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Adrenal Response to Adrenocorticotropic Hormone in Dogs before and after Surgical Attenuation of a Single Congenital Portosystemic Shunt

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Background: Dogs with single congenital portosystemic shunts (CPSS) often develop postoperative hypoglycemia and prolonged anesthetic recovery. These abnormalities could be attributable to inadequate adrenal response. However, adequacy of adrenal response after CPSS surgery is unexplored.

Hypothesis: Dogs with CPSS have inadequate postoperative adrenal response.

Animals: Eight nonoperated, 8 ovariohysterectomy (OHE), and 16 CPSS dogs.

Methods: Consecutive day ACTH stimulation tests were performed on nonoperated healthy dogs, healthy dogs before and after OHE, and CPSS dogs before and after surgery. Adequate response was defined as $>50\%$ or >30 ng/mL increase in cortisol after ACTH administration. Blood glucose (BG) was monitored before and after surgery. Prolonged anesthetic recovery and refractory hypoglycemia episodes were recorded.

Results: Results of consecutive day ACTH stimulation tests did not vary in normal dogs. Results of preoperative ACTH stimulation tests of CPSS and OHE dogs were not significantly different. Dogs with CPSS had higher postoperative baseline cortisol concentrations (median, 329 ng/mL) than OHE dogs (median, 153 ng/mL). Postoperative cortisol increase after ACTH in CPSS was $\leq 50\%$ in 10/16 and ≤ 30 ng/mL in 6/16. After surgery, BG was ≤ 60 mg/dL in 7/16 CPSS dogs. Cortisol concentrations were not correlated with BG. Two CPSS dogs had refractory hypoglycemia and 4 had delayed recovery; all improved with dexamethasone administration (0.1–0.2 mg/kg/IV).

Conclusions and Clinical Importance: Contrary to previous reports, baseline cortisol concentrations in CPSS and healthy dogs are similar. Many CPSS dogs have postoperative hypercortisolemia. Response to ACTH does not correlate with postoperative hypoglycemia or prolonged anesthetic recovery.

Key words: ACTH stimulation test; Adrenal insufficiency; Dexamethasone; Hypoglycemia.

Hypoglycemia occurs in 22–47% of dogs with congenital portosystemic shunts (CPSS) and is associated with poor muscle mass, low body fat, low hepatic glycogen stores, and impaired gluconeogenesis.[1–6] Fasting or concurrent conditions such as intestinal parasites, diarrhea, hypothermia, or poor diet can increase the risk of hypoglycemia.[1] Toy breed dogs such as Yorkshire Terriers are prone to hypoglycemia and CPSS.[2–4] Treatment of hypoglycemia associated with CPSS includes frequent feedings, IV supplementation of dextrose, and, if possible, closure of the CPSS to improve hepatic portal perfusion. It is our impression that approximately 25% of dogs undergoing ameroid constrictor placement for CPSS at our hospital developed postoperative hypoglycemia (glucose ≤ 60 mg/dL) despite postoperative IV dextrose supplementation, and some dogs have prolonged anesthetic recovery with or without hypoglycemia. In some dogs, postoperative recovery and blood glucose (BG) concentrations seemingly improve after administration of supraphysiologic doses of dexamethasone (0.1–0.2 mg/kg IV), suggesting reduced adrenal function or dampened peripheral glucocorticoid effects.

Relative adrenal insufficiency (RAI) in humans can result in refractory hypoglycemia, poor anesthetic recovery, or refractory hypotension.[7–9] Recently, RAI has been correlated with refractory hypotension in dogs with sepsis.[10] RAI remains a controversial diagnosis in humans[11] and has not been documented in dogs with CPSS. The purpose of this study was to (1) evaluate preoperative and postoperative adrenal function in clinically healthy dogs and dogs with CPSS and (2) document the occurrence and relationship of postoperative hypoglycemia and duration of postoperative recovery with adrenal function tests in dogs with CPSS.

Materials and Methods

The study protocol was approved by the Institutional Animal Care and Use Committee of the University of Tennessee (UT), and informed consent was obtained from all owners.

Dogs

The study population included client-owned dogs that presented to the UT Veterinary Teaching Hospital from April 2004 to April 2006. Dogs did not receive any steroids within 6 weeks before the study, and control dogs had no known underlying medical abnormalities. All dogs were between 6 months and 6 years of age. Suspicion of CPSS in study dogs was based on signalment; clinical signs; increased concentrations of serum bile acids; biochemical and urinalysis abnormalities consistent with liver dysfunction (microcytosis, hypoalbuminemia, decreased blood urea nitrogen, ammonium biurate crystalluria)[3,5,6]; presence of shunting on trans-

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splenic (12 dogs) or colorectal (4 dogs) portal nuclear scintigraphy; and identification of the shunt at abdominal exploratory surgery.

Procedures

In 8 healthy control dogs, 2 ACTH stimulation tests were performed 24 hours apart to verify consistency of consecutive day testing. Dogs were fasted for 12 hours and venous blood for cortisol assay was collected before and 1 hour after IV administration of Cortrosyn[a] (5 μg/kg). Serum was separated and stored at −80°C for up to 72 hours until cortisol analyses in the UT Clinical Endocrinology Laboratory using a canine validated solid-phase radioimmunoassay procedure.[b,12,13] Eight healthy female dogs scheduled for ovariohysterectomy (OHE) and 16 dogs with CPSS underwent pre- and post-ACTH stimulation tests 1 day before surgery. Scintigraphy confirming CPSS was performed in dogs after the preoperative ACTH stimulation test was completed.

BG concentrations were measured at the time of cortisol sampling with a portable glucose meter[c] validated in a previous study. In that study, glucose concentrations were evaluated in 63 dogs, including 6 dogs with BG concentrations ≤73 mg/dL (mean 62; range, 42–73 mg/dL), 17 dogs with BG of 83–100 mg/dL, 26 dogs with BG of 101–140 mg/dL, and 14 dogs with BG concentrations ≥209 mg/dL, as measured simultaneously with an in-house Hitachi 911 clinical chemistry analyzer.[d] Pearson's correlation coefficient for the two methods was 0.99, and combined imprecision (inter- and intra-assay variability) was 3%. The AccuCheck Active had a proportional bias at higher glucose concentrations. At BG concentrations ≤73 mg/dL, glucose concentrations measured by AccuCheck glucometer were an average of 2 mg/dL higher than those measured by the Hitachi chemistry analyzer. At glucose concentrations of 83–100 and 101–140 mg/dL, the AccuCheck glucometer measurements averaged 12 mg/dL lower than the Hitachi measurements, and at glucose concentrations ≥209 mg/dL, the AccuCheck glucometer measurements averaged 38 mg/dL lower than Hitachi measurements.

On the day of surgery, dogs were premedicated with hydromorphone[e] (0.1 mg/kg IM), atropine (0.04 mg/kg IM), and midazolam[f] (0.2 mg/kg IM) and induced with propofol[g] (2–6 mg/kg IV). General anesthesia was maintained with isoflurane.[h] An 18-G jugular catheter was placed during the anesthetic period for postoperative sampling in CPSS patients. Normosol R[i] with 5% dextrose (10 mL/kg/h IV) was administered during anesthesia in OHE and CPSS dogs. Parameters measured every 5 minutes during anesthesia included pulse and respiratory rates, systolic blood pressure, pulse oximetry, and end tidal carbon dioxide level. Ameroid ring constrictor placement and liver biopsy in dogs with CPSS were performed by a board certified small animal surgeon or surgical resident. Concurrent OHE was performed in 8 CPSS dogs, and 2 of them had extraction of retained deciduous teeth. Healthy female dogs underwent routine OHE performed by a 4th year veterinary student under the supervision of a board certified surgeon or surgical resident. Surgery time was recorded for all dogs.

Postoperative Monitoring

After surgery, OHE and CPSS dogs were maintained on Normosol R with 5% dextrose (2 mL/kg/h IV) for 6 hours. Fluid therapy was then adjusted according to individual hydration and glycemic status. Hydromorphone (0.05 mg/kg IV) was administered every 4 hours for analgesia. Acepromazine[j] (0.05 mg/kg IV) was given with the 1st dose of hydromorphone to all OHE and CPSS dogs to reduce anxiety. BG was measured at 0, 1, 2, 3, 4, 5, and 6 hours after surgery in dogs with CPSS and twice (at the time of cortisol sampling) in dogs undergoing OHE. ACTH stimulation tests were repeated 4–5 hours after surgery in normoglycemic dogs and as early as 2 hours after surgery if postoperative hypoglycemia was documented before the scheduled testing time. Dogs were offered food once they were completely recovered.

Dogs with CPSS were monitored in the intensive care unit for hypoglycemia (≤60 mg/dL) and prolonged recovery. Prolonged recovery was defined as reduced mentation; hypothermia (temperature <98°F for more than 2 hours); prolonged capillary refill time (normal, <2 seconds); pale mucous membranes; and weak peripheral pulses. Blood pressures were not measured postoperatively. Dogs with prolonged recovery that failed to improve with the application of forced air warmers or increased fluid rate (up to 3 mL/kg/h) were treated with dexamethasone[k] (0.1 mg/kg IV). Because all dogs received a 5% continuous infusion of dextrose during the study period, dogs that developed hypoglycemia were given an IV bolus of 25% dextrose (1 mL/kg IV). Dogs that failed to become normoglycemic after dextrose supplementation or feedings were given dexamethasone (0.1–0.2 mg/kg IV).

Statistical Analysis

Data were examined for normal distribution by Shapiro-Wilk's test; a P value > .05 indicates normal distribution. In-house laboratory cortisol values for healthy, nonoperated dogs were used in statistical evaluations (baseline cortisol: 2–60 ng/mL, post-ACTH stimulated cortisol: 65–175 ng/mL)[13] (Personal communication: Dr Jack Oliver, UT Clinical Endocrinology Service, Knoxville, TN).

Results of ACTH stimulation tests on consecutive days from healthy dogs were normally distributed and were analyzed using a repeated measures ANOVA blocking. Because data for dogs undergoing OHE and CPSS repair were not normally distributed, Friedman's test was used to analyze cortisol concentrations before and after ACTH administration. Mann-Whitney U test was used to compare age, body weight, duration of surgery, systolic blood pressure at extubation, and cortisol concentrations of dogs with CPSS and OHE. Association of shunting with hypoglycemia or inadequate adrenal response (increase in cortisol ≤50% or ≤30 ng/mL over baseline) were evaluated with a Fisher's exact test. Relationship of BG and cortisol concentrations before and after ACTH administration was evaluated using Spearman's rank correlation. Significance was set at $P \leq .05$.

Results

Breeds of healthy dogs (n = 8) undergoing ACTH stimulation tests on consecutive days included mixed (n = 5), Jack Russell Terrier (n = 2), and 1 Staffordshire Terrier; median age was 3.4 years (range, 6 months to 5 years), and median body weight was 16 kg (range, 5–33 kg). Results of consecutive day ACTH stimulation tests were normal in all of these dogs (Fig 1); day 1 and day 2 median baseline and post-ACTH cortisol concentrations were not significantly different. Median increase in post-ACTH cortisol concentration was 1,150% of baseline value (range, 330–2,030%) and 820% of baseline value (range, 220–1,800%) on days 1 and 2, respectively.

Breeds of healthy female dogs (n = 8) undergoing OHE included mixed (n = 3), and 1 each of Beagle, Boston Terrier, Cocker Spaniel, Basset Hound, and English Bulldog. Median age was 3 years (range, 8 months to 6 years), and median body weight was 17 kg (range, 8–22 kg). Breeds of dog undergoing attenuation of CPSS (n = 16) included Yorkshire Terrier (n = 12), and 1 each of Maltese, Miniature Schnauzer, Shih Tzu, and Chihuahua. Nine dogs were intact females, 4 were spayed

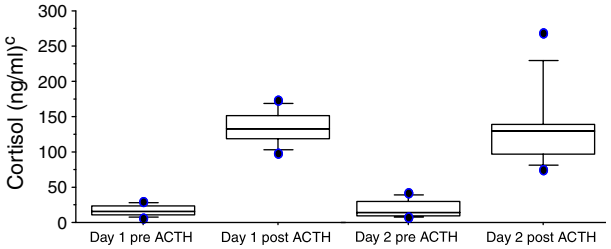

Fig 1. Box plots[a] of consecutive day ACTH stimulation test cortisol results in 8 normal dogs.[a] The horizontal line within boxes indicates median values. Boxes indicate the 25th–75th percentile, and whiskers indicate the 10th and 90th percentile. Values below the 10th or above the 90th percentile are represented as dots.

females, 2 were intact males, and 1 was a castrated male. Median age was 1 year (range, 6 months to 6 years) and median body weight was 2 kg (range, 1–7 kg). Although there was no significant difference in age of dogs undergoing OHE and CPSS attenuation ($P = .28$), dogs undergoing CPSS attenuation had a significantly lower body weight ($P < .05$) and shorter duration of surgery (median, 65 minutes; range, 40–120 minutes; $P < .05$) than dogs undergoing OHE (median, 130 minutes; range, 65–185 minutes). Systemic blood pressure was evaluated in all dogs under anesthesia but was not monitored after extubation. Hypotension was defined as a systolic blood pressure < 80 mmHg.[10] Systolic blood pressure at extubation in OHE dogs (median 150 mmHg; range, 100–180 mmHg) was significantly higher ($P < .01$) than in CPSS dogs (median, 85 mmHg; range, 70–130 mmHg). Only one CPSS dog was hypotensive (70 mmHg) going into recovery. The ACTH stimulation test results for that dog were normal before and after surgery.

No significant differences were found when comparing preoperative baseline cortisol concentrations, preoperative post-ACTH cortisol concentrations, or postoperative post-ACTH concentrations of OHE and CPSS dogs (Fig 2). Postoperative baseline cortisol concentrations were significantly higher in CPSS dogs compared with OHE dogs ($P = .003$). Seven out of the 8 dogs having other procedures done under anesthesia had high postoperative baseline cortisol concentrations. Preoperative and postoperative post-ACTH cortisol concentrations in OHE dogs were significantly increased compared with baseline cortisol concentrations taken on the same day. Preoperative post-ACTH cortisol concentrations in CPSS dogs were significantly increased compared with baseline cortisol concentrations; however, there was no significant difference in postoperative pre- and post-ACTH cortisol concentrations.

No dogs had subnormal baseline cortisol concentrations before surgery. Preoperative post-ACTH cortisol concentration was below reference range in 1 OHE dog (cortisol, 63 ng/mL). All CPSS and OHE dogs had increases in preoperative post-ACTH cortisol concentration > 50%and > 30 ng/mL over baseline. Median post-ACTH cortisol concentrations before surgery were 560% of baseline values (range, 240–1,290%) in OHE dogs and 810% of baseline values (range, 270–2,230%) in CPSS dogs.

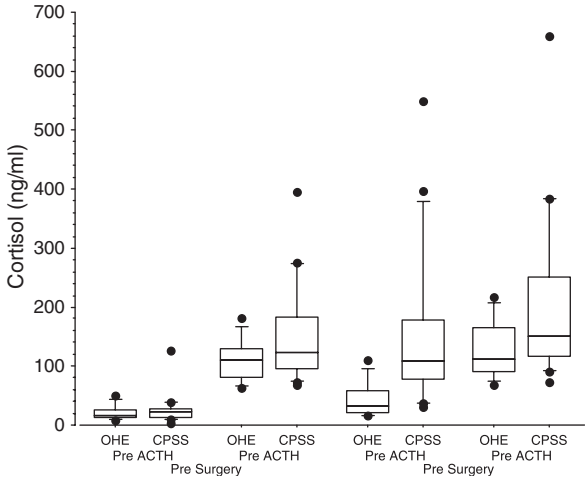

Fig 2. Box plots[a] of pre- and post-ACTH stimulation test cortisol results in 8 dogs undergoing OHE[b], and 16 dogs undergoing surgical correction of CPSS.[a,c] See Figure 1 for explanation of box plots. [b]OHE, ovariohysterectomy; [c]CPSS, single congenital portosystemic shunt.

After surgery, 2 OHE dogs had increased baseline cortisol concentrations (63 and 110 ng/mL) and 2 OHE dogs had increased post-ACTH cortisol concentrations (181 and 217 ng/mL). Baseline hypercortisolemia (median, 153 ng/mL; range, 77–550 ng/mL) was detected in 13 out of 16 CPSS dogs, and 6 out of 16 CPSS dogs had post-ACTH hypercortisolemia (median, 329 ng/mL; range, 220–660 ng/mL). Postoperative baseline hypercortisolemia was significantly more common in dogs with CPSS than OHE dogs. No OHE or CPSS dogs had subnormal postoperative cortisol concentrations before or after ACTH administration.

OHE dogs had a median increase in cortisol concentration after surgery of 270% of baseline values (range, 150–1,130%) and CPSS dogs had a median increase of 120% of baseline values (range, 93–360%). One OHE dog had an inadequate response to ACTH, with an increase in post-ACTH cortisol concentration of 29 mg/dL (46% over baseline). Ten CPSS dogs had an increase in post-ACTH cortisol concentration ≤50% (median, 6%; range, −4–46%), and 6 CPSS dogs had an increase in post-ACTH cortisol concentration ≤30 ng/mL (median, 2 ng/mL; range, −15–8 ng/mL). Five of the dogs undergoing CPSS attenuation and OHE/deciduous teeth extractions had increases in post-ACTH cortisol concentration ≤50% and ≤30 ng/mL. Inadequate response to ACTH was significantly more common after surgery in CPSS dogs when defined as ≤50% rise in post-ACTH cortisol ($P = .026$) but not when defined as an increase of ≤30 ng/mL over baseline ($P = .34$). All dogs with inadequate response to ACTH had increased baseline postoperative cortisol concentrations when compared with reference ranges for healthy, nonoperated dogs.

In OHE dogs, median BG concentration before surgery was 92 mg/dL (range, 80–109 mg/dL), and median postoperative BG on IV fluids with 5% dextrose was 117 mg/dL (range, 84–230 mg/dL). None of the

OHE dogs had a prolonged anesthetic recovery or hypoglycemia.

Median preoperative BG concentration in CPSS dogs was 71 mg/dL (range, 44–97 mg/dL); 5 of 16 dogs were hypoglycemic. Median postoperative BG concentration of CPSS dogs on IV fluids with 5% dextrose was 85 mg/dL (range, 40–292 mg/dL), and 7 of 16 CPSS dogs developed hypoglycemia within 4 hours after surgery. Postoperative hypoglycemia was significantly more common in dogs with CPSS ($P = .05$). Median postoperative BG nadir for dogs with CPSS was 69 mg/dL (range, 40–88 mg/dL) and 112 mg/dL (range, 84–175 mg/dL) in OHE dogs. Median BG concentrations and BG nadir were not correlated with postoperative baseline cortisol concentrations. Four of 7 CPSS dogs with postoperative hypoglycemia had $\leq$50% increase in post-ACTH cortisol concentrations and 1 of these 4 also had $\leq$30 ng/mL increase in post-ACTH cortisol. Preoperatively, 3 of the 4 dogs with $\leq$50% increase in post-ACTH cortisol concentrations after surgery had normal ACTH stimulation tests and 1 had increased pre- and post-ACTH stimulated cortisol concentrations. Postoperatively all 4 of these dogs had increased baseline cortisol concentrations and 3 of the 4 had increased post-ACTH stimulated cortisol concentrations. The CPSS dog with $\leq$30 ng/mL increase in post-ACTH stimulated cortisol concentration had a normal preoperative ACTH stimulation test. In that dog, postoperative cortisol concentrations before and after ACTH stimulation were increased.

Four dogs with CPSS were given dexamethasone for delayed anesthetic recovery. Two of these dogs had refractory hypoglycemia (BG 46 or 57 mg/dL before, and 50 or 56 mg/dL after, 1 mL/kg 25% dextrose IV, respectively) and 1 developed postoperative hypoglycemia (BG, 50 mg/dL) that responded to 25% dextrose administration IV. Two of the 4 dogs requiring dexamethasone had other procedures (OHE and/or deciduous teeth extractions) done under anesthesia. Dexamethasone was administered after post-ACTH sampling in 3 dogs. In 1 dog, dexamethasone was administered after baseline sampling; cortisol concentrations were 187 and 220 ng/mL, respectively, before and after ACTH administration. Hypoglycemia and signs of prolonged anesthetic recovery resolved after administration of 2 doses of dexamethasone in 2 dogs and 1 dose in 2 dogs. Three of the 4 dogs given corticosteroids had $\leq$50% increase in cortisol over baseline and 1 had $\leq$30 ng/mL increase. Inadequate adrenal response, using either criterion, was not significantly correlated with refractory hypoglycemia or prolonged anesthetic recovery.

Discussion

Consecutive day baseline and post-ACTH cortisol concentrations in clinically normal dogs did not influence adrenal responsiveness or cortisol concentrations, similar to findings when normal dogs were tested at 1–2-week intervals.[14–15] Because endogenous ACTH concentrations were not measured, effects of exogenous ACTH on postoperative cortisol concentrations could not be determined. In normal dogs, influence of Cortrosyn (5 μg/kg) on cortisol lasts approximately 2 hours.[15] In critically ill dogs, repeated daily ACTH stimulation testing did not blunt adrenal response.[16]

There was no significant difference in age of OHE and CPSS dogs; however, OHE dogs were significantly heavier and none were toy breeds. The effects of age and body size on serum concentrations of cortisol in dogs have been previously evaluated.[17–19] Small breed dogs have higher concentrations of cortisol than larger breeds.[17]

Cortisol concentrations in dogs increase after diagnostic and surgical procedures, most likely because of stress or pain.[20–22] In 1 study, dogs undergoing major abdominal, thoracic, or orthopedic surgeries had normal baseline cortisol concentrations before surgery that significantly increased within 180 minutes after surgery. Cortisol concentrations returned to baseline within 24 hours.[22] Cortisol concentrations in dogs undergoing OHE reportedly increase by 2–4-fold after surgery.[21,23–26] Baseline cortisol concentrations before and after surgery were not significantly different in dogs undergoing OHE despite less experienced operators and longer surgical duration. Preoperative analgesic and sedative administration may have reduced postoperative pain and anxiety in OHE dogs in our study.[27]

Discordant with previous studies of CPSS dogs, we found no significant differences between preoperative baseline cortisol concentrations of healthy and CPSS dogs. Previous reports describe significantly increased baseline cortisol concentrations in CPSS dogs; hypercortisolemia subsequently resolved within 4 weeks after shunt attenuation.[28–30] Potential etiologies for hypercortisolemia in dogs with CPSS include decreased hepatic synthesis of cortisol binding proteins, abnormal counter-regulatory response to hypoglycemia, reduced hepatic clearance of cortisol, peripheral resistance to cortisol, or stress associated with chronic nonadrenal illness.[21,28–33] In our study, no dog with preoperative hypoglycemia had increased cortisol concentrations; thus, postoperative hypoglycemia was unlikely to be the cause of baseline postoperative hypercortisolemia.

Baseline postoperative cortisol concentrations were significantly increased in dogs with CPSS compared with preoperative baseline concentrations in CPSS dogs and pre- and postoperative baseline concentrations in OHE dogs. Postoperative hypercortisolemia did not correlate with glucose concentrations or surgical duration. Although high cortisol concentrations may have reflected preoperative procedures (eg, scintigraphy 16 or more hours before postoperative ACTH stimulation tests, placement of a jugular catheter), previous studies contradict this likelihood.[24,34] However, 7 out of the 8 CPSS dogs having other procedures while under anesthesia developed high postoperative baseline cortisol concentrations. In healthy dogs, plasma cortisol concentrations returned to the normal range within 4 hours after major operative procedures or jugular catheter placement.[24,34]

Although 10/16 CPSS dogs failed to achieve a $>$50% relative cortisol increase, only 6 of these 10 dogs failed to increase cortisol $>$30 ng/mL after ACTH administration. Five of these 6 dogs had other procedures done

under anesthesia. Each of these dogs had a high baseline cortisol concentration. No dog had a subnormal postoperative post-ACTH cortisol concentration. Etiologies for decreased response to ACTH stimulation include testing error, lack of adrenal reserve in patients already responding maximally to stress, or adrenal insufficiency.[10,24,33,35] RAI is characterized as inadequate production of cortisol in relation to demand, particularly in critical illnesses.[9] Criteria for diagnosis of RAI in dogs are not well defined. In 1 study of septic dogs, diagnosis of RAI was based on change in cortisol values $\leq$30 ng/mL.[10] Individual values for pre- and post-ACTH concentrations were not reported in that study; thus, baseline cortisol concentrations and percent change after ACTH stimulation could not be evaluated. Reduced response to ACTH was associated with hypotension and decreased survival; however, 35% of nonhypotensive dogs and 25% of surviving dogs also had change in cortisol values $\leq$30 ng/mL.[10] Blood pressures were not measured postoperatively in our study; however, all 6 dogs with change in cortisol $\leq$30 ng/mL survived to discharge. Interestingly, the only CPSS dog with hypotension going into recovery had normal ACTH stimulation tests on both days, and no documented hypoglycemia or delayed anesthetic recovery.

The most common objective criterion for diagnosis of RAI in humans is post-ACTH cortisol concentration $<$180 ng/mL or change in cortisol concentration $<$90 ng/mL.[11] Treatment with hydrocortisone has also been recommended for humans with transient postsurgical hypoadrenalism when post-ACTH concentrations did not double.[36] Unlike our patients, however, humans with transient postsurgical hypoadrenalism had severe inflammation and sepsis, and their baseline cortisol concentrations increased as inflammation decreased.[36] Because cortisol concentrations in dogs are much lower than in humans, applying criteria of inadequate adrenal function from the human literature is inappropriate. We therefore evaluated adrenal function based on previously published criteria ($\leq$30 ng/mL increase over baseline) for septic dogs[10] and by using a relatively conservative estimate of $\leq$50% increase in post-ACTH cortisol over baseline.

Postoperative post-ACTH concentrations in some dogs with CPSS may have increased $\leq$30 ng/mL and $\leq$50% over baseline because their adrenal glands were already maximally stimulated. It is unknown whether patients that have reached maximal adrenal output can respond appropriately to additional stressors.[33,37–38] Although 6 out of 16 dogs had post-ACTH hypercortisolemia, post-ACTH cortisol concentrations were normal in 5 out of 16 dogs that had inadequate postoperative adrenal function based on both criteria ($\leq$30 ng/mL and $\leq$50% increase over baseline). At this time, we know of no method for measuring maximum adrenal reserve in individual dogs.

Objective criteria are not accurate in all human patients; therefore, physicians may base diagnosis of RAI on clinical signs such as weakness, abnormal mentation, refractory hypotension, or hypoglycemia and on resolution of signs after glucocorticoid administration.[7–9,33,37] Of 10 CPSS dogs with $\leq$50% increase in cortisol after ACTH, only 3 developed clinical signs consistent with RAI; only one of these dogs had an increase in post-ACTH cortisol over baseline $\leq$30 ng/mL. Although 1 OHE dog had inadequate adrenal response based on cortisol concentrations, it had no clinical signs of RAI. Therefore, either prolonged recovery or refractory hypoglycemia in our dogs was caused by something other than RAI, or changes in cortisol concentration cannot be used as the sole criteria for inadequate adrenal function. Measurement of postoperative blood pressures would have been helpful in detecting evidence of RAI in our dogs. However, all dogs received an α blockade dose of acepromazine that could have interfered with monitoring parameters. Hepatic clearance of acepromazine may also differ in the CPSS patients because of individual shunt differences and could have resulted in prolonged recovery in some dogs.

Postoperative hypoglycemia developed in a significant number of CPSS dogs, despite concurrent administration of IV fluids containing 5% dextrose and normal or increased postoperative cortisol concentrations. In 2 dogs with delayed anesthetic recovery, hypoglycemia was refractory to administration of 25% dextrose IV but resolved after administration of dexamethasone. Further studies evaluating insulin concentrations, hepatic glycogen stores, and other counter-regulatory hormones (glucagon, growth hormone, and epinephrine) in dogs with CPSS are warranted to determine the cause of refractory hypoglycemia.

Four CPSS dogs were administered supraphysiologic doses of dexamethasone ($\geq$0.1 mg/kg/dose) for prolonged anesthetic recovery or refractory hypoglycemia. In humans, physiologic or stress doses of steroids are recommended for treatment of RAI.[9] Although dogs with profound postanesthetic hypoglycemia attributable to glucocorticoid deficiency may respond to physiologic doses of glucocorticoids (eg, 0.2–0.4 mg/kg of prednisone),[39] 2 of 4 dogs in our study resolved clinical signs (slow postoperative recovery, hypoglycemia) after administration of supraphysiologic doses of dexamethasone (equivalent to 2 mg/kg of prednisone).

One dog with refractory hypoglycemia received dexamethasone within 1 hour before post-ACTH cortisol sampling; post-ACTH cortisol concentration in this dog increased $\leq$50% over baseline. In clinically normal dogs, cortisol is readily released after ACTH administration in dexamethasone-suppressed dogs.[40]

Limitations of our study include small sample size, lack of measurement of endogenous ACTH, insulin, other counter-regulatory hormones, postoperative blood pressure in all dogs, hourly glucose measurements in postoperative OHE dogs, and the use of a portable glucometer for BG measurement.

In conclusion, baseline cortisol concentrations in dogs with CPSS are not significantly different from normal dogs; however, postoperative baseline cortisol concentrations in CPSS dogs are significantly greater than dogs undergoing OHE. Inadequate response to ACTH was significantly more common after surgery in CPSS when defined as $\leq$50% rise in post-ACTH cortisol but not when defined as $\leq$30 ng/mL over baseline; blunted response

in most dogs was a result of high baseline postoperative cortisol concentrations. Although postoperative hypoglycemia was significantly more common in dogs with CPSS, glucose concentrations did not correlate with circulating cortisol concentrations. Irrespectively, refractory hypoglycemia in 2/16 CPSS dogs resolved after administration of supraphysiologic doses of IV dexamethasone.

Footnotes

[a] Cortrosyn, Ornanon Inc, West Orange, NJ
[b] Coat-a-Count, Diagnostic Products Corp, Los Angeles, CA
[c] AccuCheck Active portable glucose meter, Roche Diagnostics Inc, Indianapolis, IN
[d] Hitachi 911 Chemistry Analyzer, Roche Diagnostics
[e] Hydromorphone, Elkins-Sinn Inc, Cherry Hill, NJ
[f] Versed, Roche Laboratories Inc, Nutley, NJ
[g] Propoflo, Abbott Laboratories Inc, Chicago, IL
[h] Isoflo, Abbott AG, Baar, Switzerland
[i] Normosol R, Abbott Laboratories
[j] PromAce, Fort Dodge Laboratories Inc, Fort Dodge, IA
[k] Dexamathasone, Vedco Inc./Phoenix Scientific Inc, St Joseph, MO

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