Effects of administration of fluids and diuretics on glomerular filtration rate, renal blood flow, and urine output in healthy awake cats

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Objectives—To determine effects of commonly used diuretic treatments on glomerular filtration rate (GFR), renal blood flow (RBF), and urine output (UO) and compare 2 methods of GFR measurement in healthy awake cats.

Animals—8 healthy cats.

Procedure—in a randomized crossover design, cats were randomly allocated to 4 groups: control; IV administration of fluids; IV administration of fluids and mannitol; and IV administration of fluids, dopamine, and furosemide. Inulin and para-aminomphippuric acid were used for determination of plasma clearance for GFR and RBF, respectively. Plasma clearance of technetium-Tc-99m-diethylenetriaminepentacetic acid (99mTc-DTPA) was also used for GFR determination.

Results—Furosemide-dopamine induced the largest UO, compared with other groups. Both mannitol and fluid therapy increased RBF, compared with the control group. Mannitol, and not fluid therapy, increased RBF, compared with furosemide-dopamine. There were significant differences in GFR values calculated from 99mTc-DTPA and inulin clearances between the 2 groups. In all groups, use of 99mTc-DTPA caused underestimation of GFR, compared with use of inulin.

Conclusions and Clinical Relevance—In healthy awake cats, administration of furosemide-dopamine did not increase GFR or RBF despite increased UO. Fluid therapy and fluid therapy plus mannitol improved RBF. Determination of GFR by use of 99mTc-DTPA cannot always be substituted for inulin clearance when accurate measurement is required. (Am J Vet Res 2006;67:715–722)

C hronic kidney disease, including acute exacerbation of chronic kidney disease, is the most common cause for morbidity and death in cats > 10 years of age.1 The chronically diseased kidneys often reach a point of
equilibrium, at which, as long as minimal changes are made to hydration status, affected cats can survive with supportive care for extended periods of time. This often can be achieved by home administration of appropriate diets, orally administered medications, and SC administration of fluids. Acute disease, however, is associated with severe metabolic derangements that require aggressive treatment. The goal of these treatments, other than to increase UO, is to ensure diuresis of toxins, support RBF, and maintain the highest GFR possible.1

The most common modalities used to treat acute veterinary patients with renal failure are fluid administration at rates to promote diuresis; mannitol infusions with fluid administration; and a combination of dopamine, furosemide, and fluid administration. When these protocols are used in a timely manner after the discovery of renal failure, the hope is to avoid the need for peritoneal dialysis or hemodialysis. However, although UO may be increased, it is unknown whether these treatment protocols are beneficial to RBF and GFR.1

Most of our current knowledge about the mechanism of action of these diuretic agents (mannitol, furosemide, and dopamine) comes from research with dogs, rats, and humans. There is little information in the literature regarding the effects of these drugs on cats. Also, most of the research has been performed on anesthetized animals, including cats, by use of invasive measurement techniques to determine flow and pressure dynamics in the renal vessels and tubules.2,3 There is no direct information in the literature available regarding these treatment modalities in awake cats with either normal or abnormal renal function.

A few noninvasive methods have been described for determination of GFR and RBF. Inulin and creatinine clearances are the gold standards for GFR determinations, but early protocols relied on CRIs administered IV. In some centers, 99mTc-DTPA clearance is now being used in animals to determine GFR for single kidneys as well as overall GFR. Technetium-Tc-99m-diethylenetriaminepentacetic acid appears to have the

<table>
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<th>ABBREVIATIONS</th>
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<tr>
<td>RBF</td>
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<td>GFR</td>
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<tr>
<td>UO</td>
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<tr>
<td>99mTc-DTPA</td>
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<td>PAH</td>
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<td>RPF</td>
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<td>ANP</td>
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same properties as inulin, which makes it suitable for GFR determinations. Both inulin and 99mTc-DTPA are freely filtered by the kidneys, achieve equilibrium with the extracellular fluid in the body readily, and are not actively reabsorbed in the tubules. Therefore, their clearance from plasma is an estimation of GFR.

Recently, a protocol for a single SC injection of inulin was described and analyzed. Results of the single-injection method correlated well with that of CRI methods, making the former easier to perform. Clearance of 99mTc-DTPA is also based on a single injection; however, the route of administration is IV, unlike the SC route for inulin. 99m-technetium-diethyleneetriaminepentaacetic acid is a radioactive isotope and requires special facilities for handling it and the animals after administration.

Renal blood flow has been estimated by use of plasma clearance of PAH. Para-aminomimidic acid is filtered by the glomerulus and eliminated by tubular excretion in the renal solute. Clearance of PAH from plasma should be equivalent to total renal plasma flow. Because there is no known substance that is completely cleared by these mechanisms, renal plasma flow is an estimation only. Para-aminohippuric acid is approximately 90% cleared and offers the best noninvasive method to determine renal clearance. The term RBF is commonly used in the literature as well as in this study, although what is actually measured is RPF.

The purposes of the study reported here were to determine effects of commonly used diuretic treatments on GFR, RBF, and UO and to compare 2 methods of GFR measurement in healthy awake cats. We hypothesized that mannitol administration along with IV fluid-induced diuresis would improve RBF and GFR more than any other protocol but that IV fluid-induced diuresis with furosemide-dopamine would increase UO more than the other protocol. We also hypothesized that 99mTc-DTPA clearance would correlate well with inulin clearance for measurement of GFR.

Material and Methods

Cats—Eight healthy cats were obtained from a research facility for this study: cats were 9 months to 2 years of age and weighed 4.1 to 6.6 kg. Five cats were neutered males, and 3 were neutered females. The male cats were housed separately from the female cats. All cats were housed in the research animal facility at Cornell University during the study days. All cats were fed the same commercial diet and given water ad libitum between study days. Cats were determined to be healthy via results of physical examination, CBC, serum biochemical panel, and urinalysis prior to the study; bacteriologic culture of urine was performed throughout the study. Cats were handled by the investigators in accordance with Cornell University’s Animal Care and Use Protocol. An institutional and animal care and use committee approval was obtained for this study.

Study design—A randomized crossover design with 4 treatment protocols was used. Cats were randomly allocated to the protocols on each study day by lottery. The primary investigators were blinded to the initial lottery system that was designed to ensure that no cat was assigned to the same protocol more than once. Study days were referred to by numbers 1 to 4, and on each day, 2 cats were assigned to each protocol. Each study day occurred at least 6 days after the previous study day to allow for a washout period between protocols for the various drugs.

Study preparation—Cats were anesthetized by administration of isoflurane via mask. After anesthetic induction, cats were intubated and anesthesia was maintained with isoflurane alone. Intravenous catheters were placed in both a cephalic and a median saphenous vein, and a urinary catheter was placed in the urinary bladder. Vein sites were rotated throughout the study.

Cats were given a single SC injection of saline (0.9% NaCl) solution before the catheters had been placed and just prior to recovery. This injection was meant to ensure a minimal level of hydration during the study-day duration of 8 hours. Saline solution was used because it does not contain potassium and it was desired to use a type of fluid used in clinical situations in which hyperkalemia should be avoided (eg, oliguria or anuria). Also, drugs can be added to saline solution without concern for interaction or precipitation with various fluid components. Volumes for the SC injections were calculated at a maintenance rate of 60 mL/kg/d. During an 8-hour period, each cat received 20 mL/kg. At the end of each study day, no cat had evidence of a fluid pocket, indicating that the entire volume had not been absorbed. Hydration status was not assessed other than by use of physical variables (ie, skin turgor and mucous membrane perfusion). The PCV, total solids concentration, and urine osmolality were not assessed. All cats recovered from anesthesia without complications.

Treatment protocols—After recovery from anesthesia, cats received their respective diuretic protocols for a 3-hour equilibration period prior to the start of sample collection (time 0). The diuretic protocols were as follows: group 1, no treatment (ie, control); group 2, saline solution at 6 mL/kg/h (slightly less than 2.5 times the maintenance rate); group 3, saline solution at 6 mL/kg/h, a mannitol bolus (range, 0.5 g/kg to 0.8 g/kg during 15 minutes), and then a CRI of mannitol at 1 mg/kg/min; and group 4, saline solution at 6 mL/kg/h, a furosemide CRI of 0.25 mg/kg/min, and a dopamine CRI of 2.5 g/kg/min.

The mannitol bolus volume added to 8 to 13 mL (2 cats received doses > 0.5 g/kg because of technical difficulties with syringe pumps [0.65 and 0.79 g/kg, respectively]) of fluid to the volume of fluid administered to group 3, which was considered sufficient to potentially affect the outcome of the study, so fluid rates in groups 2 and 4 were increased proportionally (1 mL/h). The mannitol CRI was given at a range of 1 to 1.57 g/h, depending on the cat’s body weight.

The CRI of dopamine-furosemide was given at 1 mL/h. To be consistent with the theory that the larger total volume administered during 8 hours might affect the study outcome, the fluid rate in group 2 was increased by another administration of 1 mL/h (total, 2 mL/h [more than twice the calculated maintenance rate]). The difference in 8-hour volume between the mannitol CRI and dopamine-furosemide CRI was considered negligible, and no adjustments were made in the fluid rate of group 3.

Renal clearance measurements—At the end of the equilibration period (time 0), cats received an SC injection with inulin and PAH. A single sterile solution composed of 7.5% inulin (50 mg/kg) and 0.375% PAH (10 mg/kg) in saline solution was prepared on the day prior to each study day. Following preparation of the solution, it was autoclaved and kept at 21°C until its use within 24 hours. Cats that weighed < 5 kg received 40 mL of the solution, and cats that weighed 2 5 kg received 45 mL of the solution. An injection of 99mTc-DTPA was also given IV through the peripheral IV catheter within 5 minutes of the SC injection of inulin and PAH. The dose of 99mTc-DTPA was approximately 100 to
150 µCi/cat. The radioactivity of each injection solution was measured against a standard prior to injection. The exact time for each injection was recorded so that sampling could proceed accurately at the designated times for each cat.

Blood was collected at regular intervals for measurement of 99mTc-DTPA, inulin, and PAH concentrations. Two milliliters of blood was collected into heparinized collection tubes at 15, 30, 60, 90, 120, and 150, and 240 minutes after injection for measurement of 99mTc-DTPA concentration. The blood obtained at 60, 90, 120, and 150 minutes was also used for measurements of inulin and PAH concentrations. At 90 and 150 minutes, urine was aspirated from the urinary catheters, quantified, and analyzed for inulin and PAH concentrations to determine clearance during the previous 30 minutes. Eight total urine production was measured for each cat (mL/cat) from times 0 to 240 minutes.

The 99mTc-DTPA sample analysis and GFR calculations were performed on each day of the study. Measurements of radioactivity were obtained from the 15-, 30-, 60-, 90-, 120-, 150-, and 240-minute samples. Data were analyzed as described to reveal plasma clearance times for the radioisotope in milliliters per minute per kilogram for a GFR value per cat per protocol.

Inulin was assayed by use of an automated enzymatic procedure. The PAH was assayed by use of a colorimetric assay that used n-1 napthylethylenediamine diHCl. All samples were analyzed by technicians who were unaware of the treatment protocols for each study day. Glomerular filtration rate and RPF were calculated by use of a standard clearance formula as follows:

$$\text{RPF or GFR} = \frac{U_x \times V}{P_S} = \frac{C_s}{\text{body weight} (kg)}$$

where $$U_x$$ is urine concentration of substance, V is urine flow rate (volume/time), $$P_s$$ is plasma concentration of substance, and $$C_s$$ is clearance rate (mL/min).

For final analysis of GFR (inulin) and RPF, an averaging protocol was used to eliminate possible fluctuations in plasma clearances during the 4-hour period. Two 30-minute intervals were used to increase accuracy. Measurements were obtained from 60 to 90 minutes and from 120 to 150 minutes. For the calculations, mean plasma concentrations of inulin and PAH at times 60 and 90 were used in the clearance formula as $$P_x$$. The urine concentration of inulin and PAH at time 90 alone was used in the clearance formula as $$U_x$$. The same was done at times 120 and 150, with the urine concentration from time 150 used in the calculations. Finally, the mean of the 2 values obtained at each time was used for the final analysis. Plasma inulin and PAH concentrations were linear for each time measured (60, 90, 120, and 150 minutes).

Each time urine was collected (except at time 240), all urine was aspirated, 5 mL of sterile saline solution was injected into the urinary catheter, all fluid was again aspirated, and total volume minus 5 mL was calculated. This bladder-flushing procedure was performed to ensure catheter patency and that all urine had been removed from the bladder.

Aldosterone concentration and fractional excretion of electrolytes—Plasma aldosterone concentrations were determined from blood obtained at 0, 90, and 240 minutes. Blood and urine were also collected prior to any fluid administration (including SC administration of fluids) and at 240 minutes for analysis of sodium, potassium, and creatinine concentrations. The urine collected at 240 minutes was collected without bladder flushing so that the saline solution did not interfere with measurement of sodium concentration.

Because of concern over drawing large volumes of blood from each cat on each study day, 2 mL was the maximum volume drawn at each sampling interval. Unfortunately, for 50% of the samples, there was insufficient sample left for determinations of aldosterone and electrolytes after it had been divided into aliquots for measurements of 99mTc-DTPA, inulin, and PAH concentrations. Therefore, data from < 4 cats for each protocol were available for final evaluation of aldosterone concentrations and fractional excretions of sodium and potassium. A standard formula for calculation of fractional excretions was used as follows:

$$\text{Fex} = \left( \frac{[U_x][S_x]/([U_x][S_x])}{} \right)$$

where Fex is fractional excretion of electrolyte (%), x is electrolyte being measured, $$c_r$$ is creatinine, U is amount of substance in urine (electrolytes [mEq/L] or creatinine [mg/dL]), and S is the amount of substance in serum (same units).

Poststudy protocol—At the end of the 8-hour study period, all IV and urinary catheters were removed and the cats were given antimicrobials. For study days 1 and 2, cats received amoxicillin-clavulanic acid (62.5 mg, PO, q 12 h, for 5 days; mean dose, 13.2 mg/kg). Three of the male cats developed diarrhea while receiving amoxicillin-clavulanic acid, so for study days 3 and 4, enrofloxacin (22.7 mg, q 24 h, PO, for 5 days; mean dose, 4.5 mg/kg) was administered to all cats instead. One cat required 45.4 mg daily on the basis of body weight. Cats were administered enrofloxacin once daily at a mean dose of 4.3 mg/kg for 7 days at the end of the study while results of bacteriologic cultures of urine were pending. Urine was submitted for bacteriologic culture on study days 1 and 4. Serum biochemical analyses were performed 1 week prior to study day 1 and on study day 4. All cats were adopted into private homes after the study.

Statistical analysis—A Friedman test was used to make comparisons among the 4 groups for GFR measured by use of inulin. GFR measured by use of 99mTc-DTPA, RPF measured via PAH, and UO. The Friedman 2-way blocked nonparametric ANOVA was used to adjust for individual variations in each cat for RPF, GFR by each method, and UO. If significant differences were found when comparing the groups, the Wilcoxon signed rank test (2-tailed) was performed to compare groups (ie, group 1 vs group 2 and group 1 vs group 3). Glomerular filtration rate measured by use of 99mTc-DTPA clearance was compared with GFR measured by use of inulin clearance for rank correlation by use of the Spearman test. For all comparisons, values of $$P \leq 0.05$$ were considered significant. All calculations were performed by use of commercial software.
There was no significant difference in GFR of group 2, compared with group 3 ($P = 0.83$) or group 1 ($P = 0.18$). In all but 1 cat, the GFR was greater in group 1 cats than in group 4 cats ($P = 0.02$). There was no difference between groups 1 and 3 ($P = 0.11$; Table 1).

Correlation between results obtained via 99mTc-DTPA versus inulin clearance—There was poor correlation between GFR values obtained via these 2 techniques in groups 1 ($r^2 = 0.48; P = 0.06$) and 3 ($r^2 = 0.45; P = 0.07$). Good correlation between methods was detected in groups 1 ($r^2 = 0.94; P = 0.0007$) and 4 ($r^2 = 0.77; P = 0.007$). For group 1, use of clearance of m99Tc-DTPA resulted in underestimation of GFR in 62.5% of samples, equivalent values in 25% of samples, and overestimation of GFR in 12.5% of samples, compared with values obtained via inulin clearance. In group 2, use of clearance of 99mTc-DTPA resulted in underestimation of GFR in 37.5% of samples, and overestimation of GFR in 12.5% of samples, compared with values obtained via inulin clearance. In group 3, clearance of m99Tc-DTPA resulted in underestimation of GFR in 50% of samples and overestimation of GFR in 50% of samples, compared with values obtained via inulin clearance. In group 4, clearance of 99mTc-DTPA resulted in underestimation of GFR in 87.5% of samples and overestimation of GFR in 12.5% of samples. Therefore, use of clearance of 99mTc-DTPA resulted in underestimation of GFR more frequently than overestimation of GFR (Figures 1 and 2).

Use of PAH clearance for determination of RBF—When all groups were compared for RBF, a significant difference was detected. Among individual groups, RBF was greater than that in groups 2 and 3, compared with group 1 ($P = 0.04$ and 0.01, respectively), and RBF in group 3 was greater than that in group 4 ($P = 0.04$). No significant difference was detected between groups 2 and 3 ($P = 0.53$), groups 2 and 4 ($P = 0.29$), or groups 1 and 4 ($P = 0.55$; Table 1).

Total UO—Total UO for each cat during each protocol was calculated from time 0 (end of equilibration period) to 240 minutes (Table 1). Among all groups, there were significant ($P < 0.001$) differences in median UO. Group 4 had significantly ($P = 0.01$) more UO than did group 2 or 3. There was no difference in UO between groups 2 and 3 ($P = 0.83$). All 3 treatment groups had significantly ($P = 0.01$) greater UO than did group 1.

Fluid balance—For each protocol and each cat, total fluid given (SC and IV) and total UO were com-
pared. Excluding minimal noncalculated insensible losses, all cats, except for 1 during the furosemide-dopamine protocol, had a positive fluid balance at the end of each study day. That cat received 9.28 mL/kg/h of fluid and urinated 9.60 mL/kg/h (difference of 0.32 mL/kg/h). The cat’s GFR as determined by use of inulin and DTPA clearance was 3.15 and 1.63 mL/min/kg, respectively. The RBF was 10.98 mL/min/kg. Therefore, the cat’s GFR as determined by use of inulin clearance and the RBF were greater than the median value of all cats for the furosemide-dopamine protocol. The cat’s GFR determined by use of DTPA clearance was less than the median but was within the range of the other cats (Table 2).

Aldosterone—Given limitations of sample numbers (n = 4 for each protocol), statistical analysis was not deemed worthwhile. During each protocol, the median plasma aldosterone concentration at 90 minutes was lower than that at time 0 or at 240 minutes. Median plasma aldosterone concentration at 240 minutes was lower than that at time 0 for all protocols (Table 3).

Fractional excretion of sodium and potassium—There were insufficient sample numbers for statistical analysis. In no group were samples from more than 3 cats available for analysis of electrolytes at the end of each study day. For groups 3 and 4, median sodium and potassium excretion typically increased substan-

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**Table 1**—Renal physiologic variables (median [range]) measured during 240 minutes in 8 cats that received no treatment (control [group 1]), IV fluid therapy (group 2), IV fluid therapy plus mannitol (group 3), or IV fluid therapy plus furosemide-dopamine (group 4).

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR (inulin [mL/min/kg])</th>
<th>GFR (DTPA [mL/min/kg])</th>
<th>RPF (mL/min/kg)</th>
<th>Total UO (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.01 (1.91–4.67)</td>
<td>2.84 (1.82–4.19)</td>
<td>8.29 (4.79–12.79)</td>
<td>15.00 (13.00–39.00)</td>
</tr>
<tr>
<td>2</td>
<td>3.18 (2.11–6.36)</td>
<td>3.04 (2.16–4.67)</td>
<td>10.13 (5.96–17.90)</td>
<td>61.50 (22.00–99.00)</td>
</tr>
<tr>
<td>3</td>
<td>3.48 (2.37–5.11)</td>
<td>3.59 (1.91–4.45)</td>
<td>12.59 (7.60–15.58)</td>
<td>58.50 (35.00–101.00)</td>
</tr>
<tr>
<td>4</td>
<td>2.69 (1.11–4.11)</td>
<td>1.84 (0.69–4.05)</td>
<td>9.05 (3.28–16.97)</td>
<td>176.00 (110.00–252.00)</td>
</tr>
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</table>

*GFR as determined by use of inulin clearance. GFR as determined by use of 99mTc-DTPA clearance. RPF as determined by use of PAH clearance.
When fluid therapy alone does not sufficiently increase UO, RBF, or GFR (after euhydration has been achieved), other agents are commonly used to improve those variables. Mannitol, furosemide, and dopamine are all used clinically for acute renal failure in many species. However, it appears that although these drugs stimulate UO that can be measured clinically, they all may not have beneficial effects on RBF or GFR.19,20

Mannitol is a hyperosmotic agent with many beneficial effects. Mannitol is filtered freely by the glomeruli, is nonreabsorbable, and, therefore, acts as an osmotic agent in the tubular fluid. It also can induce profound natriuresis.2,17 Results of a recent study1 in anesthetized rats indicate that the natriuresis associated with mannitol administration is caused by inhibition of sodium and water reabsorption in the collecting ducts (a more distal location than previously thought). Another study18 revealed either a direct effect of mannitol on the atria to produce ANP or an indirect stimulation to produce ANP secondary to increased extracellular fluid load. Atrial natriuretic peptide is a powerful humoral stimulator of natriuresis and provides benefits in acute renal ischemia.15 Administration of mannitol can induce renal arteriole dilation and decrease vascular resistance, blood viscosity, and scavenging of oxygen free radicals.1 Decreases in vascular resistance and blood viscosity seem to be directly related to the ability of mannitol to increase extracellular fluid volume and secondarily dilute RBCs.17 To our knowledge, no study has examined the effects of mannitol on feline kidneys and there are variable results in studies on other species regarding mannitol's effects on RBF and GFR, despite its clinical efficacy at inducing diuresis and increased extracellular volume.

In the study reported here, mannitol was given as a bolus initially and then as a CRI, in addition to high rates of IV fluid therapy. This protocol is commonly used in practice (1 or 2 boluses of mannitol are frequently given initially for oliguria, and then a CRI is started if necessary to improve UO).2 The bolus dose range used in our study was well within the recommended range (the dose should not exceed 2 g/kg/d).19,20 The mannitol protocol was clearly superior to control and furosemide-dopamine protocols in improving RBF. Urine output, GFR, and RBF associated with this protocol were not significantly greater than with fluid therapy alone, and this may be a function of having cats with normal renal function versus cats with renal disease in this study. Given the number of mechanisms of action that mannitol may have in the kidney and elsewhere, it had been our hypothesis that it would be superior to all other protocols in achieving improvement in all variables. It is possible that cats with decreased renal function may receive larger benefits from mannitol administration than from fluid therapy alone. This hypothesis can be proven only with additional testing in cats with renal disease.

Renal arteriole dilation and decreased blood viscosity likely account for the increased RBF, whereas UO is augmented by the stimulation of ANP and natriuresis in clinically normal cats and cats with renal disease.

Another commonly used combination for conversion of oliguria to polyuria is furosemide and dopamine. Furosemide is secreted into the proximal tubules and

### Table 2—Mean ± SD volumes of fluids administered (IV and SC) and UO in the cats in Table 1.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Fluids administered (mL/min/kg)</th>
<th>Urine output (mL/min/kg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>2.71 ± 0.17</td>
<td>0.94 ± 0.23</td>
</tr>
<tr>
<td>2</td>
<td>9.85 ± 0.36</td>
<td>2.42 ± 1.30</td>
</tr>
<tr>
<td>3</td>
<td>9.90 ± 0.36</td>
<td>2.88 ± 0.77</td>
</tr>
<tr>
<td>4</td>
<td>9.81 ± 0.36</td>
<td>6.42 ± 2.06</td>
</tr>
</tbody>
</table>

See Table 1 for key.

### Table 3—Median plasma aldosterone measurements taken at 0 (before treatment) and at 240 minutes.

<table>
<thead>
<tr>
<th>Groups</th>
<th>0 min (pg/mL)</th>
<th>90 min (pg/mL)</th>
<th>240 min (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>221.49</td>
<td>34.81</td>
<td>163.97</td>
</tr>
<tr>
<td>2</td>
<td>162.34</td>
<td>0</td>
<td>14.18</td>
</tr>
<tr>
<td>3</td>
<td>181.39</td>
<td>2.94</td>
<td>18.88</td>
</tr>
<tr>
<td>4</td>
<td>213.98</td>
<td>17.65</td>
<td>102.64</td>
</tr>
</tbody>
</table>

See Table 1 for key.

### Table 4—Calculated median fractional excretions (%) of sodium (Na) and potassium (K) at time 0 (before treatment) and at 240 minutes.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pretreatment (%Na/%K)</th>
<th>240 minutes (%Na/%K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.14/10.8</td>
<td>0.50/10.10</td>
</tr>
<tr>
<td>2</td>
<td>0.15/11.75</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>0.10/11.30</td>
<td>1.95/21.75</td>
</tr>
<tr>
<td>4</td>
<td>0.21/15.70</td>
<td>8.60/37.50</td>
</tr>
</tbody>
</table>

NA = Not available. See Table 1 for key.

Discussion

The mainstay of treatment for oliguric or anuric renal failure is IV fluid therapy at rates that exceed body requirements. The goal is to correct dehydration, re-establish RBF, and stimulate urine production to remove toxins that have accumulated secondary to decreased renal filtration or function.1 Increased fluid load will increase tubular flow rates and therefore decrease solute reabsorption. In the present study, fluid therapy alone had no significant effect on GFR, compared with that in healthy, hydrated, untreated control cats. However, fluid therapy did increase RBF compared with the control group. Also, although fluid therapy did increase UO greater than that of the control group, it may not be the best method of stimulating urine production because fluid therapy has no direct action in the tubules to inhibit solute reabsorption. Instead, fluid therapy improves renal blood flow by increasing circulating blood volume and reestablishing proper blood pressure. Increased filtration at the glomerulus may also occur because of increased blood pressure. In the clinically normal cats reported here, fluid therapy alone did not significantly improve GFR. This may prove to be different for cats with oliguric or anuric renal failure.
achieve the same response. 22 Reduced number of them are present in comparison to dopaminelike receptors in the renal cortex; however, a study by Flournoy et al. 22 found that cats do have was no clear mechanism of action known. In 2003, a although dopamine was still used in cats clinically, there tubular dopamine receptors did exist in the cat but only a decrease in GFR within the first 3 hours and neither had any substantial effect on RBF. When furosemide and low-dose dopamine were administered together, renal vasodilation, high urine flow rates, and attenuation of the decrease in GFR were detected. It was hypothesized that many mechanisms may be at play but that vasodilation was caused by dopamine-enhanced transport of furosemide into the tubules, thereby making it more effective. 20 Furosemide can be given initially as a bolus for oliguric patients; however, a recent study 22 in clinically normal Greyhounds found that CRIs of furosemide alone induced a higher magnitude of diuresis than did intermittent boluses of the drug (with the same total dose). Therefore, in our study, furosemide and dopamine were administered together as CRIs without bolus doses.

In dogs, rats, and humans, dopamine-1 and dopamine-2 receptors are found on renal blood vessels and renal tubules. Stimulation of these receptors in each species with an appropriate dopamine dose stimulates diuresis and natriuresis. It has been noted that cats do not have the same response to low-dose dopamine (1 to 3 µg/kg/min) as do other species. Two opposing ideas have been published in the last 2 decades: 1) that renal tubular dopamine receptors did exist in the cat but only responded to large doses (10 to 25 µg/kg/min) of dopamine for diuresis, and 2) that there was no evidence of renal dopamine receptors in cats. Therefore, although dopamine was still used in cats clinically, there was no clear mechanism of action known. In 2003, a study by Flournoy et al. 24 found that cats do have dopaminelike receptors in the renal cortex; however, a reduced number of them are present in comparison to other species. Because of this, cats' response to the drug may be reduced, thereby requiring larger doses to achieve the same response. 22

In a recent review in humans, it was concluded that renal dose dopamine (ie, low dose) may be detrimental to kidneys because it actually decreases GFR in states of renal failure. 23 Therefore, although dopamine may improve urine diuresis, it may not be beneficial to renal function when used alone.

We chose to use furosemide and dopamine together for this study because of information in the literature 25,26 and because these 2 drugs are commonly used together to substantially improve UO in clinical practice. We wanted to evaluate protocols most commonly used in practice. Our results indicated that administration of furosemide-dopamine and IV fluid therapy was far superior to other protocols in improving UO and inducing diuresis. However, GFR measured by use of 99mTc-DTPA clearance was significantly lower than for the other groups. With inulin clearance, there was no significant change in GFR, compared with the other groups. This discrepancy is difficult to explain because correlation of the 2 methods was very good for group 4. Low-dose dopamine was used in this study, so the data do not clarify the controversy surrounding the concentration of dopamine receptors in feline kidneys.

Another variable not evaluated in this study was blood pressure. The pressor effects of dopamine, if any at the dose used, could therefore not be evaluated. Blood pressure monitoring was logistically impossible in awake cats without inducing stress and possibly changing values for renal variables.

The use of 99mTc-DTPA clearance was compared with inulin clearance for determination of GFR. Given that inulin clearance is the gold standard for a precise determination of GFR, results of testing with 99mTc-DTPA were inconsistent. Therefore, we conclude that it cannot be substituted for inulin when a precise determination of GFR is needed. However, the use of 99mTc-DTPA may be adequate to monitor an animal's response to treatment or to detect a change in GFR. In this study, GFR, as determined by use of both methods, was well correlated in groups 2 and 4 but was not well correlated in groups 1 and 3. Reasons for the discrepancies could include error caused by insufficient numbers of cats in the study or daily variations in GFR. Interestingly, use of 99mTc-DTPA clearance resulted in underestimation of the GFR, compared with inulin clearance, in all of the groups. There is variability in equilibration of different substances into the extracellular fluid pool and, therefore, variability in filtration rates. In fact, 99mTc-DTPA is a smaller molecule than inulin and may equilibrate faster. Diffusion of each substance is inversely related to solute size, which directly influences GFR as calculated with certain equations. 24 This may result in lower GFR when it is calculated with different equations, if rate constants and kinetics are not taken into account.

A positive fluid balance was maintained throughout the study for all but 1 cat, indicating that hydration was maintained even when diuresis occurred. For the cat that had a negative fluid balance during the furosemide-dopamine protocol, the GFR (as measured by use of inulin clearance) and RBF were greater than the median values reported for other cats. Therefore, despite the negative fluid balance, renal variables were not substantially affected.

Values for GFR, RBF, and UO were examined statistically for each cat to ensure that individual variation did not influence final results. However, the numbers of cats and study days were insufficient to establish whether day-to-day variation in those variables would have influenced results of the study. In individual dogs studied by use of 99mTc-DTPA clearance, GFR varies from 2.66 to 5.67 mL/min/kg over subsequent days. The authors concluded that the variability was attributable to individual characteristics of the dogs. Day-to-day variability could be accounted for by changes in water and food intake (food and water were withheld from the cats in the present study, but they were allowed access to water the night before each study day), each dog's ability to adjust to those changes, or errors in the measurement method. 25
Measurement of aldosterone concentrations was performed in an attempt to evaluate whether each of the protocols influenced the renin-angiotensin-aldosterone system. Because insufficient numbers of samples were analyzed, no direct conclusions could be made. However, similar findings were detected for all groups, including the control group. Aldosterone concentrations were less than the initial values when measured at 90 minutes. It is unknown when it decreased within that time period. Aldosterone concentrations were increased when measured again at 240 minutes. Also, the last aldosterone concentration, measured at the end of the day, was often less than that at time 0. The renin-angiotensin-aldosterone system is stimulated by low extracellular fluid volume; therefore, higher volumes will suppress the system, which could account for the decrease in aldosterone concentrations at 90 minutes but not the increase at 240 minutes. Although not significant, high aldosterone concentrations found in group 4 may have indicated subclinical dehydration because of the high rate of diuresis invoked by the furosemide-dopamine protocol.

Increased extracellular fluid volume and decreased aldosterone concentrations were also responsible for the observation that all diuretic protocols caused an increase in excretion of both sodium and potassium. There were too few samples to evaluate each protocol separately; however, it can be hypothesized that mannitol as an osmotic diuretic and furosemide as a loop diuretic may have caused larger fractional excretions of electrolytes with their mechanisms of action.26

Intensive IV fluid therapy and IV fluid therapy with mannitol improved RBF in healthy cats, and this improvement was not seen when furosemide and dopamine were used. All treatments increased UO in these healthy cats, but IV fluid therapy combined with furosemide-dopamine did so more than other treatments. Intravenous fluid therapy with mannitol did improve RBF when compared with IV fluid therapy with furosemide-dopamine and improved RBF greater than IV fluid therapy alone. Future studies will be needed to separate the effects of furosemide from those of dopamine in the kidneys of awake cats with normal renal function and with naturally occurring renal disease. Also, on the basis of these results, we cannot recommend the use of 99mTc-DTPA clearance as a test for GFR when an accurate value is required, although this method may be acceptable for detecting a response to treatment or changes in GFR if that is the only method used.

References