Diagnostic Imaging, Department of Biomedical Sciences and Public Health, Faculty of Veterinary Medicine and Animal Sciences, University of Agricultural Sciences, Sweden

Abstract

The state of hydration has been reported to affect the Glomerular Filtration Rate (GFR) value, and fluids are given to humans before measuring GFR. However, the effect of hydration on GFR in the dog has not been determined. The purpose of this study was to evaluate the effect of administering fluid on GFR of dogs examined for suspected renal disease. Nine studies were made from eight suspected kidney diseased dogs; one dog was examined twice, with a 6-month interval. The standard method for kidney scintigraphy for this laboratory was used. After the first examination was done, the dog was given fluid (Ringer-acetate) 15 ml/kg body weight intravenously using an automatic infusion pump with the rate at 5-7 ml/min/kg. The examination was then repeated. Global GFR was significantly increased after administering fluid ($p<0.05$). The mean of the GFR in normal condition and after given fluid was 2.90 and 3.22 ml/min/kg, respectively. Two dogs in this study would have been diagnosed as renal insufficiency (low GFR), if not for the second measurement after administering the fluid. Therefore, it is strongly recommended that the dog undergoing kidney scintigraphy be well hydrated as dehydration may lead to underestimation of the potential GFR.

Introduction

Kidney (renal) disease is one of the most common problems affecting dogs. The detection of reduced function is difficult in clinical practice because the clinical signs of renal failure do not appear until there is severe dysfunction. Many methods are used to evaluate renal disease. Kidney size, shape, margination and opacity can be evaluated by radiography. Ultrasound provides morphologic information such as renal size, shape and internal architecture. But the confirmation of ultrasound findings that are not severe may cause decreased renal function, they are difficult to confirm. Some structural information is also provided by scintigraphy (nuclear imaging). A biopsy can be used for pathological but not for functional change. The most common methods of diagnosis are based on analysis of blood samples to detect elevated levels of creatinine and urea nitrogen. Both are insensitive and nonspecific as they are only elevated when the kidney function is severely reduced. Glomerular filtration rate (GFR) is considered to be the best single parameter for assessing renal function (Moe and Heiene, 1995; Heiene and Moe, 1998) because it is directly proportional to the number of functioning nephrons (Ross, 1995). Urinary clearance of inulin, exogenous creatinine and single injection plasma clearance method as ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), iohexol for instance are accepted as the standard for kidney function test (Chew and DiBartola, 1989; Gleadhill and Michell, 1996). However, these methods are time consuming and labor intensive, which has prevented more extensive use in clinical practice.

Kidney scintigraphy, the application of the gamma camera for assessment of renal disease, is a relatively recent technique that has eliminated most of the above disadvantages. It is a quick, noninvasive method to evaluate renal function in terms of GFR and urine or blood samples are not required (Krawiec et al., 1986; Twardock et al., 1996). Futhermore, the gamma camera technique is the only method to determine GFR, both as a total integral value of renal function and as an individual function of each kidney, and is the only method that can be used to study the effects of interventions such as therapeutic drug monitoring.

The state of hydration has been reported to affect the GFR value (Tabaru et al., 1993). In human, patients are recommended to be in a moderately hydrated state before measurement. In dogs, the effect of hydration status on GFR in the clinic has not been determined.

The propose of this study was to evaluate the effect of administering fluid on GFR in dogs examined for suspected renal disease, and to relate the results to the kidney ultrasound changes and histological finding from kidney biopsies.

Material and methods

Eight dogs suspected of having kidney disease were selected by clinical evaluation of the patient with blood samples for urea nitrogen and creatinine, and with/without ultrasound changes indicating renal disease. The mean age of the dogs was 3 years (range 6 months to 8 years) and the mean body weight was 28.6 kg (range 7.5 to 47 kg). There were 5 females and 3 males. The dogs' breeds were rottweiler, Labrador retriever, mastiff, Bernese mountain dog, English cocker spaniel, poodle, cavalier king Charles spaniel, and mixed breed. One dog was examined again 6 months after the first examination for monitoring the kidney function. There were nine studies in total.

The selected dogs were admitted to the animal hospital, Faculty of Veterinary Medicine and Animal Sciences, University of Agricultural Sciences, Sweden. GFR was measured in each dog by scintigraphy at its normal condition and after administering fluid intravenously. An ultrasound-guided biopsy of kidney tissue to determine the histologic basic for the abnormal appearance was done the next day in the cases permitted by the owner.

Scintigraphic technique

A syringe containing 60-90 MBq ^{99m}Tc-DTPA was placed horizontally on a plexiglass platform 25 cm above the face at the center of the gamma camera using a low-energy-all-purpose collimator and a 64 x 64 x 16 pixel matrix, and preinjection counts acquired as a 30-second static image. The dog was then placed in left lateral recumbency on a table with the legs held and the gamma camera was positioned dorsally. ^{99m}Tc-DTPA was injected intravenously as a bolus followed by 4 ml saline solution flush via a catheter in the vein, and a dynamic acquisition was recorded at six frames per minute for six minutes. Immediately after the dynamic acquisition, the camera was rotated 90 degrees and a static lateral 30-second image was made to measure the kidney depth. The camera was then returned to its original position and the injection tubing, cannula and syringe were counted for remeasuring postinjection counts. The preinjection and postinjection syringe counts were corrected for radioactive decay and the net counts obtained by subtraction.

The dynamic study was examined using the sequence of frames as a movie for any displacement of the kidneys from frame to frame. If motion was present, it was corrected using a special motion correction program. In most cases, the images from 1-2 min were summed to create a single image of the kidneys with sufficient counts to define the edges of the kidneys. In some cases of poor function with slow uptake, the summed imaging time had to be extended to attempt to get sufficient count density to locate and outline the kidney. A rectangular region-of-interest (ROI) was placed closely around each kidney and automatic ROIs using the technique of interpolation were drawn. This was only to separate kidney from general abdominal background. Then a threshold of 20% maximum pixel activity was used to define the kidney ROI. A circumferential background ROI to measure extrarenal background was drawn automatically at one-pixel wide and one-pixel out from the kidney ROI for both manual and automatic kidney ROI drawing. The estimated individual kidney GFR was calculated from the percentage uptake of DTPA in each kidney between 30-120 second time interval using our own equations correlating uptake to GFR by plasma clearance (Kampa et al., 2002).

After the first scintigraphic examination was done, the dog was given fluid (Ringer-acetate, Fresenius Kabi AB, SE-751 74 Uppsala, Sweden) 15 ml/kg body weight intravenously using an automatic infusion pump with the rate at 5-7 ml/min/kg. This procedure was done in each dog within 1-1.5 hour. The scintigraphic measurement of GFR was then repeated.

Kidney biopsy

Kidney biopsy was done by ultrasound guidance under general anesthesia. Two or three samples were taken from the caudal pole of the kidney using a biopsy gun (Bard® Magnum® Reusable Core Biopsy, 730 Central Avenue Murray Hill, New Jersey, 07974, USA) with 15-cm and 16-cm long biopsy needle. If both kidneys appeared similar, the left kidney was selected.

For evaluating hydration effect, the individual and total kidney GFRs before and after giving fluid obtained by scintigraphy were compared as paired data using paired T-test. The significant difference of GFR in an individual dog was calculated based on the 95% limits of agreement of the observer variability (Bland and Altman, 1999; Kampa et al., 2006). The GFR results were compared with the results from ultrasonographic and pathologic findings.

Results

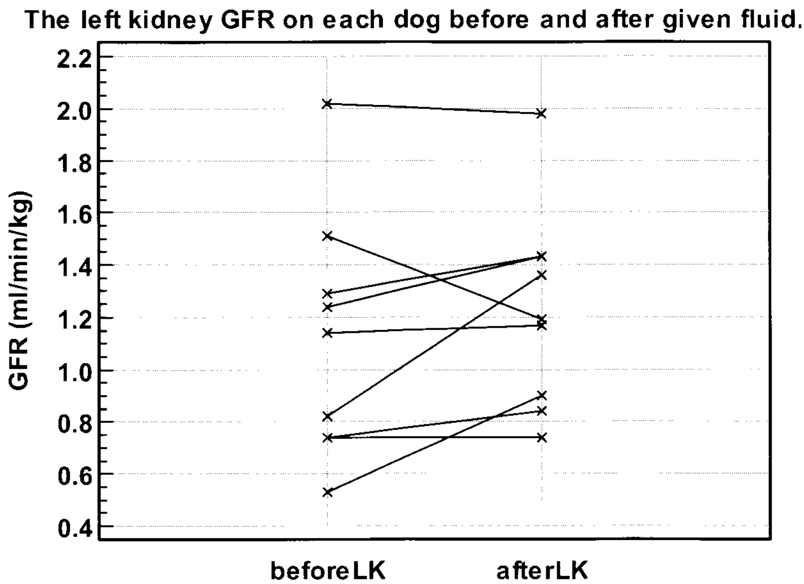
The dogs and the examinations done are shown in Table 1. The effect of fluid on the individual kidney GFR of each dog is shown in Figure 1.

Table 1 Summary of findings in each dog.

Dog no.	Ultrasound examination	Kidney scintigraphic examination (GFR ml/min/kg)						Kidney biopsy
		Normal condition			After giving fluid (15 ml/min/kg)			
		LK	RK	Total	LK	RK	Total	
1.	Very mild bilateral renal pelvic dilation, which could be due to diuresis	0.82	1.61	2.44	1.36	2.07	3.43	No pathologic finding
2.	Both kidneys hyperechoic with a complete loss of corticomedullary definition, several anechoic fluid filled (cystic lesion 5-6 mm) structures in the parenchyma. Pelvic dilatation.	1.29	2.02	3.31	1.43	2.11	3.54	Inflammatory cell, lymphocyte and plasma cell, tubular atrophy and fibrosis. Thickening of Bowman capsule in some glomeruli. Chronic interstitial nephritis.
3.	Mildly increased echogenicity of the kidney cortex and hyperechoic corticomedullary rim sign.	0.74	1.12	1.85	0.74	1.12	1.85	-
4.	Normal finding	1.51	1.58	3.08	1.19	1.9	3.09	No pathologic finding
5.	Mild bilateral pelvic dilation, right ureter moderately dilated (5mm)	2.02	3.29	5.31	1.98	3.58	5.56	No pathologic finding
6.	Severe change in both kidneys, Small and irregular shape, pelvic dilatation, no definition between cortex and medulla in the left kidney. An increased echogenicity and decreased corticomedullary definition in the right. Suspected of bilateral signs of end stage kidney.	0.74	1.68	2.42	0.84	2.42	3.27	-
7.	Bilateral severe kidney lesions of cysts, pelvis dilatation and loss of corticomedullary definition and hyperechogenicity. Similar appearance compared to the previous exam. (no.2)	1.24	1.94	3.18	1.43	2.22	3.65	-
8.	A moderate to marked amount of free anechoic abdominal fluid, both kidneys normal	1.14	1.6	2.75	1.17	1.32	2.49	-
9.	Normal	0.53	1.26	1.84	0.90	1.15	2.07	No pathologic finding

- = the examination was not done

(a)



(b)

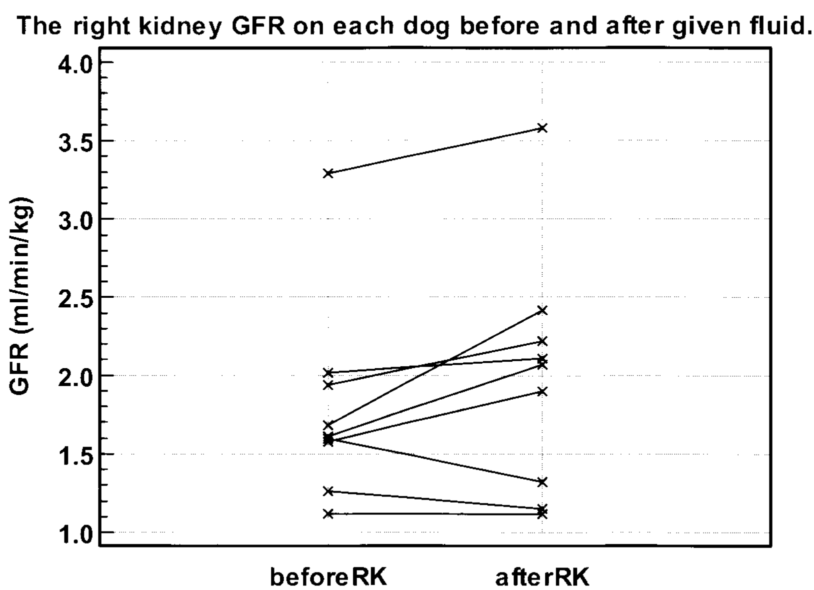


Figure 1 Comparison of GFR in each individual dog between normal condition and after administering fluid 15 ml/kg body weight. (a) the left kidney GFR, (b) the right kidney GFR.

There was no significant difference of the left kidney GFR between normal condition and after administering fluid. The mean left kidney GFR in normal condition and after given fluid was 1.11 and 1.23 ml/min/kg respectively. The mean difference of the left kidney GFR of the dogs after given fluid was 0.11 ml/min/kg higher than before given fluid. Six dogs had an increased GFR, while two dogs had a decreased GFR, and no change of GFR in one dog (Figure 1a). Based on the previous study (Kampa et al., 2006), the 95% limits of agreement of the intra-observer variability of repeatability of the method was 0.02 ± 0.37 ml/min/kg for the left kidney. The left kidney GFR difference of two dogs was higher than the upper limits of 95% limits of agreement.

There was no significant difference of the right kidney GFR between normal condition and after administering fluid. The mean right kidney GFR in normal condition and after given fluid was 1.79 and 1.99 ml/min/kg, respectively. The mean difference of the right kidney GFR of the dogs after given fluid was 0.20 ml/min/kg higher than before given fluid. Six dogs had an increased GFR, while two dogs had a decreased GFR, and no change of GFR in one dog (Figure 1b). Two of 6 dogs that had an increased the right kidney GFR had a decreased left kidney GFR after given fluid. The 95% limits of agreement of the intra-observer variability of the right kidney was 0.02 ± 0.23 ml/min/kg.

For the total kidney GFR, there was significant difference of the GFR between normal condition and after administering fluid ($p<0.05$). The mean GFR in normal condition and after given fluid was 2.90 and 3.22 ml/min/kg, respectively. The mean difference of the dogs after given fluid was 0.31 ml/min/kg higher than before given fluid. Seven dogs had an increased total GFR, while one dog had a decreased GFR, and no changed in one dog. Two dogs had a marked increased GFR.

Discussion

The changes of GFR before and after given fluid determined by kidney scintigraphy in the individual kidney could partly due to the variability of technique itself and also the observer variation. In this study, these variations were calculated using the 95% limits of agreement of the repeatability of the method using the same observer, obtained from the previous study (Kampa et al., 2006). If the difference of GFR exceeded the limits, it implied that the changes caused by fluid were significant.

Generally, the GFR varies from day to day, apparently in a response to the function of the kidneys to maintain homeostasis of fluid balance. If a dog has had low fluid intake, the GFR will be as low as possible to retain water, but if it has an excess of water from drinking for example, then the kidneys will eliminate it and the GFR will be higher. A low GFR might not be due to disease but the need to retain water. In this study, a significantly increased GFR can be seen in two dogs after administering fluid. This could be explained by that those dogs responded to a fluid load to bring GFR up to the normal level. Total GFR above 3 ml/min/kg is considered to be normal in dogs (Twardock et al., 1996). This value is similar to our previous study in the healthy dogs (Kampa et al., 2002), which the mean (± SD) GFR was 3.44 ± 0.62 ml/min/kg. The values of two dogs without fluid load would have given a false interpretation of reduced kidney function, because the GFR before the fluid load was below 3 ml/min/kg (Table 1).

Overall, the GFR tended to increase after the dogs were given fluid (Figure 1). However, in the dogs that the GFR did not significantly change or slightly decreased after given fluid, the dogs may have been well hydrated and/or had poorly functioning kidneys. In this study, four dogs had normal total GFR higher than 3 ml/min/kg before hydration, and slightly increased GFR after fluid, indicating that the dogs were well hydrated and the kidneys functioned well at the first measurement. The increased GFR was a response to the fluid overload in the body. There were three dogs that the total GFR was below the normal range both before and after given fluid, which represented a poor kidney function indicating renal insufficiency status. This suggested that the kidneys did not respond to the fluid load since they already worked at the maximum capacity. This study also showed that the individual kidney response to fluid load was not equal. The better functioning kidneys had a higher response to fluid than the less functional kidneys of the same dog. A poorly functioning single kidney may cause the other kidney to compensate therefore the total GFR was normal as in two dogs in this present study (Table 1).

In a previous study (Tabaru et al., 1993), the dogs were evaluated in states of dehydration, euhydration, and overhydration to determine effects of hydration state on renal function. In the present study, the hydration status of each dog was not known, typical for a dog undergoing an examination. It is recommended that the dog undergoing kidney scintigraphy be ensured to be well hydrated. Humans are made to drink one hour before the study to ensure good diuresis, and the maximum attainable GFR (Moonen, 1994).

In this study, only one dog had decreased GFR that related to the ultrasonographic finding. Otherwise, the GFR changes did not relate to the ultrasonographic finding. In some dogs, with severely changed kidney appearance, the GFRs were within normal limits in both normal condition and after administering fluid. This finding suggested that the morphologic changes alone cannot indicate the degree of the functional kidney damage. In this study, it appears that some morphologic changes can be detected using ultrasound before function by GFR decreases. It may imply that the morphologic changes may not always cause the reduced kidney function. However, there was one dog with no appearance changes in ultrasound but lower than the normal GFR.

Kidney biopsy has been accepted as a good method for evaluating pathologic changes. In this study, kidney biopsies were done in 5 dogs. In three dogs the pathological finding results correlated well with the GFR results. In one dog, the results revealed that the histopathologic findings did not relate to GFR changes but it seems that the pathologic finding and ultrasonographic finding were related very well on this dogs (Table 1). There was one dog that was diagnosed as chronic interstitial nephritis by biopsy but the GFR values were still in the normal range on both examinations. However, there was no pathologic finding by biopsy and ultrasonographic changes in one dog that had GFR below normal range. This could be explained that the biopsy tissue may not have been collected in the area with lesions. The focal inflammation in the parenchyma of the kidney that affects the functional change may not be seen from histopathology on the biopsy tissue. This suggested that the diagnosis of kidney disease based on the histopathologic finding alone is not reliable.

Conclusions

With these results, we strongly recommended that the dog undergoing kidney scintigraphy be well hydrated. Dehydration may lead to falsely low GFR. The dog must be given intravenously fluid 1 hr to ensure good hydration before the examination. Finally, the diagnosis based on ultrasonographic and pathologic finding alone have to be made with caution.

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