Glomerular filtration rate is determined by several factors including hydrostatic and osmotic pressures within the glomerular capillary bed, osmotic pressure outside the capillary bed within Bowman’s capsule, and permeability of the glomerular membrane. Glomerular filtration rate is also influenced by the rate of blood flow through the glomeruli.

Presently, GFR is considered one of the best indicators of renal function. Although inulin clearance was set as the gold standard for measuring GFR, the use of nuclear imaging to accurately measure renal function by determining GFR has been well documented for several years. Nuclear scintigraphy involving the use of $^{99m}$Tc-DTPA is noninvasive, rapid, and easy to perform and does not require blood or urine samples to be collected for analysis. Moreover, this technique allows the determination of overall and individual kidney function. Because $^{99m}$Tc-DTPA is completely filtered by the glomerulus, is neither secreted nor reabsorbed by the renal tubules, and is not appreciably bound to plasma proteins, it is an ideal substance for measurement of GFR.

Because renal scintigraphy requires that an individual dog remain motionless for a period as long as 16 minutes, routine examinations of dogs in clinical settings (with limited hospitalization time) require chemical sedation. Therefore, it is important to know the effects of any sedative protocol on GFR measurement to reduce potential procedural error or bias in GFR assessment in dogs.

Medetomidine and xylazine are potent $\alpha_2$-adrenoceptor agonists that induce sedation, analgesia, and muscular relaxation in dogs. Medetomidine and xylazine increase systemic vascular resistance through their effect on extrasynaptic $\alpha_2$-adrenoceptors in the...

### Influence of three anesthetic protocols on glomerular filtration rate in dogs

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**Objective**—To investigate renal function in clinically normal dogs when awake and during anesthesia with medetomidine; xylazine, ketamine, and halothane (XKH) combination; or propofol.

**Animals**—10 adult female Beagles.

**Procedures**—At intervals of 15 days, dogs were administered medetomidine (0.05 mg/kg, IV); XKH combination (xylazine [1 mg/kg, IV], ketamine [5 mg/kg, IV], and halothane [1% end-tidal concentration]); or propofol (6 mg/kg, IV) to induce anesthesia or no treatment. Glomerular filtration rate was assessed on the basis of renal uptake (RU; determined via renal scintigraphy) and plasma clearance (CL) of technetium 99m-labeled diethyleneetriamine pentaacetic acid ($^{99m}$Tc-DTPA).

**Results**—In awake dogs, mean ± SEM RU was 9.7 ± 0.4% and CL was 3.86 ± 0.23 mL/min/kg. Renal uptake and CL of $^{99m}$Tc-DTPA were not significantly modified by administration of XKH (RU, 11.4 ± 0.9%; CL, 4.6 ± 0.32 mL/min/kg) or propofol (RU, 9.7 ± 0.3%; CL, 3.78 ± 0.37 mL/min/kg). Half-life elimination time of plasma $^{99m}$Tc-DTPA decreased significantly in XKH-anesthetized dogs, compared with the value in awake dogs (14.4 minutes and 28.9 minutes, respectively). However, glomerular filtration rate was significantly decreased by administration of medetomidine (RU, 3.9 ± 0.1%), and the time to maximum kidney activity was significantly increased (867 ± 56 seconds vs 181 ± 11 seconds without anesthesia).

**Conclusions and Clinical Relevance**—Results indicated that anesthesia with propofol or an XKH combination did not alter renal function in healthy Beagles, but anesthesia with medetomidine decreased early RU of $^{99m}$Tc-DTPA. (Am J Vet Res 2007;68:807–811)
vasculature.\textsuperscript{9,7} Dissociative agents, such as ketamine, substantially increase heart rate and systemic blood pressure and decrease cardiac contractility.\textsuperscript{3} Inhalation anesthetics, such as halothane, cause dose-dependent myocardial depression (decrease in cardiac output) and vasodilation that may result in decreased cardiac output and blood pressure. Propofol is a \( \gamma \)-aminobutyric acid receptor, agonist and an N-methyl-D-aspartate receptor antagonist; the drug induces slight cardiac depression (negative inotropic effect) and a decrease in peripheral vascular resistance, leading to hypotension.

The effects of these anesthetics agents on GFR have not been clearly determined in dogs. Anesthetics agents have well-known adverse effects, and it is important to determine which drugs do not interfere with renal function. The purpose of the study reported here was to investigate renal function in clinically normal dogs when awake and during anesthesia with medetomidine, an XKH combination, and propofol.

**Materials and Methods**

**Animals**—Ten clinically normal adult female Beagles (2 years old) that weighed 7.5 to 10.5 kg were included in the study. Dogs were purpose bred\textsuperscript{a} and housed and cared for in the research unit facility. Dogs were fed a standard diet.\textsuperscript{b} Renal ultrasonography was performed for each dog to assess the absence of morphologic abnormalities. For each dog, plasma urea, creatinine, potassium, sodium, and chloride concentrations were measured at the beginning of the study by use of standard reagent kits\textsuperscript{c} and results were within reference ranges. Approval of the study was obtained from the local Ethical Committee on Animal Experiments.

**Experimental procedure**—Each dog received each of the 3 anesthetic regimens and control treatment successively. The regimens included medetomidine (0.05 mg/kg, IV); XKH combination (xylazine, 1 mg/kg, IV; ketamine, 5 mg/kg, IV; and halothane, 1% end-tidal concentration); propofol (6 mg/kg, IV); and no anesthesia. Between anesthetic regimens, a minimum wash period of 15 days was allowed to elapse.

Within 15 minutes of treatment, during stable anesthesia, and in awake dogs, renal scintigraphy was performed. Blood samples for pharmacokinetic analysis were collected from awake dogs and after XKH or propofol anesthesia.

**Renal scintigraphy**—Four megabequerels/kg of body weight (4 MBq/kg) of \(^{99m}\text{Tc}\)-DTPA\textsuperscript{i} was prepared in the injection tubing and evaluated at 30 cm from the center of the gamma camera,\textsuperscript{j} which was fitted with a low-energy all-purpose collimator (designated the predose count). The percentage of \(^{99m}\text{Tc}\) binding to DTPA was periodically analyzed and was \( > 95\% \) on each occasion. Each dog was positioned in dorsal recumbency, and the gamma camera was placed ventrally close to the animal.

The radiopharmaceutical was injected IV in the right cephalic vein as a rapid bolus, and the catheter was flushed with saline (0.9% NaCl) solution. By use of a dedicated image processing computer, 1-second sequentially acquired dynamic images were recorded into a \( 64 \times 64 \)-matrix for 1 minute and then 5-second sequentially acquired dynamic images were recorded for 14 minutes. After this, the depth of each kidney was evaluated by positioning the gamma camera laterally and a static image was obtained during a 30-second period from the right side and then from the left side. Immediately after the 16-minute period, the syringe and tubing were repositioned in a manner similar to that for the predose count and a postdose count was obtained.

The scintigraphic images were transferred to a computer for image analysis. Separate regions of interest were drawn manually around each kidney, and a background region of interest was drawn adjacent to the caudal pole of each kidney. Renal activity was corrected for background activity and depth. Percentage uptake of \(^{99m}\text{Tc}\)-DTPA in each kidney was determined as the cumulative activity in the kidney between 1 and 3 minutes after radiopharmaceutical administration divided by the injected dose\textsuperscript{k} and was then used to evaluate GFR. Time of maximum kidney activity was calculated from renal time-activity curves as the interval between injection and maximal renal uptake. To prevent analysis bias, 3 trained persons independently drew the regions of interest for each procedure and the final values were calculated as the mean of the 3 measurements and were expressed as mean ± SD values among 10 dogs.

**Pharmacokinetic analysis**—Blood samples were collected into tubes containing heparin from the IV catheter that had not previously been used for \(^{99m}\text{Tc}\)-DTPA injection at 5, 10, 15, 20, 25, 30, 45, 60, 75, 90, 105, 120, 150, and 180 minutes after the injection of the radiopharmaceutical. At the end of the blood collection period, \(^{99m}\text{Tc}\)-DTPA activity was measured in 500-µL aliquots of plasma by use of a well counter.\textsuperscript{l} Plasma activity was corrected for physical decay and plotted as a function of time. Activity of \(^{99m}\text{Tc}\)-DTPA in plasma was used to determine pharmacokinetic parameters via noncompartmental methods. Values of AUC\textsuperscript{ij} were computed by use of the linear trapezoidal rule.\textsuperscript{5} Values of AUC\textsubscript{0-t} were calculated as the sum of AUC\textsubscript{0-t} and the quotient of the last measurable concentration and \( k \). A nonlinear mixed-effects model was established as follows:

\[
Y_{ij} = A_i e^{-k_i t} + C_i + \epsilon_{ij}
\]

where \( 1 \leq i \leq 10 \) for dogs and \( 1 \leq j \leq 14 \) for times and was used to estimate the decay curve parameters (\( A, k, \) and \( C \)) for each anesthetic regimen.\textsuperscript{5} Half-life elimination time was calculated by dividing 0.693 by \( k \). Apparent total plasma body clearance was calculated as the ratio of dose to AUC\textsubscript{0-t}.

**Statistical analysis**—All results are expressed as mean ± SEM of \( n \) experiments, which represents the number of dogs. Analysis of variance for repeated measures was used to compare the 4 treatment regimens, and a contrast method analysis (means comparison) was used as a post hoc test. The \( k \) parameters are expressed as estimation ± SE. A value of \( P < 0.05 \) was considered significant.
Renal uptake of $^{99m}$Tc-DTPA was not significantly different between the right and left kidney for each dog (Figure 1). Among the 10 dogs during medetomidine anesthesia, mean ± SEM RU of the kidneys was significantly ($P < 0.001$) decreased to $3.9 ± 0.1\%$ and $T_{max}$ was significantly ($P < 0.001$) increased to $867 ± 56$ seconds, compared with values obtained in awake dogs ($9.7 ± 0.4\%$ and $181 ± 11$ seconds, respectively), dogs during XKH anesthesia ($11.4 ± 0.9\%$ and $212 ± 22$ seconds, respectively), and dogs during propofol anesthesia ($9.7 ± 0.3\%$ and $223 ± 17$ seconds, respectively). No significant changes in RU and $T_{max}$ were detected between either the XKH- or the propofol-anesthetized dogs and the awake dogs. The activity-time curves of $^{99m}$Tc-DTPA in plasma of awake and anesthetized dogs were plotted (Figure 2). Following IV administration of $^{99m}$Tc-DTPA, plasma concentration of detectable radioactivity decreased exponentially with time. Bi-exponential modeling did not fit with the data (data not shown).

Pharmacokinetic parameters for $^{99m}$Tc-DTPA in plasma of awake and anesthetized dogs were calculated. Compared with findings in awake dogs, $AUC_{0-\infty}$ and $AUC_{0-\infty}$ were not significantly different after anesthesia. The mean $t_{1/2}$ was $28.51$ minutes for awake dogs and $29.36$ minutes in dogs during propofol anesthesia (Table 1). In dogs undergoing XKH anesthesia, $t_{1/2}$ decreased significantly ($P < 0.05$) to $14.5$ minutes. The mean $CL$ of $^{99m}$Tc-DTPA was $3.86 ± 0.23$ mL/min/kg and $3.78 ± 0.37$ mL/min/kg in awake dogs and propofol-anesthetized dogs, respectively. In dogs during XKH anesthesia, $CL$ of $^{99m}$Tc-DTPA was slightly, but not significantly, increased to $4.6 ± 0.32$ mL/min/kg.

**Discussion**

The present study was performed to determine suitable anesthetic regimens that would not interfere with GFR evaluation via renal functional scintigraphy in dogs. Cardiovascular variables were not recorded during the experiments to minimize the invasiveness of the procedures. However, to complete evaluation of anesthetic regimens for which the derived nuclear scintigraphic data were not different, we undertook the pharmacokinetic analysis of $^{99m}$Tc-DTPA in plasma from the study dogs.

Despite the abundance of data regarding the cardiovascular effects of various anesthetic agents, the corresponding changes in GFR are not well-known. In general, it is believed that all anesthetic agents are likely to decrease GFR, most often by decreasing renal blood flow via either systemic hypotension or renal vasoconstriction.
Compared with findings in awake dogs, the XKH and propofol regimens did not change RU and CL of $^{99m}$Tc-DTPA, indicating that GFR was not altered during those anesthetic episodes. Conversely, during medetomidine anesthesia, the significant decrease in RU and increase in Tmax of $^{99m}$Tc-DTPA were indicative of an alteration in GFR. Pharmacokinetic analysis revealed a slight but nonsignificant increase in GFR and significant decrease in $t_{1/2}$ in dogs during XKH anesthesia, compared with findings in awake dogs. Moreover, RU was also slightly, but not significantly, increased in XKH-anesthetized dogs.

Nuclear imaging of the kidneys by use of $^{99m}$Tc-labeled compounds such as DTPA is a rapid, simple procedure that generates quantitative evaluation of individual kidney and systemic GFRs. This technique has been used to define GFRs in clinically normal cats, dogs, and horses and has been used in dogs with renal dysfunction or those treated with nonsteroidal anti-inflammatory drugs. In most of those experiments, the investigators used manual restraint only to control the animal movements during the nuclear scintigraphy. Because GFR measurement by use of nuclear scintigraphy requires an animal to remain motionless in dorsal or lateral recumbency for a minimum of 6 minutes (depending on the investigation protocol), it is typically recommended that chemical restraint with sedative or anesthetic drugs be provided to eliminate movement of the animals, thereby improving the image quality. However, all sedative or anesthetic agents are not suitable for use because of their putative interference with renal function through their cardiovascular effects.

The cardiovascular and renal effects of many of the sedative and anesthetic protocols commonly used in veterinary medicine have been described. Medetomidine and xylazine are potent $\alpha_2$-adrenoceptor agonists that act within the central and peripheral nervous systems on pre- and postsynaptic $\alpha_2$ receptors as well as on extrasynaptic $\alpha_2$-adrenoceptors located outside the nervous system. Extrasynaptic receptors are localized in vascular smooth muscle, and their activation results in vasoconstriction that leads to an increase in total peripheral resistance. The stimulation of $\alpha_2$-adrenoceptors localized in the renal vasculature induces vasoconstriction that could alter renal hemodynamics, resulting in GFR impairment. Moreover, $\alpha_2$-adrenoceptor stimulation can induce atrioventricular node conduction abnormalities (first- and second-degree atrioventricular heart block) in some animals depending on their individual susceptibility.

Ketamine is a noncompetitive N-methyl-D-aspartate receptor antagonist that is short acting and used as a dissociative anesthetic. In dogs, the cardiovascular stimulating effect of ketamine is characterized by an increase in mean arterial pressure (attributable to an increase in cardiac output) with little effect on systemic vascular resistance. When xylazine was administered with ketamine in dogs, less cardiovascular stimulation occurred. The xylazine and ketamine combination also resulted in an increase in mean arterial pressure because of an increase in systemic vascular resistance but was associated with a decrease in cardiac output. Halothane decreases blood pressure values in direct proportion to its alveolar concentration.

Propofol is a sedative and hypnotic agent that has cardiovascular effects. In dogs and other species, the drug reduces mean arterial blood pressure, cardiac output, and total peripheral resistance although heart rate remains unchanged or is increased. For recommended injected doses of propofol, the extent of the blood pressure decrease is between 11% and 16% in humans.

Hemodynamic effects of medetomidine in dogs have been described. After IV administration, medetomidine has a biphasic effect on mean arterial blood pressure; there is an initial increase (duration 5 to 15 minutes) followed by a long-lasting decrease. The initial increase in mean arterial blood pressure results from a strong increase in systemic vascular resistance because of peripheral vasoconstriction. Consequently, a reflex baroreceptor-mediated physiologic bradycardia develops that leads to a dramatic reduction in cardiac output, which is perpetuated by the central effects of sedation and reduced sympathetic tone. In the present study, GFR in medetomidine-anesthetized dogs was significantly decreased during this first phase (compared with values in awake dogs), which was probably attributable to a temporary decrease in renal blood flow. In the first phase of action of medetomidine, the strong arterial vasoconstriction associated with bradycardia could explain the decreased GFR. Our results were not consistent with those of previous investigations of the effects of medetomidine on GFR in dogs. In those studies, GFR was evaluated later (1.5 minutes or 30, 60, 90, and 120 minutes) after the medetomidine administration than it was in our study, and in 1 study, medetomidine was administered IM. Thus, the medetomidine-induced cardiovascular and renal effects in dogs were different. In those studies there was

### Table 1—Body weight, injected activity of $^{99m}$Tc-DTPA, and pharmacokinetic parameters after IV injection of $^{99m}$Tc-DTPA in 10 dogs when awake or anesthetized with propofol or an XKH combination.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No anesthesia</th>
<th>XKH anesthesia</th>
<th>Propofol anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>9.98 ± 0.36</td>
<td>8.29 ± 0.39</td>
<td>9.08 ± 0.3</td>
</tr>
<tr>
<td>Injected activity (10$^6$ Bq)</td>
<td>42.8 ± 1.1</td>
<td>36.2 ± 2.3*†</td>
<td>47.4 ± 1.4†</td>
</tr>
<tr>
<td>AUC (10$^6$ cpm·min/mL)</td>
<td>10 ± 0.5</td>
<td>9.9 ± 0.8†</td>
<td>18 ± 1</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>11.5 ± 0.6</td>
<td>10.7 ± 1*</td>
<td>14.9 ± 1.2</td>
</tr>
<tr>
<td>$t_f$ (min)</td>
<td>28.51 (23.55–36.13)</td>
<td>14.50 (13.10–16.24)*†</td>
<td>29.36 (24.13–37.5)</td>
</tr>
<tr>
<td>$k$ (min$^{-1}$)</td>
<td>0.024 ± 0.003</td>
<td>0.046 ± 0.002*†</td>
<td>0.024 ± 0.002</td>
</tr>
<tr>
<td>CL (mL/min/kg)</td>
<td>3.86 ± 0.23</td>
<td>1* 4.6 ± 0.32*†</td>
<td>3.78 ± 0.37</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SEM (estimation ± SE for k), except for $t_{1/2}$ for which the values are means (95% confidence interval).

*9 dogs. †Within a variable, value significantly (P < 0.05) different from that in awake dogs.
a slight increase in GFR following the medetomidine and butorphanol administration that was attributed to a preferential vasoconstriction of the glomerular efferent arteries or to a hypothetic increase in the ultrafiltration coefficient or other hormonal factors. Saleh et al.18 also reported an increase in GFR in dogs that was detected 30 minutes after IV injection of 0.04 mg of medetomidine/kg and persisted until at least 120 minutes after anesthetic injection. Those investigators suggested that the medetomidine-induced increase in renal blood flow and GFR could be explained by preferential vasoconstriction of the peripheral arteries that would increase glomerular hydrostatic pressure. In their study,18 a medetomidine-induced decrease in plasma antidiuretic hormone concentration was the main cause for increased urine production.

The lack of a significant difference in plasma CL of 99mTc-DTPA in dogs of the present study during propofol and XKH anesthesia may be attributed to the small variations in mean arterial pressure and vascular resistance that are induced by these anesthetic regimens. Thus, the ability of renal autoregulation to maintain constant GFR was not impaired.

The data obtained in the present study revealed discrepancies with regard to the t1/2 and CL values for awake dogs and dogs undergoing propofol or XKH anesthesia. Plasma CL during XKH anesthesia was not significantly different from values during the other 2 experimental conditions; however, the value of k was significantly increased, which then caused the t1/2 value (0.693/k) to be significantly decreased in comparison. This difference could be a result of a change in the volume of distribution for 99mTc-DTPA in dogs during XKH anesthesia because CL is the product of k and the volume of distribution. Nevertheless, according to the experimental design, dogs were only fully anesthetized 15 to 20 minutes after injection of the anesthetic agent (time needed for renal scintigraphy), which corresponded to the first part of the plasma activity-time curve. For awake dogs and dogs during propofol anesthesia, a monoeXponential model best fit the plasma activity-time course. However, for the plasma activity-time course during XKH anesthesia, the fit with a biexponential model would have been interesting to test because the slope of the curve appeared to be steeper during the first phase. Moreover, CL of 99mTc-DTPA was slightly but not significantly higher in dogs during XKH anesthesia than in awake dogs; this would indicate greater CL of 99mTc-DTPA during the active phase of XKH anesthesia.

The results of our study have indicated that renal scintigraphy may be a useful procedure for the evaluation of adverse effects of anesthetic regimens on renal function in dogs. Compared with methods of global estimation of GFR, an additional advantage of nuclear imaging is its ability to assess the function of each kidney. In young, healthy Beagles, anesthesia with medetomidine induced an alteration in the early estimation of renal function and propofol or XKH anesthesia did not change the renal function as measured by 99mTc-DTPA renal scintigraphy. To minimize the effects of anesthesia on renal function in dogs, we conclude that either propofol (administered IV) or a mixture of xylazine with ketamine (administered IV) followed by inhalation of halothane could be used, but care must be taken with the use of medetomidine (administered IV).

References