The rationale for continuous fluid therapy during anesthesia and surgery is to maintain adequate blood volume, CO, and organ perfusion. Earlier studies\(^1\)–\(^3\) revealed that fluids composed of crystalloids administered at rates of at least 5 to 10 mL/kg/h were necessary to maintain adequate organ perfusion, as quantified by UO, and better patient outcome in humans and other animals. To the contrary, other studies\(^4\)–\(^7\) reveal normal (ie, within reference range) UO, blood pressure, and organ perfusion and reduced complications with little or no fluid administration during anesthesia and surgery. To date, little information is available regarding UO, GFR, and fluid retention in dogs anesthetized for long routine surgical procedures and receiving the recommended crystalloid administration rate of approximately 10 mL/kg/h.\(^2\)\(^,\)\(^8\) In the authors' clinical experience, UO in dogs anesthetized for routine surgical procedures is variable but often less than the expected 1 to 2 mL/kg/h considered typical for dogs.\(^9\)\(^,\)\(^10\) Although normal UO is often used as an indicator of adequate renal perfusion, a decrease in UO may not reflect poor renal perfusion during anesthesia and surgery. Anesthesia and surgery are stressful events and predictably increase the physiologic stress hormones, including cortisol, catecholamines, renin-angiotensin, vasopressin, atrial natriuretic peptide, prostaglandins, aldosterone, and endothelin.\(^11\)–\(^14\) These hormones are

**Objective**—To determine fluid retention, glomerular filtration rate, and urine output in dogs anesthetized for a surgical orthopedic procedure.

**Animals**—23 dogs treated with a tibial plateau leveling osteotomy.

**Procedures**—12 dogs were used as a control group. Cardiac output was measured in 5 dogs, and 6 dogs received carprofen for at least 14 days. Dogs received oxymorphone, atropine, propofol, and isoflurane for anesthesia (duration, 4 hours). Urine and blood samples were obtained for analysis every 30 minutes. Lactated Ringer’s solution was administered at 10 mL/kg/h. Urine output was measured and glomerular filtration rate was estimated. Fluid retention was measured by use of body weight, fluid balance, and bioimpedance spectroscopy.

**Results**—No difference was found among control, cardiac output, or carprofen groups, so data were combined. Median urine output and glomerular filtration rate were 0.46 mL/kg/h and 1.84 mL/kg/min. Dogs retained a large amount of fluids during anesthesia, as indicated by increased body weight, positive fluid balance, increased total body water volume, and increased extracellular fluid volume. The PCV, total protein concentration, and esophageal temperature decreased in a linear manner.

**Conclusions and Clinical Relevance**—Dogs anesthetized for a tibial plateau leveling osteotomy retained a large amount of fluids, had low urinary output, and had decreased PCV, total protein concentration, and esophageal temperature. Evaluation of urine output alone in anesthetized dogs may not be an adequate indicator of fluid balance. (Am J Vet Res 2010;71:501–507)
capable of changing renal function and fluid retention independently from renal perfusion.\textsuperscript{15,16} For these reasons, the purpose of the study reported here was to determine fluid retention and changes in GFR and UO in dogs anesthetized for a surgical orthopedic procedure. A separate group was used to evaluate the effect of carprofen on fluid balance, GFR, and UO.

Materials and Methods

Animals—Twenty-three adult dogs were studied. All dogs were client owned and anesthetized for surgical correction of a ruptured cranial cruciate ligament by use of the tibial plateau leveling osteotomy technique. The inclusion criteria were age from 1 to 7 years, body weight > 15 kg, no known systemic illness, ruptured cranial cruciate ligament requiring unilateral correction, no abnormal results of physical examination with the exception of moderate hind limb lameness, and no abnormal findings of CBC, serum biochemical profile, and urinalysis. A written informed consent was obtained from each dog owner. The study was approved by the University of California-Davis Animal Care and Use Committee.

All dogs received oxymorphone\textsuperscript{a} (0.08 mg/kg, SC) and atropine\textsuperscript{b} (0.02 mg/kg, SC) for premedication 15 to 30 minutes before placement of an IV catheter in a cephalic vein. Anesthesia was induced with propofol\textsuperscript{c} administered to effect and maintained with isoflurane at a concentration needed to maintain a moderate depth of anesthesia, as judged by an experienced anesthetist. An IV infusion of lactated Ringer's solution\textsuperscript{d} was started at a rate of 10 mL/kg/h, by use of a volumetric fluid pump,\textsuperscript{e} starting at induction and maintained throughout surgery. The volumes of heparinized saline (0.9% NaCl) solution used to flush the arterial catheter and the isotonic saline solution used for CO measurements were taken into account to achieve a total fluid administration of 10 mL/kg/h. Cefazolin\textsuperscript{f} (20 mg/kg) was administered IV for antimicrobial prophylaxis after induction and then every 2 hours until closure of the surgical site. During anesthesia, end-tidal PCO\textsubscript{2}, isoflurane concentration, inspired O\textsubscript{2}, and respiratory rate were measured continuously by use of an infrared-paramagnetic analyzer.\textsuperscript{g} The analyzer was calibrated daily with a mixture containing 5% CO\textsubscript{2}, 54.9% O\textsubscript{2}, 36% N\textsubscript{2}O, and 3% isoflurane\textsuperscript{h} according to the manufacturer’s recommendations. A lead II ECG was used to monitor heart rate, rhythm, and electrical conformation. A transesophageal temperature probe was used to measure body temperature, and an arterial catheter was placed in a dorsal pedal artery to measure arterial blood pressure by use of an electronic multiparameter monitor.\textsuperscript{i} A Foley catheter was placed in the urinary bladder immediately after induction. The bladder was emptied manually, and a catheter-tip syringe was connected, creating a closed collection system for subsequent urine collection.

Mean arterial pressure was maintained from 70 to 100 mm Hg, and PaCO\textsubscript{2} was maintained from 35 to 40 mm Hg throughout anesthesia. The MAP was maintained by changing anesthetic depth and PaCO\textsubscript{2} by use of positive-pressure ventilation. No inotropes were required for any dog. At the end of anesthesia, the urinary and arterial catheters were removed. Oxymorphone (0.05 mg/kg) in combination with carprofen (4 mg/kg) was administered SC for pain management prior to recovery.

Procedures—A urine sample (free catch) and a blood sample were collected before anesthesia in the awake dogs as the first sample. During anesthesia, urine was collected and quantified volumetrically every 30 minutes starting from anesthesia induction. Similarly, 1 mL of blood was collected via the arterial catheter every 30 minutes starting from the time of anesthesia induction. Representative urine and plasma aliquots were stored at –70°C for creatinine measurement.

Pack cell volume was measured by use of microcapillary tubes centrifuged for 5 minutes (11,000 to 13,000 X g).\textsuperscript{j} Total protein concentration was measured by use of refractometry.\textsuperscript{k}

Body fluid balance for each dog was assessed via the difference in body weight measured immediately before and after anesthesia with a calibrated scale; the total volume of administered fluids, compared with the total volume of urine produced; and the difference between total body water, ECF, and ICF before and after anesthesia measured by use of multifrequency bioimpedance spectroscopy.

Multifrequency bioimpedance spectroscopy performed with intradermal tetrapolar platinum electrodes consists of passing multiple nonperceptible low-strength electric currents through the body to measure the body’s impedance.\textsuperscript{17,18} Small electric currents were used at 50 logarithmically spaced frequencies ranging from 5 to 1,000 kHz by use of a bioimpedance spectrometer.\textsuperscript{l} Total body water, ECF, and ICF volumes were predicted from the respective resistances by use of the Cole-Cole model for current conduction through heterogeneous biological tissues and the Hanai mixture theory by use of algorithms derived for use with the bioimpedance spectrometer.\textsuperscript{17} Currents with low frequencies will pass only through the ECF, whereas higher frequencies will cross cell membranes and measure ECF and ICF volumes. The use of body impedance to calculate ECF, ICF, and total body water has been described in humans,\textsuperscript{19} horses,\textsuperscript{18} and dogs.\textsuperscript{20}

Glomerular filtration rate was estimated by use of endogenous creatinine urinary clearance as described in dogs\textsuperscript{21–23} by use of the following equation:

$$\text{GFR} = \frac{\text{Urine creatinine concentration} \times \text{urine volume}}{\text{Body weight} \times \text{plasma creatinine concentration} \times \text{time}}$$

where time is 30 minutes, which is the interval between measurements. Body weight was obtained before anesthesia. The creatinine concentration was measured in duplicate for urine and plasma aliquots by use of an automated enzymatic kinetic assay not affected by non-creatinine chromagens.\textsuperscript{24}

Of the 23 dogs studied, 12 were untreated and used as the control group. These dogs had not received any medication for at least 10 days prior to the study. A second untreated group including 5 dogs was used to measure CO by use of a lithium dilution technique. The third group, composed of 6 dogs, included dogs that had received carprofen daily (75 to 100 mg, PO, q 12 h;
mean ± SD, 4.2 ± 2.5 mg/kg/d) for at least 14 days before the day of surgery (carprofen group).

For the CO group, CO was measured by use of the lithium dilution technique according to the manufacturer’s indications and as described in dogs.24-27 The dose of lithium chloride recommended by the manufacturer for the dog’s body weight was injected through the cephalic vein catheter and flushed with 10 mL of isotonic saline solution. Cardiopulmonary output was measured via lithium detection in arterial blood according to the predetermined formula. The analytic system withdrew 3 to 4 mL of blood from the dorsal pedal artery catheter to measure CO during each measurement. The CO measurements were started 2.5 hours after induction of anesthesia and obtained every 30 minutes by use of the same intervals as blood and urine collections. Urine output and GFR were compared before versus during CO measurements because high plasma lithium concentrations might influence renal function, GFR, and UO.26,27

Statistical analysis—Dependent variables measured at a single time point were transformed as necessary to satisfy a Wilk-Shapiro test of normality. Variables were analyzed in raw form, in logarithmic form, or following a rank transformation. The raw and logarithmically transformed variables were analyzed over time by use of 1-way ANOVA, followed by paired comparisons by use of the Tukey method. Rank transformed variables were analyzed by use of Kruskal-Wallis tests. Dependent variables that were measured at multiple time points were first logarithmically transformed to satisfy the normality assumption and then analyzed by use of repeated-measures ANOVA methods. Post hoc comparisons were done to compare treatments at each time point (by use of the Tukey method) or to compare time points against the control measurement within each treatment (by use of the Dunnett method). Data are reported as median (range) values when not normally distributed. If data such as body weight, total fluid administered, fluid balance, GFR, and UO, were normally distributed, they are reported as mean ± SD values. The anesthesia data are reported as range values. The UO, GFR, and CO values reported in the results were obtained during durations of anesthesia up to 4 hours to make the comparison among groups consistent. Significance was set at values of P < 0.05.

Results

Dogs—The control group had 5 males and 7 females that were 4.5 ± 2.8 years old and weighed 33.9 ± 5.5 kg; the group included 3 Labrador Retrievers, 1 Tibetan Terrier, 1 Akita, 1 pit bull–type dog, 1 Newfoundland, 1 Bullmastiff, 1 Rottweiler, 1 Boxer, and 2 mixed-breed dogs. The CO group had 1 male and 4 females that were 3.8 ± 1.7 years old and weighed 30.7 ± 7.6 kg; the group included 1 Rottweiler, 1 Boxer, 1 German Shepherd Dog, and 2 mixed-breed dogs. The carprofen group had 3 males and 3 females that were 5.3 ± 2 years old and weighed 31.6 ± 5.5 kg; the group included 1 Golden Retriever, 1 pit bull–type dog, and 4 mixed-breed dogs.

Anesthesia variables—During the anesthesia period, the end-tidal isoflurane concentration was maintained from 0.9% to 2.2%, and inspired O₂ was > 95% at all times. The respiratory rate was maintained from 8 to 12 breaths/min; heart rate was 82 to 102 beats/min, systolic arterial pressure was 110 to 145 mm Hg, and MAP was 71 to 94 mm Hg; diastolic arterial pressure was 56 to 78 mm Hg; esophageal temperature was 35.3⁰ to 38.7°C; Paw was 460 to 565 mm Hg; Paco₂ was 36 to 40 mm Hg; pH was 7.31 to 7.35; and LRS administration was maintained at 10 mL/kg/h. No alterations in cardiac rhythm or ECG conformation were observed during anesthesia. Total anesthesia time (induction to discontinuation of isoflurane administration) was from 3.5 to 5 hours (< 4 hours in 1 dog and > 4.5 hours in 2 dogs). No surgical or anesthetic complication was observed for any dog.

UO—The UO did not change significantly over time in any group (Figure 1). The median (range) UO for the control group was 0.39 mL/kg/h (0 to 1.13 mL/kg/h), for the CO group was 0.44 mL/kg/h (0 to 2.2 mL/kg/h), and for the carprofen group was 0.72 mL/kg/h (0.03 to 1.68 mL/kg/h). No significant differences were observed among groups. Urine output in the CO group did not change after lithium administration. The median (range) UO for all 23 dogs was 0.46 mL/kg/h (0 to 2.2 mL/kg/h).

GFR—The estimated GFR did not change significantly throughout the anesthesia period in any group (Figure 2). The median (range) GFR for the control
group was 1.73 mL/kg/min (0 to 5.5 mL/kg/min), for the CO group was 1.95 mL/kg/min (0 to 2.7 mL/kg/min), and for the carprofen group was 2.17 mL/kg/min (0.8 to 10.9 mL/kg/min). No significant differences were observed among groups. The GFR did not change after lithium chloride administration to measure CO. The median (range) GFR for all 23 dogs was 1.84 mL/kg/min (0 to 10.9 mL/kg/min).

**Fluid balance**—The 3 variables used to assess fluid balance were change in body weight, difference between volume of fluids administered and UO, and values obtained via multifrequency bioimpedance (Figures 3 and 4). Before anesthesia, the mean body weight for the control group was 33.9 ± 5.4 kg, for the CO group was 30.7 ± 7.5 kg, and for the carprofen group was 31.8 ± 4.9 kg. No differences were observed among groups. After anesthesia, the mean body weight for the control group was 34.9 ± 5.3 kg, for the CO group was 32 ± 7.4 kg, and for the carprofen group was 32.9 ± 5.4 kg. When weights in the different groups were pooled, the postanesthesia weight (33.7 ± 5.7 kg) was significantly greater than the preanesthesia weight (32.6 ± 5.6 kg).

Mean total fluid administration rate after 4 hours of anesthesia for the control group was 39.9 ± 3.9 mL/kg, for the CO group was 39.1 ± 1.2 mL/kg, and for the carprofen group was 40 ± 0.5 mL/kg (Figure 4). No differences were observed among groups. Mean total UO after 4 hours of anesthesia for the control group was 1.8 ± 0.7 mL/kg, for the CO group was 2.3 ± 1.9 mL/kg, and for the carprofen group was 3.1 ± 1.6 mL/kg. All groups received a larger volume of fluids, compared with the total volume of urine produced. The fluid retention or mean difference between fluid administered and UO for the control group was 37.6 ± 4 mL/kg, for the CO group was 38.1 ± 4.8 mL/kg, and for the carprofen group was 36.9 ± 1.5 mL/kg. Mean fluid retention for all 23 dogs after 4 hours of anesthesia was 37.5 ± 3.6 mL/kg.

The mean ECF and ICF measured by use of bioimpedance before anesthesia for the control group were 6.9 ± 2.1 L and 11.4 ± 6 L, for the CO group were 6.1 ± 1.3 L and 11.3 ± 4.1 L, and for the carprofen group were 6.4 ± 1.7 L and 12.4 ± 6.1 L, respectively. The ECF and ICF volumes after anesthesia for the control group were 7.9 ± 1.9 L and 13.2 ± 3.9 L, for the CO group were 6.8 ± 1.6 L and 11.5 ± 2.5 L, and for the carprofen group were 7.2 ± 1.5 L and 13.8 ± 6.2 L, respectively. No differences were observed among groups. No significant difference was observed in values obtained before versus after anesthesia for any group. However, when
results from all groups were pooled, ECF increased significantly from 6.0 ± 1.8 L to 7.5 ± 1.8 L, whereas ICF did not significantly change (before anesthesia, 11.7 ± 5.4 L; after anesthesia, 13 ± 5.3 L [Figure 3]). Total body water content increased from 18.4 L to 20.5 L. All 3 methods revealed fluid retention with a gain in body weight of 1.1 ± 0.6 kg, positive fluid balance of 37.5 ± 3.6 mL/kg, increased total body water volume of 2 ± 3 L, and increased ECF of 0.9 ± 0.6 L.

CO, PCV, and TP—The CO did not change throughout the anesthesia period measured (from 130 to 240 minutes). Mean CO was 3.5 ± 0.6 L/min or 114 ± mL/kg/min. The PCV and TP decreased during anesthesia for all 3 groups (Figure 5). Control, CO, and carprofen groups had PCVs before anesthesia of 47.4 ± 4.8%, 49.8 ± 2.5%, and 47.6 ± 2.3%, respectively, whereas the TP concentrations were 6.7 ± 0.4 g/dL, 6.6 ± 0.7 g/dL, and 7 ± 0.4 g/dL, respectively. No differences were observed among groups. The PCV and TP decreased in all 3 groups in a linear manner until the end of anesthesia (P = 0.01). The PCVs after 4 hours of anesthesia were 32.6 ± 4.8%, 29.5 ± 1.7%, and 33.8 ± 2.6% for the control, CO, and carprofen groups, respectively, whereas the TP concentrations were 5.1 ± 0.3 g/dL, 4.3 ± 0.3 g/dL, and 5.1 ± 0.4 g/dL for the control, CO, and carprofen groups, respectively. The TP after 4 hours of anesthesia was different, compared with that of the control and CO groups. No differences in PCV were detected among groups after 4 hours of anesthesia.

Body temperature—The esophageal temperature during anesthesia decreased for all dogs (Figure 5). Control, CO, and carprofen groups had a temperature at induction of 37.3 ± 0.4°C, 37 ± 0.6°C, and 37.3 ± 0.2°C, respectively. After 4 hours of anesthesia, the temperatures had decreased to 35.3 ± 1.2°C, 35.7 ± 0.7°C, and 36.3 ± 0.7°C, respectively, which were significantly (P = 0.01) different over time but not among groups. Mean temperature of all 23 dogs together decreased from 38.5 ± 0.7°C before anesthesia to 35.7 ± 1°C during anesthesia despite active warming with warm air blankets.

Discussion

In the present study, healthy dogs anesthetized for a prolonged routine surgical procedure and receiving lactated Ringer’s solution at 10 mL/kg/h had lower UO and GFR, compared with reference range values reported in dogs (1 to 2 mL/kg/h and 2.5 to 5.5 mL/kg/min, respectively).9,10 Median UO and GFR were 0.46 mL/kg/h and 1.84 mL/kg/min, respectively. The low UO and GFR correlated with fluid retention, which occurred primarily in the extracellular space as ECF. Total body fluid retention was quantified as 1 to 2 L of fluids (for a 30-kg dog) after 4 hours of anesthesia. No difference was found between control values and those of dogs that received lithium chloride for CO measurement or carprofen for pain management. An unanswered question from the study was whether volume overload or a decrease in GFR and UO occurred first.

One of the disadvantages of use of crystalloids for fluid administration is the property of crystalloids to diffuse across membranes and leave the vascular space. Thus, 30 to 45 minutes after administration of crystalloids to a patient, only approximately 30% remains in the vascular space.38 The remaining 70% of the crystalloid volume is either excreted through the kidneys as urine or accumulated in the extravascular space, causing fluid retention.

In the present study, we maintained MAP and Paco2 constant during anesthesia to prevent their influence on renal perfusion. An MAP of 70 to 100 mm Hg and Paco2 of 35 to 40 mm Hg should have had little effect on renal perfusion.15,20–31 The hypothermia observed in the dogs could have influenced CO, renal perfusion, GFR, and UO. Hypothermia commonly increases sympathetic nervous system activity and vascular resistance.32,33 However, CO, GFR, and arterial blood pressure did not change significantly relative to the decreasing body temperature over time. Moderate hypothermia decreases GFR but increases UO in research animals.34 Nonetheless, we could not determine the influence of hypothermia on GFR, UO, and fluid retention in the present study.

Typically, the dogs had low UO with variable GFR. The discrepancy between GFR and UO suggested fluid reabsorption in the kidneys. Glomerular filtration rate depends on filtration, whereas UO depends on filtration, reabsorption, and excretion of the ultrafiltrate. Adequate CO and MAP should have maintained renal perfusion and normal GFR.15,21 The constant low UO could be attributed to reabsorption of the ultrafiltrate. Various drugs, blood flow, and hormones could interfere with renal function. Drugs used during the study were oxymorphone, atropine, propofol, isoflurane, and cefazolin.

The effect of oxymorphone on GFR and UO has not been reported. The effect of opioids on GFR and UO is variable. Opioids can interfere with renal function by increasing or decreasing GFR and UO. In dogs, a decrease in UO has been observed.35–37 The role of opioids in systemic fluid retention, independent of renal function and its effect on other stress hormones, is unknown.

Cephalosporin antimicrobials could potentially decrease GFR and UO by causing interstitial nephritis. However, the newer cephalosporins such as cefazolin cause no renal damage and little or no change in GFR and UO.38 In the present study, no signs of renal damage were reported up to 2 weeks after discharge.

Results of previous studies39,40 indicate that atropine and propofol may have mild to no direct influence on GFR and UO. In addition, the systemic effect and half-lives for atropine and propofol in dogs are short: < 60 minutes for atropine and < 30 minutes for propofol. Thus, the effect of atropine and propofol during a 4-hour study is expected to be minor. The effect of atropine and propofol on systemic fluid retention, independent of renal function, is unknown.

Isoflurane causes minimal changes in GFR and UO when blood pressure and renal blood flow are maintained.41 However, anesthesia and surgery can cause increases in plasma cortisol, catecholamines, renin-angiotensin, vasopressin, atrial natriuretic peptide, prostaglandins, aldosterone, and endothelin concentrations.11–14 Any of these hormones could influence
GFR and UO. Vasopressin is the hormone responsible for water reabsorption at the level of the distal tubules and collecting ducts. Water transport across cell membranes is mediated by aquaporin channels and diffusion. The expression and activity of the aquaporin channels and the membrane diffusion coefficient could be altered by the release of vasopressin, cortisol, catecholamines, angiotensin, prostaglandins, and endothelin. The concentrations of the stress hormones were not measured in the present study. Further studies are necessary to identify the role of stress hormones in fluid extravasation and retention.

The TP concentration decreased during the anesthesia period. Total protein, and especially albumin, are responsible for maintenance of intravascular oncotic pressure. The decrease in TP concentration during anesthesia will predispose to fluid loss from the vascular space. The TP values after 4 hours of anesthesia (approx 5 g/dL) could have contributed to fluid retention.

Oral administration of carprofen for at least 14 days prior to surgery did not appear to influence UO, GFR, and fluid retention. This lack of effect should be interpreted with caution because of the small number of dogs treated with carprofen in the study. Carprofen is a mostly selective cyclooxygenase-2 inhibitor commonly used in dogs for pain management. Inhibition of prostaglandin synthesis may have an important effect on renal function and renal blood flow. Prostaglandins prevent vasoconstriction and promote renal blood flow, whereas inhibition of prostaglandin synthesis by cyclooxygenase-2 decreases renal blood flow. The absence of effects on UO, GFR, or fluid retention associated with carprofen could be attributable to the small number of dogs used in the study or to a mild effect from carprofen on these variables during anesthesia. Results of previous studies in dogs reveal mild to no change in renal function when carprofen is administered before or during anesthesia.

Three important limitations of the study are the small number of dogs used in each group, the lack of confirmation of bladder volume, and the estimation of GFR by use of endogenous creatinine clearance measurements. The low statistical power may have prevented detection of small differences among groups. The use of endogenous creatinine clearance to calculate GFR has been validated in dogs; however, the GFR values obtained do not perfectly correlate with the gold standard calculations obtained from inulin clearance. Endogenous creatinine clearance was used because it is technically easier to measure than is inulin clearance and did not require administration of another chemical in these client-owned animals. Actual GFR could be slightly different (± 10% to 20%) than the GFR measured by use of endogenous creatinine clearance. It is unlikely that the small difference would have influenced the interpretation of the results.

Dogs receiving anesthesia with no open cavity and did not require administration of another chemical in these client-owned animals. Actual GFR could be slightly different (± 10% to 20%) than the GFR measured by use of endogenous creatinine clearance. It is unlikely that the small difference would have influenced the interpretation of the results. We recommend considering fluid administration in anesthetized dogs by use of a goal-directed approach for each case and to monitor central venous pressure and collodion pressure simultaneously with UO if adequate fluid balance is desired.

References

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