Evaluation of clinical status, renal function, and hematopoietic variables after unilateral nephrectomy in canine kidney donors

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Objective—To determine clinical status and renal and hematopoietic function after kidney donation and identify risks associated with kidney donation in dogs.

Design—Prospective study.

Animals—14 dogs that underwent unilateral nephrectomy for kidney donation.

Procedures—Records were reviewed retrospectively to collect data regarding prenephrectomy clinicalopathologic variables. Dogs were reexamined prospectively at various times after nephrectomy, and pre- and postnephrectomy CBC, serum biochemical analyses, urinalysis, and urine protein-to-urine creatinine ratio were compared. Six dogs had postnephrectomy renal volume determined ultrasonographically, and 4 of those dogs also underwent scintigraphic determination of glomerular filtration rate and renal biopsy.

Results—All dogs were clinically normal at the time of reevaluation. There were no significant differences between prenephrectomy and postnephrectomy values for BUN concentration or urine specific gravity. Mean postnephrectomy serum creatinine concentration was significantly greater than prenephrectomy concentration. Mean serum phosphorus concentration was significantly decreased after nephrectomy, and mean Hct, corpuscular volume, and corpuscular hemoglobin concentration were significantly increased after nephrectomy. Postnephrectomy renal volume was greatest in dogs < 12 months old at the time of surgery. Mean postnephrectomy glomerular filtration rate was 2.82 ± 1.12 mL/kg/min (1.28 ± 0.51 mL/lb/min). Renal biopsy specimens obtained during and after nephrectomy were histologically normal.

Conclusions and Clinical Relevance—Renal and hematopoietic variables were within reference ranges in dogs examined up to 2.5 years after unilateral nephrectomy. Compensatory renal hypertrophy was greatest in dogs < 1 year of age at donation. Donor age, along with histocompatibility, may be an important factor in selecting dogs for kidney donation.


Renal failure is a common disease of dogs and may result from genetic, toxic, infectious, malignant, vascular, and degenerative causes. Medical and nutritional management with mineral- and protein-restricted diets, gastrointestinal protectants, phosphate binders, antihypertensive medications, and erythropoietin supplementation may temporarily ameliorate the clinical manifestations of mild to moderate renal failure. Progressive nephron loss ultimately results in end-stage renal disease, which is only variably responsive to conventional medical treatment. Definitive treatment is possible only with hemodialysis or renal transplantation. Hemodialysis is now available in many universities and referral hospitals and can alleviate many of the

<table>
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<th>ABBREVIATION</th>
<th>Glomerular filtration rate</th>
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signs of end-stage renal disease, but patients require dialysis 2 to 3 times/wk. Renal transplantation has been the treatment of choice for end-stage renal disease in humans for > 30 years and in cats for > 15 years, but transplantation in dogs has not yet been performed as commonly.

Human renal transplant programs rely on cadaveric and living kidney donors. Donor kidneys from related living donors are optimal because delay of allograft function is less common, optimal histocompatibility matching is possible, and donation and transplantation can better be coordinated. Longitudinal studies in humans clearly reveal that kidney donation is associated with minimal surgical risk and is safe for the donor. Moreover, kidney donation does not increase the risk of long-term metabolic complications or early renal disease.

Veterinary renal transplant programs rely on living kidney donors because of impracticalities associated with cadaveric renal transplantation. Most reports in
the literature have emphasized preoperative, operative, and postoperative care of the recipient, but the health of donor dogs is of equal importance, and preoperative screening is paramount to ensure that donors are not put at risk as a result of donation. The purpose of the study reported here was to assess clinical status and renal and hematopoietic function in healthy dogs after unilateral nephrectomy for kidney donation and to identify potential problems resulting from kidney donation.

Materials and Methods

Animals—Medical records of dogs serving as kidney donors at the Auburn University veterinary teaching hospital between April 2004 and April 2005 were reviewed (n = 19). In addition, owners of the donor dogs were contacted and asked to complete a questionnaire about their dog. Owners were asked to have their veterinarian obtain and send blood and urine samples to the veterinary teaching hospital for a CBC, serum biochemical profile, complete urinalysis, and urine protein-to-creatinine ratio determination. This step was taken so that all samples would be processed by the same laboratory. All donor dogs with a complete medical record and appropriate sample submission were included in the study (n = 14). All results of clinical pathology tests were shared with the owners and their regular veterinarian. The study was approved by the Auburn University Institutional Animal Care and Use Committee, and owners consented to the use of their animals.

Imaging—All imaging was performed at the veterinary teaching hospital. However, because of the widespread geographic distribution of the donor dogs, the number of dogs available for postnephrectomy imaging was limited (n = 6). Of these 6 dogs, all had ultrasonographic evaluation of the remaining kidney and 4 of 6 had dynamic renal scintigraphy. Sedation for ultrasonographic examinations was performed by administration of butorphanol (0.4 mg/kg [0.18 mg/lb], IM or IV). Sedation for dynamic renal scintigraphy was performed by administration of butorphanol (0.2 to 0.4 mg/kg [0.09 to 0.18 mg/lb], IM) and medetomidine (5 µg/kg [2.3 µg/lb], IM). Reversal of sedation with atipamizole was performed at the discretion of the supervising veterinarian. Glomerular filtration rate was determined in 4 dogs by means of dynamic renal scintigraphy with 3 mCi of technetium Tc 99m pentetate. Six dogs underwent ultrasonographic evaluation of the retained kidney with calculation of renal volume by use of the prolate ellipsoid formula (renal length \times width \times height \times \pi/6).1-13

Renal histology—All 14 dogs underwent renal biopsy of the retained kidney at the time of nephrectomy for kidney donation. Renal biopsy specimens were obtained with a 14-gauge biopsy needle.4 In all but 1 dog, the left kidney was collected for transplantation. Follow-up kidney biopsy specimens were obtained from the 4 dogs that underwent nuclear scintigraphy determination of GFR. Biopsy specimens were collected via an exploratory laparotomy. All biopsy specimens were fixed in neutral-buffered 10% formalin solution and stained with H&E and periodic acid–Schiff stains.

Statistical analysis—Statistical analysis was performed with statistical software. Descriptive statistics and 2-sided P values were calculated for each variable. Differences in normally distributed pre- and postnephrectomy laboratory values were evaluated by use of a paired Student t test. Data that were not normally distributed were analyzed by use of the Wilcoxon test. Association between pairs of variables was evaluated by use of Pearson product moment correlation. Values of P ≤ 0.05 were considered significant; data are reported as mean ± SD.

Results

Determination of clinical status—The clinical status of all 14 dogs was considered to be normal. Mean age at time of donation was 24.8 ± 24.7 months, and mean time between donation and the reevaluation examination was 18.7 ± 5.1 months. Donor dogs represented various breeds and included 7 Greyhounds or Greyhound crosses, 2 German Shepherd Dogs, 1 Bull Terrier, 1 English Setter, 1 Labrador Retriever, and 2 mixed-breed dogs. Four dogs were castrated males, and 10 were spayed females.

Results of physical examination were normal in 11 dogs. Of the remaining 3 dogs, 1 dog was obese, 1 dog had chronic seborrheic dermatitis of unknown etiology, and 1 dog was pyrexic at the time of examination (rectal temperature, 40.4°C [104.7°F]; however, this was attributed to anxiety. No dog was reported to be polydipsic or polyuric. Mean systolic blood pressure was 136 ± 14 mm Hg (range, 117 to 155 mm Hg; n = 8), and median systolic pressure was 133 mm Hg. None of the dogs were receiving medications other than heartworm and flea-tick preventatives. All owners reported that their dog’s overall health was excellent.

Clinicopathologic findings—Results of serum biochemical analyses, CBC, and urinalysis were summarized (Table 1). There was no significant (P = 0.092)

Table 1—Summary of clinicopathologic data collected before and after nephrectomy for kidney donation in 14 dogs.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before nephrectomy</th>
<th>After nephrectomy</th>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>Median (range)</td>
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<tr>
<td>BUN (mg/dL)*</td>
<td>13.33 ± 2.92</td>
<td>12.56 (6.2–20.0)</td>
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<tr>
<td>Creatinine (mg/dL)*</td>
<td>1.22 ± 0.22</td>
<td>1.2 (0.8–1.7)</td>
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<tr>
<td>Phosphorous (mg/dL)*</td>
<td>5.23 ± 1.56</td>
<td>5.15 (2.6–8.4)</td>
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<tr>
<td>USG*</td>
<td>1.038 ± 0.009</td>
<td>1.038 (1.02–1.05)</td>
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<tr>
<td>UPC</td>
<td>NA</td>
<td>NA</td>
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*For values obtained before nephrectomy, n = 12.

USG = Urine specific gravity, UPC = Urine protein-to-creatinine ratio. NA = Not available.
difference between mean pre- and postnephrectomy BUN concentrations. Mean postnephrectomy serum creatinine concentration was significantly ($P < 0.001$) increased, compared with prenephrectomy values, but both pre- and postnephrectomy values ($1.22 \pm 0.22$ mg/dL and $1.66 \pm 0.27$ mg/dL, respectively) were within reference range. Mean serum phosphorus concentration was significantly ($P = 0.001$) higher before nephrectomy than after nephrectomy ($5.23 \pm 1.56$ mg/dL and $3.56 \pm 0.71$ mg/dL, respectively), but concentrations remained within reference range. There were no significant differences between pre- and postnephrectomy albumin concentrations ($3.89 \pm 0.38$ g/dL and $3.77 \pm 0.25$ g/dL, respectively; $P = 0.42$) and pre- and postnephrectomy total protein concentrations ($6.50 \pm 1.11$ g/dL and $6.46 \pm 0.54$ mg/dL, respectively; $P = 0.868$). All other biochemical values were within reference ranges.

Mean urine specific gravity was $1.038 \pm 0.0091$ before nephrectomy and $1.037 \pm 0.0107$ after nephrectomy; the difference that was not significant. Five pre-nephrectomy urine specimens had trace ketones, 3 had trace blood, and 1 had positive results of bacterial culture. Five postnephrectomy urine specimens had trace bilirubin, 7 had trace ketones, 1 had triple phosphate crystals, 1 had calcium oxalate crystals, and 1 had amorphous crystals. Mean urine protein-to-creatinine ratio was $0.104 \pm 0.156$ after nephrectomy. One dog had 3+ proteinuria and a protein-to-creatinine ratio of $0.64$ (reference value, < 0.5).

Mean Hct values before and after nephrectomy were $47.42 \pm 6.18\%$ and $55.2 \pm 5.83\%$, respectively. There was a significant ($P = 0.016$) increase in Hct after nephrectomy, but both values were within reference range. The RBC count was also significantly ($P = 0.015$) increased after nephrectomy (mean prenephrectomy value, $6.86 \pm 0.81 \times 10^6$ cells/µL; mean postnephrectomy value, $7.70 \pm 0.65 \times 10^6$ cells/µL). Mean corpuscular volume was significantly ($P < 0.001$) increased after nephrectomy (mean prenephrectomy value, $67.88 \pm 1.67$ fL; mean postnephrectomy value, $71.42 \pm 2.56$ fL). Mean corpuscular hemoglobin concentrations before and after nephrectomy were $34.96 \pm 0.84$ g/dL and $33.12 \pm 0.84$ g/dL, respectively, a difference that was significant ($P = 0.001$). Although the changes in pre- and postnephrectomy values for Hct, RBC count, mean corpuscular volume, and mean corpuscular hemoglobin concentration were significant, all values were within reference range.

**Imaging**—Six dogs underwent ultrasonographic evaluation to determine length, width, and height of the remaining kidney at the time of reevaluation; mean values were $7.64 \pm 0.69$ cm, $4.21 \pm 0.75$ cm, and $4.09 \pm 0.47$ cm, respectively. Mean calculated renal volume for all 6 dogs was $70.54 \pm 24.62$ mL. Mean renal volume of young dogs ($< 1$ year; $n = 3$) was significantly ($P < 0.001$) higher than that of older dogs ($n = 3$; $102.15 \pm 4.27$ mL and $54.72 \pm 2.23$ mL in younger and older dogs, respectively).

Glomerular filtration rate was determined in 4 dogs at the time of follow-up examination. Mean GFR in these dogs was $2.82 \pm 1.12$ mL/kg/min ($1.28 \pm 0.51$ mL/lb/min; Table 2). A correlation between age at kidney donation and GFR could not be established on the basis of the number of dogs in which GFR was determined, but GFR was highest in dogs younger than 12 months of age at donation.

### Renal histopathologic findings

All 14 dogs used for kidney donation had histologically normal kidneys, as determined by microscopic examination of prenephrectomy biopsy specimens. Follow-up biopsy specimens were obtained from 4 dogs. Two of those specimens were microscopically normal, and 2 had changes indicating minimal local glomerulosclerosis (2 affected glomeruli/60 glomeruli counted and 2 affected glomeruli/52 glomeruli counted).

### Discussion

In the 14 dogs reported here, BUN and serum creatinine concentrations remained within reference range after nephrectomy, although there was a significant increase in serum creatinine concentration. Renal concentrating ability was also considered normal on the basis of urine specific gravity values. The urine protein-to-creatinine ratio was within reference limits for 13 of 14 dogs, and the ratio in the remaining dog (0.6) was only slightly greater than the reference limit (< 0.5). That dog had 3+ proteinuria, but the urine sample was collected via free-catch rather than via cystocentesis, and it is possible that the protein originated from the lower portion of the urinary tract. Proteinuria is a common finding in human kidney donors but usually is neither progressive nor associated with decreased GFR or hypertension. In a previous study in dogs, proteinuria developed after experimental unilateral nephrectomy, but the dogs did not develop hypertension and renal function remained stable.

One half of normal renal mass has been determined to be adequate to sustain normal erythropoiesis in dogs, but a decrease to 25% of normal renal mass may not be sufficient to maintain adequate erythropoietin synthesis. Although none of the donor dogs had a decrease in Hct, RBC count, or other hematologic variables, significant differences between pre- and postnephrectomy samples were found via CBC. The RBC count, mean corpuscular volume, and mean corpuscular hemoglobin concentration were significantly increased, compared with prenephrectomy values; however, all RBC indices were within reference ranges. Postnephrectomy hypochromasia and macrocytosis suggest accelerated RBC production, but the mechanism is unclear and further investigation was beyond the scope of this study.
Serum phosphorus concentration was lower after nephrectomy, compared with prenephrectomy values. Because several donor dogs were young Greyhound crosses, this finding was attributed to the higher phosphorus concentrations often detected in young, large-breed dogs; the lower serum phosphorus concentrations detected after surgery were believed to be indicative of skeletal maturity and normal renal function. An increase in phosphorus excretion has been reported in 30% of human kidney donors, but urine phosphorus concentration was not determined in dogs of the present study. Therefore, the true reason for the decreased phosphorus concentration was not known and warrants further investigation.

Microscopic examination of biopsy specimens from the remaining kidney, collected at the time of kidney donation, indicated that kidneys in all dogs were histologically normal. Follow-up biopsy specimens were available for only 4 dogs. The specimens were normal in 2 dogs, and only minor histologic changes were detected in the other 2 dogs. It is not known whether these changes were natural, related to prior biopsy, or related to the increased workload in the remaining kidney after nephrectomy.

The ultrasonographic appearance of the retained kidneys was considered normal. Interestingly, the mean renal volume of the retained kidneys was normal or high, compared with weight-adjusted normal ranges. In dogs that were <1 year of age at the time of nephrectomy, mean renal volume at the time of reevaluation was 102.15 ± 4.27 mL, which was significantly higher than that in the older dogs (54.72 ± 2.23 mL).

The GFR directly reflects the number of functioning nephrons. Four dogs were available for GFR measurement after kidney donation. The reference limit for GFR in dogs with 2 kidneys is > 3 mL/kg/min (1.35 mL/lb/min). However, dogs with unilateral dysfunction or a single kidney may have a GFR > 1.5 mL/kg/min (> 0.68 mL/lb/min) because of compensatory hypertrophy. The GFRs in the present study were within the reference range for dogs with a single kidney, although the degree of compensation varied substantially. On the basis of GFR measurements, younger dogs had greater compensation for the loss of renal mass. Although it would have been ideal to have performed prenephrectomy GFR studies, this imaging modality was not available at the time of nephrectomy. Remnant kidney GFRs of 70% to 75% of preoperative values have been reported in human kidney donors, suggesting that the remaining kidney undergoes functional hypertrophy. This compensatory ability maintains normal kidney function in donors.

The capacity for and mechanisms underlying the compensatory renal hypertrophy and hyperplasia seen in young animals is not fully understood. Renal hypertrophy is influenced by age, reduction in functional renal mass, and dietary protein intake. Because all dogs in the present study had a reduction of 50% in renal mass and none of the dogs were on protein-restricted diets, age at time of donation was the greatest variable affecting renal hypertrophy. The implication that younger dogs may have greater renal compensatory abilities deserves further study.

These results suggest that donor age as well as histocompatibility should be considered in the selection of canine kidney donors. Furthermore, the difficulty of finding related donors that are younger than 12 months of age underscores the need for alternative approaches to standard immunosuppressive protocols to induce renal allograft tolerance. Living donor transplantation programs should be designed to minimize risks to the donor while maximizing the potential benefits to the recipient.

References

1. Langston C. Advanced renal therapies: options when standard treatments are not enough. Vet Clin N Am Dec;999–1008.