Creatinine in the Dog: A Review

J. P. Braun, H. P. Lefebvre, A. D. J. Watson

Creatinine is the analyte most frequently measured in human and veterinary clinical chemistry laboratories as an indirect measure of glomerular filtration rate (GFR). Although creatinine metabolism and the difficulties of creatinine measurement have been reviewed in human medicine, similar reviews are lacking in veterinary medicine. The aim of this review is to summarize information and data about creatinine metabolism, measurement, and diagnostic significance in the dog. Plasma creatinine originates from the degradation of creatine and creatine phosphate, which are present mainly in muscle and in food. Creatinine is cleared by glomerular filtration with negligible renal secretion and extrarenal metabolism, and its clearance is a good estimate of GFR. Plasma and urine creatinine measurements are based on the nonspecific Jaffé reaction or specific enzymatic reactions; lack of assay accuracy precludes proper interlaboratory comparison of results. Preanalytical factors such as age and breed can have an impact on plasma creatinine (P-creatinine) concentration, while many intraindividual factors of variation have little effect. Dehydration and drugs mainly affect P-creatinine concentration in dogs by decreasing GFR. P-creatinine is increased in renal failure, whatever its cause, and correlates with a decrease in GFR according to a curvilinear relationship, such that P-creatinine is insensitive for detecting moderate decreases of GFR or for monitoring progression of GFR in dogs with severely reduced kidney function. Low sensitivity can be obviated by determining endogenous or exogenous clearance rates of creatinine. A technique for determining plasma clearance following IV bolus injection of exogenous creatinine and subsequent serial measurement of P-creatinine does not require urine collection and with additional studies may become an established technique for creatinine clearance in dogs. (Vet Clin Pathol. 2003;32:162-179)

Key Words: Clearance, creatinine, dog, renal disease

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Introduction

Plasma creatinine is the analyte most frequently measured in human and veterinary clinical chemistry laboratories as an indirect measure of glomerular filtration rate (GFR). Some reviews have dealt with creatinine metabolism and the difficulties of its measurement in human medicine.1-5 In veterinary clinical chemistry such reviews are not available, although summarized information can be found in general textbooks.6-10 The aim of this review is to summarize information and data about the metabolism, measurement, and diagnostic significance of creatinine in the dog.a

Metabolism of Creatinine in the Dog

Creatinine is a small molecule (molecular mass 113 daltons) produced by cyclization from creatine phosphate and creatine (Figure 1). It is highly water soluble (~750 mmol/L, ~85 g/L). Creatine and creatinine originate mainly from biosynthesis from the amino acids glycine, arginine, and methionine and partly from alimentary supply. The latter is more important in carnivores than in other animals due to the high concentration of creatine and, to a lesser degree, creatinine in meat.

Alimentary supply

Creatine concentration is high in meat, whereas creatinine concentration is about 10 times lower, with values of 30-45 µmol/g and 2-4 µmol/g, respectively, in raw beef.11 About 20 to 65% of creatine is transformed to creatinine by cooking. In commercial food, creatine and creatinine concentrations are much lower, generally in the 0.5-2.0 µmol/g range.11

Biosynthesis of creatine and creatinine

The first step of the main route of creatine biosynthesis (Figure 2) takes place in the kidney, where transamination from arginine to glycine produces guanidinoacetic acid (= glycocyanine). The mitochondrial enzyme, arginine:glycine amidinotransferase (AGAT), is retroinhibited and repressed by creatine, thus regulating creatine production. Although AGAT exists in the liver of some mammals, such as cattle and humans, it is not detected in canine liver. N-methylation of guanidinoacetate is catalyzed by guanidinoacetate methyltransferase (GAMT), using methyl groups donated by S-adenosylmethionine, leading to production of creatine, which has no known function in hepatocytes. Creatine is distributed by blood to the rest of the body and via a Na+/Cl−-dependent transporter penetrates brain and muscle cells where it is reversibly phosphorylated to creatine phosphate by creatine kinase. Skeletal muscle contains about 95% of total body creatine. Plasma creatine filtered by renal glomeruli undergoes renal tubular reabsorption, so that urine creatine elimination is weak, except after oral loading.3,5,6

Creatinine is the product of the spontaneous, irreversible, nonenzymatic, internal dehydration of creatine and dephosphorylation of creatine phosphate. This conversion to creatinine occurs at an almost constant rate and affects about 2% of the total pool of body creatine daily. Endogenous production of creatinine has been estimated as 380 ± 45 µmol/kg/d in healthy Beagle dogs having a GFR (mean ± SD) of 3.3 ± 0.23 mL/min/kg, plasma creatinine (P-creatinine) concentration of 80 ± 12 µmol/L, and daily urine creatinine (dU-creatinine) output of 425 ± 45 µmol/kg/d.12 Endogenous creatinine production was lower (300 ± 27 µmol/kg/d) in dogs with a 60% experimental reduction of renal mass, but was not correlated clearly with reduced body mass.12 In humans with chronic renal failure, it has been reported that some

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aAll concentrations are expressed in SI units. To convert from SI to conventional units for creatinine concentration, use the calculation: 1 µmol/L = 0.113 mg/L = 0.0113 mg/dL; for reverse conversions, use: 1 mg/L = 8.85 µmol/L; 1 mg/dL = 88.5 µmol/L.
Creatinine diffuses into the intestine, where it is hydrolyzed to creatine, which is partly reabsorbed and partly degraded by the intestinal flora and excreted in feces. This process seems to be negligible in dogs, since more than 95% of administered creatinine is recovered in urine within 24 hours; however, it cannot be excluded in advanced renal failure.

After endogenous production or exogenous administration, creatinine diffuses into the total body water compartment. Its volume of distribution has been variously estimated as 400-500 mL/kg and, more recently, as 600 mL/kg in healthy dogs and dogs with surgical renal reduction. Creatinine has also been found in peritoneal fluid, where its concentration was low (<80 μmol/L), synovial fluid, bronchoalveolar lavage fluid, and aqueous and vitreous humors, where its concentration was about twice that in serum.

Urinary elimination of creatinine

Creatinine in plasma is freely filtered by glomeruli so that its concentration in glomerular filtrate is the same as that in plasma. Creatinine is weakly secreted in renal proximal tubules in dogs, especially in males, but this is of negligible significance, even in males with chronic renal failure (CRF).

As the input of creatinine into plasma depends mainly on muscle mass, urinary elimination of creatinine is constant over time. In the dog, it was reported variously that there was no difference in creatinine elimination according to sex or that it was higher in males than in females. Urine creatinine (U-creatinine) concentration did not differ between day and night, but U-creatinine was increased or was not increased after meals. Interindividual variations of U-creatinine are very large, even in urine collected for 24 hours.

Total U-creatinine excretion differs greatly according to studies, with means ranging from 170 to 425 μmol/kg/d. These differences may be due to food composition, as dogs fed a meat-based diet (31.4% protein) eliminated more creatinine than dogs fed a casein-based diet (10.4% protein), but probably also are due to differences in the accuracy of creatinine measurement (see below). Variation in U-creatinine concentration is even larger, mainly due to changes in urine dilution/concentration, and ranges from 4.7 to 42.0 mmol/L.

Plasma Creatinine Measurement

Preanalytical factors of variation

Specimen. Creatinine concentration is about 5-10 μmol/L higher in serum than in plasma of the same animal (range of values 100-120 μmol/L).

Stability. In whole blood with or without anticoagulant, creatinine concentration progressively increased at room temperature, by up to 35% on the 4th day, whereas it was stable at 4°C. In serum or heparinized plasma creatinine concentration was stable for up to 4 days at room temperature and up to 3 months at –20°C, and it increased moderately afterwards. Creatinine decreased by more than 25% at –20°C in serum after 1 month and in EDTA plasma after 1 day. Long-term stability of creatinine is better with storage at –70°C.

Effect of food. P-creatinine is increased for the first few hours and remains increased for up to 12 hours after meals of raw or cooked meat. Following ingestion of commercial food of undetermined creatine/creatinine content, increases, decreases, or no change in P-creatinine have been reported. Oral loading with creatine for 2-4 weeks caused a dose-dependent increase in P-creatinine.

Interindividual differences in postprandial changes in P-creatinine were significant. Postprandial decreases in P-creatinine were attributed to protein-induced increases in GFR. The quality and amount of protein in dog food have no effect on fasting P-creatinine in healthy dogs and dogs with CRF. In dogs with experimental CRF, P-creatinine was unchanged or lower in dogs fed ω3-fatty acids than in dogs fed ω6-polyunsaturated fatty acids.

Analytical techniques

P-creatinine has been measured for many years by the nonspecific Jaffé reaction, which is being replaced progressively by specific enzymatic techniques that give values approximately 20 μmol/L lower. Enzymatic techniques have not been validated for canine plasma, but with human samples they were reported to be more accurate and to allow better interlaboratory comparisons.

Jaffé’s reaction. This method is based on the formation of a yellow-orange chromogen by the action of picrate ions on creatinine at alkaline pH. The Jaffé reagent (picrate ion) also acts on many other substances such as bilirubin, lipids, and acetoacetate, which cause a negative bias, and acetone and glucose, which cause a positive bias. Jaffé’s reaction overestimates P-creatinine by up to 45% in healthy dogs. Interferences from these noncreatinine chromogens vary from dog to dog, and,
therefore, a “correction factor” cannot be applied to convert Jaffé creatinine measurements to true creatinine concentration. Interferences are progressively less in dogs with renal failure, as true creatinine concentration increases.68 Hemoglobin interference is negligible at concentrations \( < 16 \text{ g/L} \).69 Because interfering substances are proportionately less abundant in urine than in plasma, results of U-creatinine measurements by Jaffé’s reaction were reported not to be overestimated68 or only moderately so by an average of 6%.59

Enzymatic reactions. These methods are based on the use of creatinine amidohydrolase (= creatininase, EC 3.5.2.10) or of creatinine iminohydrolase (= creatinine deiminase, EC 3.5.4.21) (Figure 3). Interferences are limited to bilirubin at concentrations \( \geq 50 \mu\text{mol/L} \).67

Reference intervals

The value of reported P-creatinine reference intervals in dogs is highly questionable. Many textbooks report “normal ranges”, with no indication of the characteristics of the population or assay method used. This may account for the remarkably large overall range of values reported, from 35 to 250 \( \mu\text{mol/L} \), including some intervals that do not even overlap.70 It is thus recommended not to use data or thresholds indicated in the literature, but to compare results with the reference interval of the laboratory or analyzer used.

Interindividual factors of variation

Sex. There is little or no effect of sex on P-creatinine in dogs, whatever the age.71-74

Age. Published data regarding the effect of age on P-creatinine are conflicting. In most studies P-creatinine decreased in the first days of life, and then was stable up to 2 months or increased moderately up to 1 year.75-78 P-creatinine was stable72,76 or increased moderately79 in adult dogs up to 8-10 years of age, then it decreased, whereas body weight (BW) remained unchanged (Figure 4).80,81 No difference was observed in P-creatinine between dogs aged 0.5-5.0 and 6.0-13.5 years82 or between dogs less than 1 year old and more than 9 years old.83

Weight/muscle mass. In newborns, P-creatinine was higher in large dog breeds.79 In adults P-creatinine increased with the BW of dogs,73,83 and U-creatinine did as well,83 but interindividual variability was high. P-creatinine was higher in Greyhounds and other sight hounds than in other breeds.85,86 P-creatinine was reported to be lower in some cachectic dogs, although no original study is available.87

Housing. P-creatinine was moderately higher (5-15 \( \mu\text{mol/L} \)) in dogs living outside than in kennelled dogs, although their weight and food intake were similar.88,89

Intraindividual factors of variation

Season. P-creatinine was slightly higher in summer and autumn than in winter and spring in laboratory Beagles.90

Biological rhythms. A circadian rhythm was observed in fasting animals with a moderate increase in P-creatinine at 3 PM,91 whereas others observed no change over the whole day.12,46 In dogs sampled at the same time of the day, an 18% difference was observed between the peak (acrophase) in midspring to midsummer and the trough in winter; monthly and weekly rhythmic components also were observed.92 A circadian rhythm also was observed for U-creatinine, probably mainly due to meals (Figure 5).28

Site of blood sampling. P-creatinine was moderately higher in samples obtained from the jugular vein than those from the cephalic vein by a mean value of 5 \( \mu\text{mol/L} \), which is much lower than the interindividual variability in samples obtained from the same site.93

![Figure 3](image-url) Enzymatic reactions used to measure creatinine concentration.

![Figure 4](image-url) Variation of P-creatinine according to age in male (o) and female (◊) dogs; data from Fukuda.80,85
Hydration state. Dehydration caused increases of P-creatinine only when it was greater than 5%. Changes in P-creatinine were not proportional to dehydration and showed large interindividual variability.

Physical effort. It was reported that P-creatinine was unchanged in sled dogs after very long races or decreased by ~10% in untrained Beagles 8-10 hours after running for 1 hour. P-creatinine was also decreased in the 30 minutes following sprints (14-28 km) in well-trained sled dogs and increased following the same effort during abatement of training. On the contrary, P-creatinine was reported to increase about 50% after exhaustive exercise in sled dogs. During training, P-creatinine was reported to be unchanged or to be decreased by a mean of 33%. In Greyhounds, P-creatinine was slightly increased (by ~20 µmol/L) after races and remained so for at least 1 hour. P-creatinine was moderately increased in dogs after searching for drugs.

Effects of drugs

Most drugs affect P-creatinine by reducing GFR through one of 3 mechanisms.

Damage to the kidney. Gentamicin has been reported to cause no or moderate increases in P-creatinine, except when severe damage occurred especially in dogs with pre-existing renal failure. Similar effects were observed with platinum derivatives, oxytetracycline, high-dose netilmicin and tobramycin (>50 mg/kg for 2 weeks), amphotericin B, calciferol and its derivatives, ivermectin in one case, trimethoprim-sulfadiazine, and methoxyflurane plus flunixin.

Altered renal hemodynamics. Moderate and transient increases in P-creatinine were observed after treatment with morphine, oxymorphone, ketoprofen, carprofen, ketorolac, and butorphanol; others observed no increase with piroxicam and carprofen. The angiotensin-converting enzyme (ACE) inhibitors captopril and benazepril caused moderate increases in P-creatinine, whereas enalapril had the same effects as a placebo or also caused moderate increases. Cyclosporin and insulin-like growth factor-1 (IGF1) also caused moderate increases in P-creatinine, but cyclosporin was reported to have no effect on P-creatinine in another case. Paradoxically, growth hormone treatment, which induces an increase of IGF1, caused a moderate decrease in P-creatinine.

Extracellular dehydration. Prerenal kidney insufficiency caused by furosemide in dogs with heart failure, digoxin, intraperitoneal administration of iodinated povidone-iodine were reported to cause increases of P-creatinine.

Glucocorticoids caused a moderate decrease of P-creatinine in normal dogs, but not in dogs with hypoadrenocorticism. Ethionine also has been reported to cause a moderate decrease of P-creatinine. The mechanisms by which glucocorticoids and ethionine affect P-creatinine are unknown.

Pathologic Variations in P-Creatinine

Relationship between P-creatinine and GFR

When P-creatinine and GFR were determined independently (ie, not by endogenous creatinine clearance), the relationship was hyperbolic, exponential, or curvilinear (Figure 6). A similar relationship can also be derived from GFR measured by exogenous creatinine clearance.

The shape of the curve and the dispersion of values have several consequences. At both ends, a large variation of one variable corresponds to a very small change in the other, which means that a reduction of GFR from 3.5 to 2.5 mL/min/kg has little effect on P-creatinine and that a large decrease of P-creatinine from 500 to 300 µmol/L (5.7 to 3.4 mg/dL) corresponds to only a minor increase in GFR. Interindividual variations are so large that the same P-creatinine concentration can correspond to normal or reduced GFR.
Effects of experimental reduction of GFR

Reduction of renal function by surgery or by injection of microspheres produces a simultaneous increase in P-creatinine and decrease in creatinine clearance. The effects are more intense during the first days, then compensatory hypertrophy of the remaining kidney tissue causes a decrease and stabilization of P-creatinine,151-154 which is not attributable to the reduction in muscle mass of the dogs (Figure 7).153 For instance, a reduction of renal mass by 3/4 to 7/8 caused a 1.5- to 2-fold increase in P-creatinine109,155-157 and a simultaneous decrease in mean creatinine clearance from 3.5 to 1.3 mL/min/kg109; about a 60% reduction of kidney mass caused a 2-fold increase in P-creatinine,12,158 and a 50% reduction of renal mass produced no change in P-creatinine for 4 years, regardless of the amount of protein in the diet, in dogs aged 7 years at the beginning of the study.159

Diagnostic efficiency of P-creatinine for diagnosis of chronic renal failure

The diagnostic efficiency of increases in P-creatinine for the diagnosis of CRF has been evaluated in only one study,144 the criterion for CRF being GFR \( \leq 2 \text{ mL/min/kg} \) (Table 1). If the predictive values of positives (PVP) and negatives (PVN) are calculated from these data, it can be observed that the diagnostic efficiency of P-creatinine is relatively limited. For instance, at the 150 µmol/L (1.7 mg/dL) threshold, a pretest probability of 0.5 leads to a PVP of 0.86 and a PVN of 0.76 (Figure 8). It is generally considered that at least ~75% of nephrons must be nonfunctional before P-creatinine is increased above the upper limit of the reference interval.

P-creatinine is efficient for monitoring the progression of CRF 160 or the efficiency of a treatment, eg, hemodialysis161; the critical difference has been estimated to be 35 µmol/L (0.4 mg/dL) in the range of “normal” values.162 In dogs with CRF, P-creatinine increased progressively with time, but interindividual variability was marked, and in some dogs P-creatinine was a poor predictor of change in GFR.163 Time of death can be estimated from the point where the regression line of 1/P-creatinine vs. time intercepts the time axis.160

P-creatinine is more efficient than plasma urea concentration for the diagnosis of CRF.148 In dogs with spontaneous or surgically-induced CRF, the correlation between plasma concentrations of urea and creatinine was reported to be high98,148,164-167 or low;168 P-creatinine variations correlated well with the concentration of plasma cystatin C, a small protein that is eliminated only by glomerular filtration.43,169-171

In human medicine, equations are proposed to esti-

Table 1. Sensitivity and specificity of P-creatinine at different thresholds for the diagnosis of chronic renal failure (GFR \( \leq 2 \text{ mL/min/kg} \)) in the dog. The reference interval for the method used in this study was 124 ± 28 µmol/L (range 71-193) (data from Gleadhill144).

<table>
<thead>
<tr>
<th>Threshold Plasma Creatinine Concentration (µmol/L)</th>
<th>&gt;110</th>
<th>&gt;130</th>
<th>&gt;150</th>
<th>&gt;170</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>0.95</td>
<td>0.84</td>
<td>0.72</td>
<td>0.58</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.46</td>
<td>0.60</td>
<td>0.89</td>
<td>0.97</td>
</tr>
</tbody>
</table>
mate GFR from P-creatinine, sex, and age. In the dog, an equation relating GFR and 1/P-creatinine was calculated but not advocated to derive GFR from P-creatinine: GFR = \( \frac{227}{\text{H}^{1003}} \times (1/\text{P-creatinine}) \) [recalculated from the original data to accommodate SI units: P-creatinine as µmol/L, GFR as mL/min/kg], with a 95% confidence interval of ± 0.5 mL/min/kg.145 This equation is very similar to the one calculated from data of Westhoff et al146,147 and Haller et al145: GFR = \( \frac{246}{\text{H}^{1003}} \times (1/\text{P-creatinine}) – 0.1 \).

Clinical disorders causing increased P-creatinine

P-creatinine is increased in both acute and chronic renal failure, whatever the cause, but one cannot differentiate between them.172,173 More or less severe increases in P-creatinine have been reported in various percentages of dogs with urinary disorders.

Primary renal disease. P-creatinine is increased in primary renal diseases such as amyloidosis,160,174 polycystic disease,175 glomerulosclerosis,160 and postoperative uremic crisis,176 and in intoxications by sodium arsenate,177 citrin,178 sodium fluoride,179 and vitamin D and its analogs.180,181 P-creatinine was reported to decrease progressively after kidney grafts182 and to be increased during rejection episodes, when very high concentrations could occur (>800 µmol/L).183-187

Secondary renal disease. Underlying disorders causing secondary renal disease and subsequent increases in P-creatinine include babesiosis,166,188,189 leishmaniasis,190-194 leptospirosis,195-198 borreliosis,199-200 trypanosomiasis,201,202 heartworm disease,203 encephalitozoonosis,204 malignant histiocytosis,205 pyometra,206-209 experimental intestinal obstruction,210 gastric dilatation/torsion,211 diabetes melitus,212,213 and hypercalcemia caused by hyperparathyroidism214 or lymphoma.215 The magnitude of increase in P-creatinine differed greatly according to the severity of the underlying disorder.

Congenital or familial renal disease. Progressive increases of P-creatinine were observed in young dogs with congenital or familial renal disease, including Samoyeds with hereditary nephritis,216,217 Bernese Mountain dogs with congenital renal dysplasia,218 Soft-coated Wheaten Terriers,219,220 Bull Terriers and Samoyeds with a condition resembling Alport syndrome,221,222 Newfoundland dogs with glomerulosclerosis,223 Cocker Spaniels with familial nephropathy224 and Greyhounds with glomerular vasculopathy.225 Idiopathic increases in P-creatinine also have been observed in different groups of dogs up to 3 years of age.226,227 P-creatinine was moderately increased in 4 of 10 dogs with Fanconi syndrome.228

Urinary tract obstruction or rupture. Ureteral obstructions261 and bladder rupture26 result in increased P-creatinine. In the latter, creatinine concentration was higher in peritoneal fluid than plasma, allowing identification of the fluid as urine.

Clinical disorders causing decreased P-creatinine

A moderate decrease in P-creatinine was reported in 80% of dogs with portosystemic shunts229 or dogs with a surgically placed portocaval shunt,230 whereas it was unchanged in dogs after surgical portocaval anastomosis associated with periarterial neurectomy.231 A decrease also was noted in early babesiosis.225

Creatinine Clearance

Because the input of creatinine into plasma is almost constant over time and creatinine is excreted by glomerular filtration with only negligible renal tubular secretion or extrarenal metabolism, urine creatinine clearance is almost equal to GFR (see a critical review in animals by Reder et al233). This may also be true for plasma creatinine clearance.12

Techniques

Creatinine clearance, ie, the volume of plasma cleared of creatinine per minute, can be evaluated in several ways

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**Figure 8.** Predictive values of positives (PVP) and of negatives (PVN) of P-creatinine for the diagnosis of chronic renal failure in the dog according to pretest probability and thresholds of decision (in µmol/L), calculated from data from Gleadhill.144 PVP and PVN are the conditional probabilities that an animal testing positive/negative at a given threshold of decision is truly diseased/nondiseased according to the pretest probability that the animal had/did not have the disease for which the test was used.
Endogenous creatinine clearance. Endogenous clearance is determined by measuring both the total amount of endogenous creatinine eliminated in urine over a period of time and the P-creatinine. The determination of endogenous creatinine clearance requires measurement of both plasma and urine creatinine concentrations and the exact volume of urine eliminated over periods of time ranging from 20 min to 24 h, depending on the method.\textsuperscript{235,236}

Exogenous creatinine clearance. The clearance of exogenous creatinine can be evaluated after administration of a precisely known amount of creatinine by bolus SC, IM, or IV or during IV infusion of creatinine. It can also be determined from repeated P-creatinine measurement after IV administration (Figure 9).\textsuperscript{12}

Analytical variability

It has been reported that results of endogenous creatinine clearance were lower than those of urine/plasma exogenous creatinine clearance when creatinine concentrations were measured by Jaffé’s reaction. This likely occurred because the overestimation of P-creatinine is proportionately lower after exogenous infusion of creatinine,\textsuperscript{59,237} unless assay methods unaffected by interfering substances were used, such as enzymatic procedures.\textsuperscript{59,68}

Reference values

Values of creatinine clearance are generally expressed as mL/min/kg, which may not be optimal because it has been demonstrated that GFR (urinary inulin clearance as mL/min/kg) was a decreasing function of BW in healthy dogs,\textsuperscript{143} and variability of urine creatinine clearance expressed per square meter was lower than when expressed per kg BW\textsuperscript{245} or was identical in dogs less than 20 kg BW.\textsuperscript{246} However, BW can be measured accurately, whereas corporal surface is calculated. The main results of a previous review\textsuperscript{209} of creatinine clearance are presented in Table 2.

Interindividual factors of variation

Substantial interindividual differences have been observed.\textsuperscript{247}

Sex. Creatinine clearance was the same in males and females.\textsuperscript{237}

Body weight. A positive correlation was observed between the weight of a dog and endogenous creatinine clearance (mL/min/dog).\textsuperscript{84}

Age. Creatinine clearance has not been reported in very young puppies, although inulin clearance increased
Table 2. Reported endogenous and exogenous creatinine clearance measurements in dogs.

### Endogenous Creatinine Clearance

<table>
<thead>
<tr>
<th>Animals†</th>
<th>Clearance Technique†</th>
<th>Special Conditions</th>
<th>Mean ± SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 dogs, 2045 determinations over 7 years</td>
<td></td>
<td></td>
<td>94 ± 36 mL/min/m²</td>
<td>247</td>
</tr>
<tr>
<td>7 dogs</td>
<td></td>
<td></td>
<td>86 ± 4 mL/min/m²</td>
<td>68</td>
</tr>
<tr>
<td>6 adult F Beagle dogs, 5.7-12.7 kg</td>
<td>2 times 24 h, metabolic cage, no food</td>
<td></td>
<td>2.9 ± 0.23* mL/min/kg</td>
<td>155</td>
</tr>
<tr>
<td>5-6 M/F Beagle dogs, 9.3-3.5 kg</td>
<td>3 times 20 min</td>
<td>Dehydrated</td>
<td>2.15 ± 0.09* mL/min/kg</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Euvhydrated</td>
<td>2.66 ± 0.14* mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperhydrated</td>
<td>2.94 ± 0.12* mL/min/kg</td>
<td></td>
</tr>
<tr>
<td>3 M + 3 F Beagle dogs, 2.8 ± 0.4 kg</td>
<td>48 h, metabolic cage</td>
<td>9 wks old</td>
<td>4.05 ± 0.61 mL/min/kg</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 wks old</td>
<td>4.43 ± 0.51 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>27 wks old</td>
<td>2.49 ± 0.10 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td>10 dogs, 0.5-8 yrs old, 5-35 kg</td>
<td>24 h, metabolic cage</td>
<td></td>
<td>3.12 ± 0.85 mL/min/kg</td>
<td>249</td>
</tr>
<tr>
<td>Not specified</td>
<td>24 h, metabolic cage</td>
<td></td>
<td>2.96 ± 0.48 mL/min/kg</td>
<td>237</td>
</tr>
<tr>
<td>36 F dogs, 6-12 mos old, 7-11 kg</td>
<td>24 h, metabolic cage</td>
<td></td>
<td>3.77 ± 0.77 mL/min/kg</td>
<td>250</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57.6 ± 9.3 mL/min/m²</td>
<td>251</td>
<td></td>
</tr>
<tr>
<td>9 M + 2 F dogs</td>
<td>24 h, metabolic cages</td>
<td></td>
<td>2.34 ± 0.83* mL/min/kg</td>
<td>59</td>
</tr>
<tr>
<td>10 dogs</td>
<td>2 times 20 min</td>
<td></td>
<td>48.3 ± 9.5 mL/min/m²</td>
<td>251</td>
</tr>
<tr>
<td>26 M dogs, 18.1 ± 7.5 kg</td>
<td>20 min</td>
<td></td>
<td>2.93 ± 0.96 mL/min/kg</td>
<td>252</td>
</tr>
<tr>
<td></td>
<td></td>
<td>60.6 ± 21.9 mL/min/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 M + 18 F dogs, 22 ± 2.6 kg</td>
<td>2 times 30 min</td>
<td></td>
<td>4.10 ± 0.14* mL/min/kg</td>
<td>244</td>
</tr>
<tr>
<td>11 M + 12 F dogs, 7-13 kg</td>
<td>6 times 4 h</td>
<td></td>
<td>2.6 ± 0.6 mL/min/kg</td>
<td>28</td>
</tr>
<tr>
<td>7 M + 9 F dogs</td>
<td>6 times 4 h</td>
<td></td>
<td>2.6 ± 0.7 mL/min/kg</td>
<td>32</td>
</tr>
</tbody>
</table>

### Exogenous Creatinine Clearance

<table>
<thead>
<tr>
<th>Animals†</th>
<th>Clearance Technique†</th>
<th>Special Conditions</th>
<th>Mean ± SD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 F Beagle dogs, 9.5-17.5 mos old</td>
<td>Water loading, IV constant infusion, 3 times 10 min</td>
<td></td>
<td>4.35 ± 0.26 mL/min/kg</td>
<td>245</td>
</tr>
<tr>
<td>3 M + 28 F dogs, 7-8 yrs old</td>
<td>Bolus + IV constant infusion 18% protein diet 35% protein diet</td>
<td></td>
<td>3.25 ± 0.23* mL/min/kg</td>
<td>153</td>
</tr>
<tr>
<td>5 M + 5 F dogs, 7.7-20.4 kg</td>
<td>SC, 100 mg/kg, 3 times 20 min</td>
<td></td>
<td>3.12 ± 0.16* mL/min/kg</td>
<td>237</td>
</tr>
<tr>
<td>8 F dogs, 12.0-17.5 kg</td>
<td>PO, 8.8 mmol in 50 mL water, 3 times 20 min after 1 h</td>
<td>14 mmol Na/kg food 2 mmol Na/kg food</td>
<td>4.89 ± 0.83 mL/min/kg</td>
<td>243</td>
</tr>
<tr>
<td>8 M + 22 F dogs, 14.8 ± 4.5 kg</td>
<td>IV, 88 mg/kg, 3 times 30 min</td>
<td></td>
<td>4.13 ± 0.51 mL/min/kg</td>
<td>16</td>
</tr>
<tr>
<td>5-6 M/F Beagle dogs, 9.3-13.5 kg</td>
<td>IV, 875 mg</td>
<td>Dehydrated</td>
<td>2.78 ± 0.06* mL/min/kg</td>
<td>238</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Euvhydrated</td>
<td>3.64 ± 0.10* mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperhydrated</td>
<td>4.14 ± 0.20* mL/min/kg</td>
<td></td>
</tr>
<tr>
<td>6 M Beagle dogs, 9.4-14.0 kg</td>
<td>24 h, metabolic cage</td>
<td>40 mg/kg</td>
<td>2.5 ± 0.42 mL/min/kg</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg/kg</td>
<td>3.0 ± 0.37 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>160 mg/kg</td>
<td>3.4 ± 0.70 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Determination from plasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>40 mg/kg</td>
<td>3.0 ± 0.44 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>80 mg/kg</td>
<td>2.9 ± 0.31 mL/min/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>160 mg/kg</td>
<td>3.0 ± 0.52 mL/min/kg</td>
<td></td>
</tr>
</tbody>
</table>

* Variance is expressed as standard error rather than SD.
† M indicates male; F, female; IV, intravenous; PO, per os; SC, subcutaneous.
progressively during the first 2 months of life. Creatinine clearance steadily decreased (by approximately 50%) in puppies aged 2 to 7 months, when values were approximately the same as in adults. Clearance did not change over 4 years in 7 to 8-year-old dogs fed an 18% or 35% protein diet. It was moderately higher in the 4 hours following a morning meal.

Nutrition. Creatinine clearance was lower in dogs with reduced renal function fed low-protein diets than in dogs fed high-protein diets or was reported to be unaffected by dietary protein content or by the source of protein in healthy dogs and dogs with renal failure. Creatinine clearance decreased in dogs with renal reduction fed ω6-fatty acids and not in dogs fed ω3-polyunsaturated fatty acids.

Hydration state. Exogenous and endogenous creatinine clearances were lower (~15%) in 10%-dehydrated than in normally hydrated dogs, in which it was lower (~15%) than in hyperhydrated dogs (dogs given 30 mL/kg oral water).

Effect of food. Creatinine clearance was the same in fed (~45% protein) and unfed dogs, except in 3 cases where clearance was increased by 10%. It was moderately higher in the 4 hours following a morning meal.

Anesthesia. Creatinine clearance was approximately 1/3 lower in dogs anesthetized with thiopental/halothane than in awake dogs.

Pathologic and toxicologic variations

In remnant kidney models, creatinine clearance was decreased and then progressively increased and stabilized as compensatory hypertrophy of the remaining nephrons occurred.

Creatinine clearance was reduced by approximately 20% following repeated urography with iothalamate. It was also decreased in dogs treated with cisplatin, amphotericin B, and gentamicin. Creatinine clearance was reported to be very low just after renal transplantation, then to progressively increase as animals recovered, or to remain low if animals experienced rejection. Creatinine clearance was decreased by approximately 1/4 in dogs injected with endothelin-1.

Creatinine clearance was reported to be low in dogs poisoned by sodium arsenate and in pyometra and hypercalcemia of malignancy. It was also reported to be unchanged after adenoviral delivery of genes into the kidneys.

Summary

Plasma creatinine concentration is the best routine indirect marker of GFR in dogs. However, analytical methods, age, body weight, and timing of meals can significantly affect results and should be taken into account when interpreting results, especially when values approach the lower and upper limits of reference intervals. Creatinine clearance is a better indicator of GFR than P-creatinine, but its measurement should be limited to situations in which history, physical examination, and routine biochemical results are ambiguous.

References


Braun, Lefebvre, Watson


Creatinine in the Dog


Creatinine in the Dog


