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## **Relationship of Serum Creatinine and Glomerular Filtration Rate by <sup>99m</sup>Tc-DTPA Scintigraphy in Dogs with Renal Failure**

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### **ABSTRACT**

Glomerular Filtration Rate (GFR) is considered as the best single parameter for assessing renal function because it is directly proportional to the number of functioning nephrons. Serum creatinine is the most frequently measured analyze in clinical biochemistry as an indirect indicator of glomerular Filtration Rate (GFR). Renal scintigraphy has been used as direct measurement of the glomerular Filtration Rate (GFR) either of individual kidney or global (both kidneys). By this technique, the GFR is calculated by a regression equation relating the percent of the injected dose of radiopharmaceutical, technetium-99m Diethylene-Triaminepentaacetic acid (DTPA), taken up and filtered by the kidneys. This communication reports the relationship of direct (scintigraphy) and indirect (creatinine) methods of GFR measurement. Scintigraphy is a quick, noninvasive diagnostic technique in which a two-dimensional picture of internal body tissue is produced through the detection of the gamma radiation emitted by radioactive substances injected into the body within 15 min with a gamma camera. Serum creatinine increases in renal failure correlating with a decrease in GFR forming a curvilinear relationship. Based on the study undertaken in 44 dogs with renal failure, it was found that 86.36% dogs suffering from renal failure showed a conventional pattern of curvilinear relationship between creatinine and GFR. Inter-individual variations were observed in 11.36% of dogs. False positive results were obtained in 9% of total dogs, where creatinine was within normal reference range but GFR decreased on scintigraphic analysis. False negative observations were seen in 4.5% of dogs, where normal GFR with marginally high creatinine values was reported.

**Key words:** Gamma camera, glomerular filtration rate, renal failure, scintigraphy, serum creatinine, <sup>99m</sup>-tc-diethylene triaminepentaacetic acid (DTPA)

### **INTRODUCTION**

Incidence of renal disease increases with age due to progressive loss of nephron mass in every mammalian species, except horses (Grauer, 1992). Renal failure is a common clinical problem

occurring in 2-5% of dogs (Lora-Michiels *et al.*, 2001) and third leading cause of death in canines. Robertson (2001) reported that by the age of 5 years, nearly 60% of dogs show renal lesions and decrements in renal function which approaches 90% by ten years. Management of renal failure is most successful if initiated early which (Grauer and Lane, 1995). Early recognition of renal dysfunction is also essential for monitoring of patients receiving nephrotoxic drugs. GFR is considered as best single parameter for assessing renal function (Heiene and Moe, 1998), because it is directly proportional to the number of functioning nephron. Renal dysfunction is routinely identified by elevations in Blood Urea Nitrogen (BUN) and serum creatinine, but azotemia is usually not present until an animal has lost which approximately 75% of its total renal function (Ross, 1995). Under steady state conditions, the rate of creatinine excretion is equal to the rate of its production in skeletal muscles which (Guyton and Hall, 1998), so its measurement indirectly reflects the GFR. The determination of GFR is especially valuable as it can detect renal dysfunction in patients (Ettinger *et al.*, 2000). Scintigraphy is a quick, noninvasive diagnostic technique in which a two-dimensional picture of internal body tissue is produced through the detection of the gamma radiation emitted by radioactive substances injected into the body within 15 min with a gamma camera. Gamma camera technique is the only method to determine GFR, both as a global value of renal function and as an individual function of each kidney (Kampa, 2007). The 99 mTc-DTPA is the radiopharmaceutical of choice for GFR study by scintigraphy, because DTPA meets the criteria for GFR measurement and energy of the emitted radiation of 99 mTc is at 140 Kev is ideal for effective detection by the gamma camera. This agent is excreted principally by kidney and can be used to measure GFR; accumulation by the kidneys reflects reduced renal function. The agent can also be used to assess renal blood flow, suspected renovascular hypertension and obstructive uropathy (ACR practice guideline, ACR (2006)). Present communication reports a relationship between serum creatinine and glomerular filtration rate in dogs suffering from renal failure.

## **MATERIALS AND METHODS**

The present research was carried out at the Veterinary Nuclear Medicine Center of the Department of Medicine, Bombay Veterinary College in 2006 to 2008. The study was performed on 44 canine patients with renal disorder referred from Bai Sakarabai Dinshaw Pettit Hospital for Animals (affiliated from Bombay Veterinary college). The kits of DTPA (TCK-7\*) and molybdenum (Mo-99) were obtained from Board of Radiation and Isotope Technology, Mumbai.

A total of 44 dogs of either sex, breed weighing about  $21.11 \pm 2$  kg, height  $40.13 \pm 2.32$  cm and age about  $7.56 \pm 0.92$  year were selected. The inclusive criterion for the dogs was serum creatinine level more than  $2.0 \text{ mg dL}^{-1}$ . All the dogs underwent routine hematology and serum biochemistry analysis along with electrolyte analysis as per standard procedure suggested by Benjamin (1978). Based on clinical examination and findings of Packed Cell Volume and urine specific gravity, best possible oral hydration done approximately 2 h prior to the study as state of hydration has been reported to affect the Glomerular Filtration Rate (Kampa, 2007). After oral rehydration, if required, intravenous hydration was also done using normal saline @  $15 \text{ mL kg}^{-1}$  body weight over a period of 30 min before the study.

Scintigraphy was performed using  $6.44 \text{ Mbq kg}^{-1}$  ( $174 \text{ } \mu\text{Ci kg}^{-1}$ ) of 99 mTc-Diethylene-triaminepentaacetic acid injected through a cephalic vein (Kampa *et al.*, 2006). Counting of activity

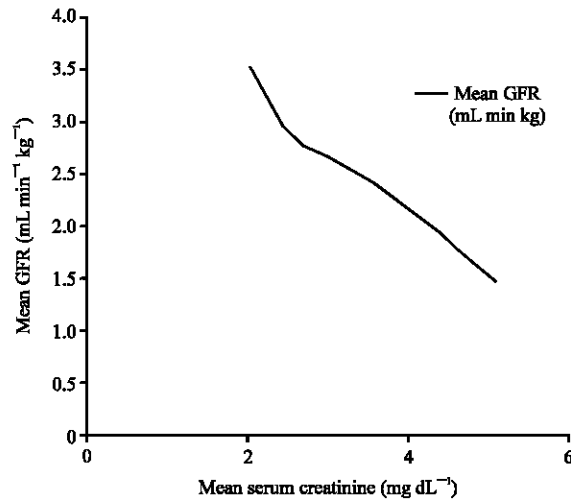


Fig. 1: Curvilinear relationship between GFR and serum creatinine

in front of the gamma camera before and after injection and correction for radioactive decay during the time interval was done. The dog was laid down in sternal recumbency and camera positioned with the collimator facing down, gantry 0° without any tilt, to include the kidneys, bladder and the thorax including heart whenever possible (Fig. 1). A dynamic acquisition was started of six frames per minute for 20 min. Immediately after starting acquisition, 99m Tc-DTPA was injected intravenously as a bolus. A low energy all purpose (LEGP) collimator on a gamma camera was used and 64×64 pixel matrix for the dynamic study and 128×128 matrix was selected for static study. Immediately after the dynamic acquisition period, the camera was rotated 90 degree above the dog and a static lateral 30 sec image was made to measure the kidney depth. The camera was then returned to its original position and the activity in the syringe was counted to exclude it from injected dose. All data were kept in the computer and calculated using eNTEGRA work station.

Gates Analysis programming was used to generate time activity curve. Manual drawing of kidney ROI was done with the background (Region of Interest) ROI at 2 pixels out from the kidney (Kampa *et al.*, 2006). For correction of background activity, small crescent shape areas were manually drawn at the caudal pole of the kidneys (Liedtke and Duarte, 1980). Correction for soft tissue attenuation was done using the known attenuation coefficient for 99m Tc in soft tissue [linear absorption coefficient in soft tissue = 0.153 cm<sup>-1</sup> (Gates, 1982)].

## RESULTS

Based on the creatinine level which ranging from 1.8 to 5.5 mg dL<sup>-1</sup>, total 44 dogs suffering from renal disorders were divided in 6 groups ( Table 1). Serum creatinine is used as screening test of renal function as it is handled primarily by glomerular filtration and essentially reflects GFR. All the dogs underwent 99mTc-DTPA scintigraphy for estimation of GFR by using Gates protocol. Maximum observed GFR was 4.0 mL min<sup>-1</sup> kg<sup>-1</sup> at creatinine level 1.8 mg dL<sup>-1</sup>, while minimum was 1.1 mL min<sup>-1</sup> kg<sup>-1</sup> at creatinine concentration of 5 mg dL<sup>-1</sup> (Table 1) and a curve was plotted between mean serum creatinine and mean GFR (Fig. 1). In our study 38 dogs (86.36%) out of 44, showed a conventional pattern of curvilinear relationship between creatinine and GFR. Interindividual variations was observed in 5 (11.36%) dogs where at the same creatinine

Table 1: Distribution of animal on basis of creatinine range and mean GFR and mean serum creatinine

Group	No. of animals	Range of serum creatinine	Range of GFR	Mean serum creatinine (mg dL <sup>-1</sup> )	Mean GFR (mL min <sup>-1</sup> kg <sup>-1</sup> )
1	7	1.8-2.3	2.3-4.0	2.03	3.52
2	6	2.4-2.9	1.9-3.4	2.53	2.87
3	9	3.0-3.5	1.4-3.6	3.30	2.52
4	8	3.6-4.1	1.2-2.8	3.91	2.21
5	6	4.2-4.7	1.3-1.9	4.35	1.95
6	8	4.7-5.5	1.1-1.6	5.06	1.48

Table 2: Statistical analysis of the creatinine and GFR relationship

Parameters	Values	(%)
Total dogs in study	44	86.36
Dog showing curvilinear relationship	38	9.09
False positive (reduced GFR with normal creatinine)	4	4.54
False negative (normal GFR with marginally high creatinine)	2	
Interindividual variation at creatinine level of 2.3 mg dL <sup>-1</sup> was observed in 11.36 % (5 dogs)		

concentration (2.3 mg dL<sup>-1</sup>), different GFR values were obtained ranging from normal (4.0 mL min<sup>-1</sup> kg<sup>-1</sup>) in 2 dogs to reduced (2.2 to 3.2 mL min<sup>-1</sup> kg<sup>-1</sup>) in 3 dogs. False positive results were obtained in 4 (9%) dogs), where on scintigraphic analysis, creatinine was within normal reference range but GFR decreased (3.2 to 3.5 mL min kg). False negative observations were seen in two (4.5%) of the dogs, where normal GFR with marginally high creatinine values (2.3 mg dL<sup>-1</sup>) were observed (Table 2).

## DISCUSSION

The shape of the curve plotted between serum creatinine and GFR is not a straight line but more or less curvilinear (Fig. 1) which is in agreement with Toutain *et al.* (2000). The pattern of curve has several consequences. At both ends, a large variation of one parameter corresponds to a very small change in the other which means that a reduction of GFR has modest effect on serum creatinine and a huge decrease of creatinine corresponds to only a minor increase in GFR, therefore in early stages of renal disease, these tests could create a false sense of security. These which observations are in agreement with Finco *et al.* (1994) who reported that 50% reduction of renal mass produced no change in creatinine for 4 years in dogs. Serum creatinine is also an unreliable indicator of renal function and often overestimates GFR in chronic renal failure. Interindividual variations were observed in 11.36% of dogs where at the same creatinine concentration (2.3 mg dL<sup>-1</sup>) there were different GFR values ranging from normal in 2 dogs to reduced in 3 dogs. In such dogs creatinine was found a poor predictor of change in GFR. The findings are in agreement with Finco *et al.* (1999) who reported that at same creatinine concentration there may be normal or reduced GFR.

In two dogs, creatinine was within normal range but there was decrease in GFR on scintigraphic analysis, the suggested reason for this observation is presentation of dogs in phase of early renal failure, this observation is in accordance with Bauer *et al.* (1982) who stated that in the early stages of renal disease, creatinine could create a false sense of security. Ross (1995) also reported similar findings in dogs and stated that biochemical markers like creatinine and blood urea nitrogen are relatively insensitive in detecting renal dysfunction because about 70-75% of the

nephrons should be nonfunctional before these values rise above the normal range. In four dogs, normal GFR with marginally high creatinine values was observed, the possible cause for this may be the diet of dogs as reported by Watson *et al.* (1981), who suggested that creatinine is increased for the first few h and remains up for almost 12 h after meals of raw or cooked meat or following ingestion of commercial food (Evans, 1987). In this study both kenneled dogs and stray dogs were included, that may be another possible cause of interindividual variation as reported by Rautenbach and Joubert (1988) who found a higher creatinine in dogs living outside than in kenneled dogs, although their weight and food intake were similar.

## CONCLUSION

Based on the present study, it is concluded that biochemical markers like serum creatinine are not too sensitive in detection of early renal damage. Also usefulness of creatinine estimation is limited in early renal failure when marked reduction of GFR may be associated with little change in creatinine concentration, therefore serum creatinine should only be used for screening of animal for renal diseases, monitoring the progression of renal disease or the efficiency of a treatment. In contrast, scintigraphy has the advantage of physiological imaging and can be used in early diagnosis of renal failure in dogs to enable timely application of therapeutic intervention. This imaging technique has added advantage of estimating global and individual kidney function which can not be obtained by creatinine estimation.

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