Effects of general anesthesia and surgery on renal function in healthy dogs

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Objectives—To evaluate renal function in healthy dogs undergoing general anesthesia and ovariohysterectomy without concurrent IV administration of fluids.

Animals—35 healthy client-owned dogs.

Procedure—Dogs were medicated with promazine hydrochloride (0.05 mg/kg of body weight, SC) approximately 45 minutes before induction of anesthesia with thiopental sodium (10 to 15 mg/kg, IV). Anesthesia was maintained with 2% halothane in oxygen. Ovariohysterectomies were performed by senior veterinary students under the direct supervision of a veterinary surgeon. Renal function was assessed (serum urea and creatinine concentrations, fractional clearance of sodium, urine alkali phosphate [ALP] and y-glutamyltranspeptidase [GGT] activities, urine specific gravity, and enumeration of renal tubular epithelial cells in urine sediment) prior to and 24 and 48 hours after surgery.

Results—Duration of general anesthesia ranged from 80 to 310 minutes. Urine specific gravity and ALP activity and serum urea and creatinine concentrations did not change over time. Fractional clearance of sodium decreased 24 and 48 hours after surgery, whereas urine GGT activity and the ratio of urine GGT activity to urine creatinine concentration increased 24 hours after surgery, compared with presurgery values. Renal tubular epithelial cells increased in number in urine sediment from 11 of 35 (31.4%) dogs and 5 of 35 (14.3%) dogs 24 and 48 hours after surgery, respectively. However, this increase was not clinically relevant.

Conclusions and Clinical Relevance—Intravenous administration of fluids to healthy anesthetized dogs is, however, controversial. The indications for IV administration of fluids during surgery are treatment of anesthetic-induced hypotension, insensible fluid losses from evaporation, and hemorrhage. Potential complications that may develop after fluid administration include circulatory overload, pulmonary edema, and renal medullary wash out. If fluids are administered correctly, then these complications are rare.

Primary or intrinsic acute renal failure (ARF) is a syndrome that is characterized by the sudden onset of impaired renal function that results in azotemia, increased fractional clearance of sodium (FCNa), and renal tubular epithelial (RTE) cells or casts in urine sediment. Any toxic or ischemic renal insult may result in cellular degeneration or necrosis, with consequent loss of RTE cells into urine. A common cause of ARF is acute tubular necrosis, resulting from either renal ischemia or exposure to nephrotoxins. Necrosis results in increases in urine enzyme activities, FCNa, and RTE cells and casts in the urine sediment, as well as histopathologic changes. In humans, tubular dysfunction is a uniform hallmark of this form of ARF even though overt necrosis is not evident in all cases.

A considerable number of cases of ARF are hospital acquired, because certain diagnostic and therapeutic procedures are potentially nephrotoxic or can cause hypotension and renal ischemia. Ischemic injury occurs when renal blood flow is attenuated by decreased blood pressure or renal vasoconstriction.

Glomerular afferent arteriolar vasoconstriction caused by the effects of angiotensin II and ADH in response to increased renin release is a proposed mechanism of decreased glomerular filtration rate in ARF. Decreased renal blood flow results in a reduction in the amounts of oxygen and metabolic substrates delivered to tubular cells, and this cellular starvation initiates a cycle of events. Ischemic insult to the kidney can be caused by a variety of factors, including a deep surgical plane of general anesthesia and extensive surgery. With routine surgery an animal can develop subclinical...
ARF that may be missed if the animal does not have overt clinical signs.

Results of a recent study indicate that IV administration of fluids is not necessary to maintain adequate blood pressure in young, healthy halothane-anesthetized dogs undergoing routine elective surgery lasting less than 2 hours. Renal function was, however, not assessed in that study; so it is possible that the blood pressure was maintained at the expense of renal blood flow. The purpose of the study reported here was to evaluate renal function in healthy dogs undergoing general anesthesia and ovariohysterectomy without concurrent IV administration of fluids.

Materials and Methods

Dogs—Thirty-five of 80 dogs that were admitted to the Onderstepoort Veterinary Academic Hospital (OVAH) for routine ovariohysterectomy during a 10-week period were included in this study. Because each dog acted as its own control, there was no need for a control group. For dogs to be included in the study, they had to weigh >5 kg and be healthy. Dogs that had pre-existing signs of renal dysfunction detected during initial assessment (n = 1) or that developed complications during ovariohysterectomy (3) were removed from the study. Thus, dogs that received fluids during or after the surgery or developed intra- or postoperative hemorrhage were excluded. These dogs were removed from the group of 80 so that at the end, 35 dogs completed the study. Procedures were performed with the written consent of the dogs’ owners and approval of the Research and Ethics committees of the Faculty of Veterinary Science, University of Pretoria.

Anesthesia and surgery—Food and water were withheld from the dogs for 10 hours prior to anesthesia. Dogs were medicated with promazine hydrochloride (0.05 mg/kg, SC) approximately 45 minutes prior to induction of anesthesia. General anesthesia was induced with thiopental sodium (10 to 15 mg/kg, IV), and the trachea was intubated. After induction, morphine sulfate (0.1 mg/kg, SC) was administered as an analgesic. Anesthesia was maintained with a 2% halothane and oxygen mixture. Ventilatory assistance was not provided, and dogs were maintained at a surgical plane of anesthesia. Ovariohysterectomies were performed by senior veterinary students operating under direct supervision of a veterinary surgeon. Because of the inexperience of the students, the procedure was usually protracted (as long as 300 minutes [5 hours]).

Sample collection—Twenty-four hours before and 24 and 48 hours after ovariohysterectomy, blood was collected from the cephalic vein of each dog into a serum vacuum tube. Blood was allowed to clot at room temperature (25°C), centrifuged, and serum was stored at −4°C until determination of serum urea and creatinine concentrations. At the same time that blood samples were collected, urine samples were collected aseptically via cystocentesis by 1 of the investigators (RL). Urine specific gravity and alkaline phosphatase (ALP) and γ-glutamyltransferase (GGT) activities were measured, FC\textsubscript{Na} was calculated, and urine sediment was evaluated microscopically.

Evaluation of renal function—Serum urea and creatinine concentrations were determined on an automated system, using a modification of the kinetic method to measure urea concentration and the alkaline picate reaction modified as a first order rate reaction to measure creatinine concentration. Sodium concentration was determined by use of an ion selective analyzer. Fractional clearance of sodium was calculated, using the following formula:

\[
\text{FC}\textsubscript{Na} = \frac{\text{serum creatinine}}{\text{Urine creatinine}} \times \frac{\text{Urine sodium}}{\text{Serum sodium}} \times \text{body weight (kg)}
\]

Urine ALP and GGT activities were determined on an automated system, using a modification of the p-nitrophenyl phosphate substrate method in AMP buffer to measure ALP activity and glutamyl-p-nitroanilide substrate with glycyglycine peptide acceptor to measure GGT activity. Urine specific gravity was determined, using a refractometer.

Microscopic evaluation of urine was done by 1 investigator (RL) after sediment was stained with Sternheimer-Malbin stain, which allowed RTE cells to be differentiated from other urinary epithelial cells. Detection of RTE cells was scored on a scale of 1 to 4. An RTE cell score of 1 represented 1 RTE cell per 2 to 3 HPF (400X magnification), 2 represented 1 to 2 RTE cells/HPF, 3 represented 2 to 4 RTE cells/HPF, and 4 represented >5 RTE cells/HPF.

Statistical analyses—Variables that were statistically analysed included urine specific gravity, serum urea and creatinine concentrations, FC\textsubscript{Na}, urine ALP and GGT activities, and urine ALP and GGT activities expressed as a ratio to urine creatinine concentration. Data were compared between 0 (before surgery) and 24 hours, 0 and 48 hours, and 24 and 48 hours, using both repeated measures ANOVA and a two-sample t-test. A value of P < 0.05 was considered significant. The Pearson test was used to check for correlation between duration of general anesthesia, body weight, and age of dogs and urine specific gravity, serum urea and creatinine concentrations, FC\textsubscript{Na}, and urine enzyme activities.

Results

Thirty-five dogs admitted to the OVAH for routine ovariohysterectomy during a 10-week period met the inclusion criteria for this study. During this time, 80 dogs were ovariohysterectomized at the OVAH; thus, 44% of dogs admitted for routine ovariohysterectomy met our inclusion criteria. Age of the 35 dogs ranged from 6 to 84 months (mean ± SD, 24.06 ± 19.64 months). Body weight ranged from 6 to 46 kg (22 ± 10.21 kg). Duration of anesthesia ranged from 80 to 310 minutes (184.43 ± 59.55 minutes). Surgery time ranged from 70 to 260 minutes (148.46 ± 53.81 minutes).

We did not detect changes over time in urine specific gravity, serum urea and creatinine concentrations, FC\textsubscript{Na}, and urine enzyme activities that we believed were indicative of renal dysfunction. However, compared with presurgery values, FC\textsubscript{Na} decreased significantly 24 and 48 hours after surgery, whereas urine GGT activity and the ratio of urine GGT activity to serum creatinine concentration increased significantly only at 24 hours (Table 1). Urine specific gravity and ALP activity and serum urea and creatinine concentrations did not change significantly over time. Mean ± SD presurgery values for each of the latter 4 variables were: urine specific gravity, 1.031 ± 0.011 (range, 1.008 to 1.053; reference interval, >1.030); urine ALP activity, 14.23 ± 19.94 U/L (range, 3 to 124 U/L; reference interval, 0 to 55 U/L); serum urea concentration, 5.44 ± 1.56 mmol/L (range 2.4 to 8.5 mmol/L; reference interval, 3.6 to 8.9 mmol/L); and serum creatinine concentration, 106.29 ± 14.79 µmol/L (range, 74 to 134 µmol/L; reference interval, <133 µmol/L). Renal tubular epithelial cells were not detected in urine of any of the dogs before surgery. Eleven dogs for which an increase in urine GGT activity was detected 24 hours after surgery and 5 dogs for which an increase...
in GGT activity was detected 48 hours after surgery also had a concomitant increase in RTE cell score. However, increases in RTE cell score were not clinically relevant. In all but 1 dog for which RTE cells were detected, scores were 1 or 2. Twenty-four hours after surgery, 1 dog had an RTE cell score of 3. At 48 hours, the score for this dog was 1.

We did not detect a correlation between duration of general anesthesia, body weight, and age of dogs and urine specific gravity, serum urea and creatinine concentrations, FCNa, and urine enzyme activities.

**Discussion**

Results of this study suggest that sufficient renal function can be maintained in healthy dogs undergoing elective surgery under general anesthesia without concurrent IV administration of fluids. Transient renal damage, however, was indicated by a slight but significant increase in urine GGT activity and detection of RTE cells in the urine 24 hours after surgery. These results support those of Stone et al, indicating that prolonged general anesthesia with surgery in dogs with reduced renal mass resulted in development of hypotension and only a transient decrease in renal function. It has also been reported that canine kidneys appear to be resistant to ischemia induced by hypotensive shock. In another study by Fleming et al, severe renal dysfunction was not detected during and for 5 days after laparotomy in anesthetized dogs. Thus, results of our study are similar to those of Gaynor et al, who found that IV administration of fluids was not necessary in young, healthy dogs undergoing elective surgery.

Although we did not detect clinically relevant renal dysfunction, there was a significant increase in urine GGT activity and ratio of urine GGT activity to urine creatinine concentration 24 hours after surgery, compared with presurgery values. However, by 48 hours after surgery, GGT activity had decreased to baseline value. Increased urine GGT activity is both an early and persistent indicator of renal tubular damage. Other enzymes for which urine activity also increases in response to renal tubular damage include ALP, N-acetyl-β-D-glucosaminidase, lactate dehydrogenase, and alanine aminopeptidase. Although urine GGT activity increased transiently after anesthesia and surgery, urine ALP activity did not change over time. Gamma-glutamyltransferase and ALP are brush border enzymes found in the proximal convoluted tubule of the kidney. Gamma-glutamyltransferase is more deeply anchored in the membrane matrix, whereas ALP has a higher excretion rate. However, other factors such as degree of protein binding, shape, and size of the enzyme are responsible for the different excretion rates. These factors may explain the disproportionate increase in urine GGT activity versus ALP activity in this study.

The increase in urine GGT activity was considered transient and not clinically relevant, particularly because serum urea and creatinine concentrations and FCNa did not increase. Serum urea and creatinine concentrations, however, are insensitive markers of renal dysfunction that increase only with a pronounced reduction in glomerular filtration rate. The increase in urine GGT activity suggested that there was some degree of transient tubular damage. However, this degree of damage did not affect the urine specific gravity or FCNa. Moreover, 48 hours after anesthesia and surgery, urine GGT activity had decreased to baseline value, indicating that any damage to the renal tubules was transient. Although determination of 24-hour urine enzyme activity provides a more accurate measurement of tubular damage, evaluation of the ratio of urine GGT activity to urine creatinine concentration in a spot urine sample is technically simpler and correlates with 24-hour urine enzyme activity.

A number of dogs had an increase in both RTE cells in the urine sediment (1 to 2 RTE cells per HPF) and urine enzyme activity. There was, however, no correlation between RTE cells and urine enzyme activity, RTE cells and duration of general anesthesia, and urine enzyme activity and duration of general anesthesia. The increase in RTE cells and urine enzyme activity was not clinically significant, although RTE cells in urine sediment does indicate transient renal damage.

Fractional clearance of sodium > 1% is indicative of acute tubular dysfunction. Some dogs in this study had a FCNa > 1% prior to surgery without obvious renal injury. Therefore, the possibility that a FCNa > 1% is an indicator of acute tubular dysfunction is not true and, in fact, may reflect an increased salt intake. We did not detect an increase in FCNa after anesthesia and surgery; instead, FCNa decreased significantly 24 and 48 hours after surgery, compared with presurgery values. The majority of extracellular sodium is actively reabsorbed in the kidneys from the proximal convoluted tubules, which results in passive water reabsorption. Further sodium reabsorption takes place in the distal convoluted tubules, secondary to active reabsorption of chloride ions, and in the collecting ducts. The latter is controlled by aldosterone. Results of our study suggest that, at least in some of the dogs, tubular reabsorption of sodium was 100% (FCNa of 0%), which may be interpreted to indicate renal retention of sodium secondary to aldosterone secretion as a result of activation of the renin-angiotensin-aldosterone (RAA) system. A presurgery FCNa of 0% could be explained by transient dehydration caused during the transport of the dogs to the OVAH and a reluctance to drink in a strange environment. The RAA system can

<p>| <strong>Table 1—Renal variables (mean ± SD [range]) measured during analysis of urine samples collected from 35 healthy dogs before (0 h) and after general anesthesia and ovariohysterectomy without concurrent IV administration of fluids</strong> |</p>
<table>
<thead>
<tr>
<th><strong>Time</strong></th>
<th><strong>FCNa (%)</strong></th>
<th><strong>Urine GGT activity (U/L)</strong></th>
<th><strong>GGT:creatinine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 h</td>
<td>0.65 ± 0.48†</td>
<td>39.86 ± 23.3,37¹</td>
<td>2.88 ± 1.40²</td>
</tr>
<tr>
<td></td>
<td>(0–2.09)</td>
<td>(8–112)</td>
<td>(0.38–7)</td>
</tr>
<tr>
<td>24 h</td>
<td>0.13 ± 0.14³</td>
<td>72.14 ± 34.7,69²</td>
<td>3.94 ± 1.32²</td>
</tr>
<tr>
<td></td>
<td>(0–0.46)</td>
<td>(0–218)</td>
<td>(0–16.31)</td>
</tr>
<tr>
<td>48 h</td>
<td>0.17 ± 0.14³</td>
<td>59.4 ± 50.0,9²</td>
<td>2.18 ± 1.75²</td>
</tr>
<tr>
<td></td>
<td>(0.85)</td>
<td>(2–219)</td>
<td>(0.36–7.01)</td>
</tr>
</tbody>
</table>

*Reference range, < 1%. †Reference range, 0 to 100 U/L. ‡Reference range, 0 to 5.6.*

FCNa = Fractional clearance of sodium. GGT = γ-Glutamyltransferase. GGT:creatinine = Ratio of urine GGT activity to urine creatinine concentration.

**•** Within a column, values with different superscripts are significantly different. (P < 0.05) different.
be activated in response to renal arterial hypotension or by sympathetic pathways that are stimulated by the stress of surgery and anesthesia.\(^{25,26}\) In our study, prolonged surgical and anesthetic times could have resulted in activation of the RAA system. Another possible activator of this system is halothane.

We did not detect clinically relevant signs of renal dysfunction in this group of healthy dogs undergoing elective surgery. Although we only monitored these dogs for 2 days, our results suggest that IV administration of fluids to healthy dogs undergoing anesthesia may not be necessary for maintenance of renal homeostasis.

References