Effect of laparotomy on the pituitary-adrenal axis in dogs

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Received July 15, 2016.
Accepted October 31, 2016.

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OBJECTIVE
To assess effects of major abdominal surgery on serum cortisol and aldosterone and plasma canine ACTH (cACTH) concentrations.

ANIMALS
39 healthy dogs undergoing laparotomy during veterinary student surgical laboratories.

PROCEDURES
Blood samples were obtained before and at completion of surgery. Serum cortisol and aldosterone and plasma cACTH concentrations were measured by use of validated radioimmunoassays. Changes in concentrations (postoperative concentration minus preoperative concentration) were calculated. Data were analyzed by use of the Wilcoxon signed rank test, Pearson correlation analysis, and Mann-Whitney rank sum test.

RESULTS
Cortisol, aldosterone, and cACTH concentrations increased significantly from before to after surgery. Although cortisol and aldosterone concentrations increased in almost all dogs, cACTH concentrations decreased in 6 of 32 (19%) dogs. All dogs had preoperative cortisol concentrations within the reference range, but 24 of 39 (62%) dogs had postoperative concentrations above the reference range. A correlation between the change in cACTH concentration and the change in cortisol concentration was not detected.

CONCLUSIONS AND CLINICAL RELEVANCE
Laparotomy caused a significant increase in serum cortisol and aldosterone concentrations. In most dogs, but not all dogs, plasma cACTH concentrations increased. Lack of correlation between the change in cACTH concentration and the change in cortisol concentration suggested that increased postoperative cortisol concentrations may have been attributable to ACTH-independent mechanisms, an early ACTH increase that caused a sustained cortisol release, or decreased cortisol clearance. Further studies are indicated to evaluate the effects of various anesthetic protocols and minimally invasive surgical techniques on the stress response. (*Am J Vet Res* 2017;78:919–925)

The stress response is defined by activation of the hypothalamic-pituitary-adrenal axis and activation of the sympathetic nervous system. Increases in ACTH and cortisol concentrations ensue in humans within minutes after initiation of surgery, with maximal cortisol concentrations occurring approximately 4 to 6 hours after the start of surgery.[1] The magnitude and duration of the increase in postoperative cortisol concentrations correlates with the degree of surgical stress.[1] Plasma ACTH and cortisol concentrations are defined as dissociated when the ACTH concentration is low and the cortisol concentration remains high.[2] Cortisol and ACTH concentrations are often dissociated in human patients after surgery,[3–5] which may be attributable to altered adrenocortical sensitivity to ACTH, changes in glucocorticoid metabolism or clearance (or both), and ACTH-independent mechanisms that influence adrenal gland glucocorticoid synthesis and secretion (eg, influence of nervous stimulation and neuropeptides or interaction with the immune system through cytokines, paracrine factors derived from endothelial cells, and adipocyte-derived adipokines).[2] The main cytokines released after major abdominal surgery in humans are IL-1, TNF-α, and IL-6,[6] which can stimulate the hypothalamic-pituitary axis alone or in synergy with each other.[2]

The stress response may not be beneficial in surgical patients because it may adversely alter homeostasis and impair tissue healing.[7] Prolonged surgical stress may lead to increased morbidity and delayed postoperative recovery.[8] Cortisol has profound inhibitory effects on the inflammatory and immune responses and may contribute to morbidity, fatalities, and increased duration of hospitalization in human surgical patients.[1]

ABBREVIATIONS

cACTH	Canine ACTH
IL	Interleukin
TNF	Tumor necrosis factor

Aldosterone secretion is stimulated by 3 primary mechanisms: angiotensin II, increased extracellular potassium concentrations, and ACTH. Stimulation of aldosterone secretion by ACTH is part of the stress response.[9] Aldosterone restores circulatory volume in hypovolemic states and increases blood pressure by acting on the vasculature and CNS.[10] Patients undergoing surgery are at risk of developing hypotension or hypovolemia (or both) as a result of blood loss and the effects of anesthesia. Aldosterone concentrations increase after surgery in humans[11–13]; ACTH as well as renin may be involved in this increase.[13]

Studies have been conducted to assess the cortisol response of dogs to surgery. Surgeries evaluated were typically minor or of short duration, including ovariohysterectomy,[14–27] orchiectomy,[18,28] or orthopedic procedures.[29–33] In addition, use of laparoscopic versus open surgery for nephrectomy or pancreatectomy of dogs has been compared.[34–36] To our knowledge, aldosterone response to surgery has not been evaluated in dogs, and ACTH concentrations have been evaluated in only 2 studies.[16,25] Furthermore, median or mean surgery duration has been < 2 hours in all previous studies. Because the magnitude and duration of surgery affect cortisol concentrations in people,[1] further assessment of the endocrine response of dogs to prolonged or major procedures would be of benefit.

Therefore, the purpose of the study reported here was to assess the effect of surgery on cortisol, aldosterone, and endogenous cACTH concentrations in dogs undergoing major abdominal surgery. We hypothesized that major abdominal surgery would activate the pituitary-adrenal axis in dogs; concentrations of cortisol, aldosterone, and cACTH would increase significantly after surgery; and there would be postoperative cACTH dissociation in dogs similar to that seen postoperatively in human patients.

Materials and Methods

Animals

Thirty-nine sexually intact adult mixed-breed dogs that underwent laparotomy as part of a veterinary student surgical laboratory were included in the study. Dogs were obtained from USDA-licensed vendors and were considered healthy on the basis of results of physical examination. Dogs were housed in standard university kennels, fed a dry food formulated for adult maintenance, and had ad libitum access to water. The study was approved by the Auburn University Institutional Animal Care and Use Committee.

Surgical procedures

Each dog underwent major abdominal surgery. A standard anesthetic and analgesic protocol was used for all dogs. Each dog was premedicated with acepromazine maleate (0.1 mg/kg, IM) and morphine (0.5 mg/kg, IM). Anesthesia was induced with propofol (6 mg/kg, IV) and maintained with 1% to 3% isoflurane delivered via a semidisposable circle anesthesia circuit. The vaporizer setting was adjusted to maintain a surgical plane of anesthesia, which was determined on the basis of eye position, jaw tone, and lack of response to noxious stimuli. All dogs received a constant rate infusion of saline (0.9% NaCl) solution at a surgical fluid rate (approx 10 mL/kg/h). After anesthesia was induced, each dog received an epidural injection consisting of preservative-free morphine (0.1 mg/kg) and a volume of bupivacaine equivalent to that of the morphine. In addition, at the discretion of the anesthetist, morphine (0.5 mg/kg, IV) was given to each dog during surgery as needed for pain control.

Abdominal surgery of each dog comprised 4 procedures: ovariohysterectomy or castration, enterotomy or resection-anastomosis, cystotomy, and liver biopsy. After the surgical procedures were completed, the anesthetized dogs were euthanized with pentobarbital (7.7 mg/kg, IV). Anesthesia time was defined as the interval from anesthetic induction to euthanasia. Surgery time was defined as the interval from the start of the skin incision to completion of skin sutures.

Sample collection and assay procedures

Blood samples (3 mL/sample) were obtained via jugular venipuncture. Samples were obtained prior to anesthesia and from anesthetized dogs immediately after surgery. An aliquot of blood for determination of cortisol and aldosterone concentrations was placed in anticoagulant-free glass tubes, allowed to clot for at least 30 minutes, and centrifuged at 1,300 × *g* for 10 minutes; serum was separated and frozen at –20°C until analysis in a single batch. Serum samples were assayed in duplicate by use of previously validated radioimmunoassays for cortisol[37,a] and aldosterone[38,b] concentrations. An aliquot of blood for determination of cACTH concentrations was placed into EDTA-containing glass tubes. A preservative, aprotinin, was added immediately,[39] and the sample was stored on ice until it was centrifuged (1,300 × *g* for 10 minutes), which was performed within 10 minutes after sample collection. Plasma was separated and frozen at –20°C until analysis in a single batch. Plasma samples were assayed in duplicate by use of a previously validated immunoradiometric assay.[40,c] Limit of detection of the assays was 0.5 µg/dL, 13 pg/mL, and 7 pg/mL for cortisol, aldosterone, and cACTH concentrations, respectively. For statistical purposes, values below the limit of detection of the assay were recorded as 6 pg/mL for aldosterone concentrations and 3 pg/mL for cACTH concentrations; none of the measured serum cortisol concentrations were below the limit of detection of the assay.

Statistical analysis

Statistical analysis was performed by the use of a commercial program.[d] Normality of data was assessed via the Shapiro-Wilk test, and it was determined that data distribution was nonparametric. For each hormone, preoperative and postoperative con-

centrations were compared by use of the Wilcoxon signed rank test. Change in concentrations (postoperative concentration minus preoperative concentration) was calculated for each hormone. Pearson correlation analysis was performed for 32 dogs for which preoperative and postoperative ACTH, cortisol, and aldosterone concentrations were available; these 32 dogs were selected on the basis that they had preoperative and postoperative blood samples with sufficient volume to allow measurement of all 3 hormones. Comparisons included preoperative concentrations of cortisol and cACTH, postoperative concentrations of cortisol and cACTH, postoperative concentrations of aldosterone and cACTH, and change in hormone concentrations. Additionally, Pearson correlation analysis was performed to compare the change in hormone concentrations with total volume of fluid administered (number of milliliters), total fluid volume administered (milliliters per kilogram of body weight), anesthesia time, and surgery time. Finally, preoperative and postoperative hormone concentrations and the change in hormone concentrations were compared between male and female dogs by use of the Mann-Whitney rank sum test. Correlations were interpreted as follows: $r = 0$ to 0.10, no correlation; $r = 0.11$ to 0.30, weak correlation; $r = 0.31$ to 0.70, moderate correlation; and $r > 0.71$, strong correlation. Data were reported as median and range. Values were considered significant at $P \leq 0.05$.

Results

A total of 39 sexually intact (26 females and 13 males) adult mixed-breed dogs were used in the study. Exact ages of dogs were not available. Median body weight was 13.6 kg (range, 7.0 to 26.0 kg). Median surgery time was 228 minutes (range, 125 to 285 minutes).

Preoperative and postoperative cortisol concentrations were available for 39 dogs. Median preoperative cortisol concentration was 1.8 µg/dL (range, 0.5 to 5.0 µg/dL). Median postoperative cortisol concentration was 7.1 µg/dL (range, 2.8 to 11.6 µg/dL), which was significantly ($P < 0.001$) higher than the median preoperative concentration **(Figure 1)**. Cortisol concentration increased in 35 of 39 (90%) dogs. Median change in cortisol concentration was 5.0 µg/dL (range, –1.0 to 10.6 µg/dL). Postoperatively, 24 of 39 (62%) dogs had a cortisol concentration above the reference range for basal cortisol concentration[f] (0.5 to 5.8 µg/dL). Preoperative and postoperative cortisol concentrations and the change in cortisol concentration were not significantly different between males and females (data not shown).

The preoperative aldosterone concentration was below the limit of detection of the assay for 31 of 39 (79%) dogs. For the 8 dogs with a detectable preoperative aldosterone concentration, the median concentration was 44 pg/mL (range, 18 to 63 pg/mL). Median postoperative aldosterone concentration was 215 pg/mL (range, 15 to 678 pg/mL) for all 39 dogs and 211 pg/mL (range, 75 to 678 pg/mL) for the 8 dogs with detectable preoperative aldosterone concentrations. The postoperative aldosterone concentration was significantly ($P < 0.001$) higher than the

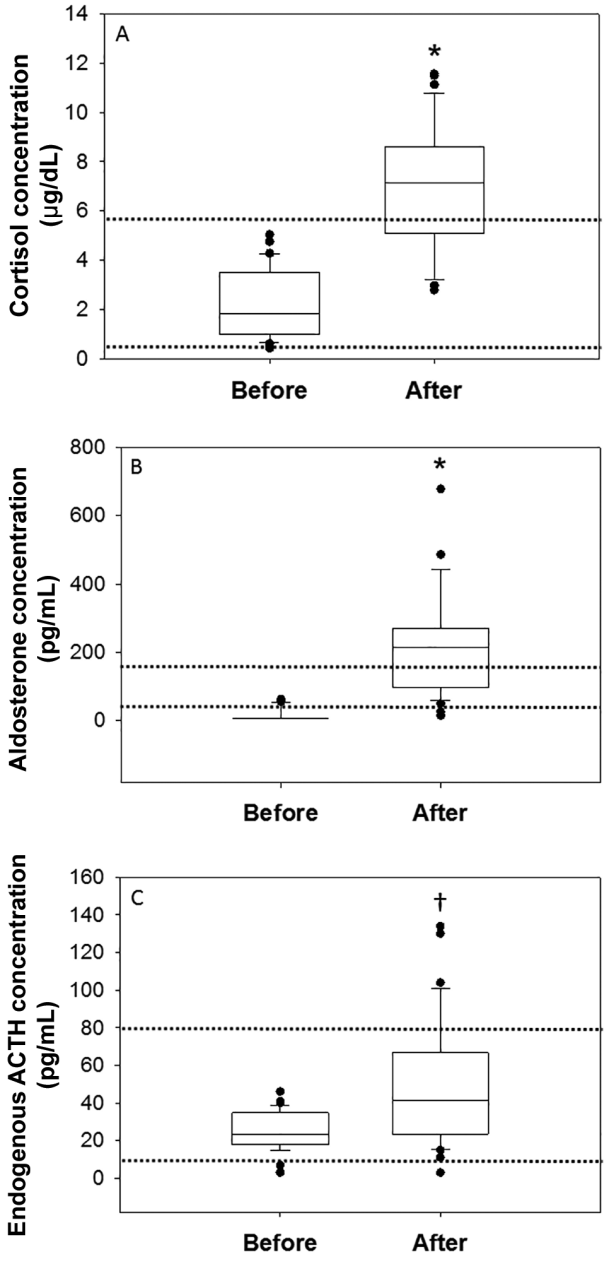

Figure 1—Box-and-whisker plots of serum cortisol concentrations (A), serum aldosterone concentrations (B), and plasma endogenous cACTH concentrations (C) measured in samples obtained from dogs before and after major abdominal surgery. Each box represents the interquartile (ie, 25th to 75th percentile) range, the horizontal line in each box represents the median, the whiskers represent the 10th to 90th percentiles, and the circles represent outlying datum points. In panels A and C, the area between the horizontal dotted lines represents the reference range. In panel B, the area between the horizontal dotted lines represents the range for historical control subjects.[e] *†Value differs significantly (*$P < 0.001$; †$P = 0.001$) from the value before surgery.

preoperative aldosterone concentration (Figure 1). Median change in aldosterone concentration was 201 pg/mL (range, 9 to 623 pg/mL) for all 39 dogs and 167 pg/mL (range, 54 to 623 pg/mL) for the 8 dogs with detectable preoperative aldosterone concentrations. Preoperative and postoperative aldosterone concentrations and the change in aldosterone concentration were not significantly different between males and females (data not shown).

Preoperative and postoperative cACTH concentrations were available for 32 dogs. Median preoperative cACTH concentration was 23.5 pg/mL (range, 3 to 46 pg/mL), and median postoperative cACTH concentration was 41.5 pg/mL (range, 3 to 134 pg/mL). The median postoperative cACTH concentration was significantly ($P = 0.001$) higher than the median preoperative concentration (Figure 1); however, the cACTH concentration decreased in 6 of 32 (19%) dogs. Median change in cACTH concentration was 20.5 pg/mL (range, −29 to 115 pg/mL). The cACTH concentration decreased in 3 of 4 dogs in which the cortisol concentration decreased. Two dogs had a preoperative cACTH concentration below the reference range[f] (10 to 80 pg/mL); in one of these dogs, the postoperative concentration was also below the reference range, whereas in the other dog, the postoperative concentration was within the reference range. No dogs had a preoperative cACTH concentration above the reference range. Preoperative and postoperative cACTH concentrations and the change in cACTH concentration were not significantly different between males and females (data not shown).

A moderate significant correlation ($r = 0.357$; $P = 0.045$) was detected between preoperative cortisol and cACTH concentrations (data not shown). However, there was not a significant correlation ($r = 0.215$; $P = 0.236$) between postoperative concentrations of cortisol and cACTH (data not shown). A moderate significant correlation ($r = 0.423$; $P = 0.004$) was detected between postoperative concentrations of cortisol and aldosterone ($r = 0.423$; $P = 0.004$ [data not shown]) and between the change in cortisol concentration and the change in aldosterone concentration ($r = 0.557$; $P < 0.001$ [data not shown]). There was not a significant correlation between the change in cACTH concentration and the change in cortisol concentration ($r = 0.265$; $P = 0.143$ [data not shown]) or between the change in cACTH concentration and the change in aldosterone concentration ($r = 0.166$; $P = 0.363$ [data not shown]). Correlations between preoperative aldosterone concentrations and preoperative cortisol or cACTH concentrations were not assessed because the preoperative aldosterone concentration was below the limit of detection of the assay for the majority (31/39) of dogs.

A moderate significant inverse correlation was detected between total fluid volume administered per kilogram of body weight and the change in cortisol concentration ($r = -0.366$; $P = 0.022$ [data not shown]) and between total fluid volume administered per kilogram of body weight and the change in aldosterone concentration ($r = -0.588$; $P < 0.001$ [data not shown]). There was not a significant correlation between total volume of fluid administered and the change in hormone concentrations or between the total fluid volume administered per kilogram of body weight and the change in cACTH concentration (data not shown).

There was not a significant relationship between anesthesia time and postoperative cortisol ($r = -0.151$; $P = 0.364$), aldosterone ($r = -0.159$; $P = 0.341$), or cACTH ($r = -0.103$; $P = 0.581$) concentrations (data not shown). Similarly, there was not a significant relationship between anesthesia time and the change in cortisol concentration ($r = -0.077$; $P = 0.646$), change in aldosterone concentration ($r = -0.195$; $P = 0.241$), or change in cACTH concentration ($r = -0.092$; $P = 0.622$ [data not shown]).

There was not a significant relationship between surgery time and postoperative cortisol ($r = -0.062$; $P = 0.709$), aldosterone ($r = -0.263$; $P = 0.106$), or cACTH ($r = 0.094$; $P = 0.608$) concentrations (data not shown). Similarly, there was not a significant relationship between surgery time and the change in cortisol concentration ($r = -0.016$; $P = 0.921$), change in aldosterone concentration ($r = -0.288$; $P = 0.075$), or change in cACTH concentration ($r = 0.094$; $P = 0.608$ [data not shown]).

Discussion

The measurement of cortisol, aldosterone, and cACTH concentrations in the study reported here provided a more comprehensive evaluation of the pituitary-adrenal axis in dogs undergoing a surgical procedure than has previously been available. In addition, dogs of the present study underwent major abdominal surgery of long duration. Laparotomy, as expected, caused a significant increase in serum cortisol concentrations. Interestingly, however, there may have been dissociation between cACTH and cortisol concentrations for 6 of 32 (19%) dogs (ie, changes in cACTH and cortisol concentrations were in opposite directions). Aldosterone concentrations after surgery were increased significantly. To our knowledge, this was the first study conducted to evaluate aldosterone concentrations in canine surgical patients.

The postoperative cortisol concentration was significantly higher than the preoperative cortisol concentration, but the cortisol concentration decreased postoperatively in 4 dogs. Interestingly, the cortisol concentration in other studies[15,27,29,32] was not significantly increased immediately postoperatively, compared with the preoperative concentration. The reason for this lack of increase in some other studies is not apparent. Choice of anesthetic or analgesic protocol can significantly affect cortisol concentrations during and immediately after surgery.[15,16,24,25,28,32] However, for the 4 studies[15,27,29,32] in which investigators did not document an increase in cortisol concentration, no factor was consistent among those studies, including type of surgery or agent used for premedication or anesthetic induction or maintenance. Dura-

tion of the surgical procedure was not stated for 3 of those studies,[27,29,32] but for the fourth study,[15] it was approximately 50 minutes (ie, not extremely short or long). In addition, in the present study, the postoperative cortisol concentration was higher than the basal reference range for 24 of 39 (62%) dogs, which suggested that the majority of dogs were under physiologic stress.

In the present study, no relationship was detected between surgery time and postoperative cortisol concentration or the change in cortisol concentration. In contrast, in 1 study[36] in which dogs underwent laparoscopic nephrectomy, the change in cortisol concentration was significantly correlated with surgery time. The reason for the difference between studies is not apparent and is likely multifactorial, including considerations such as surgical procedure performed and the type, dose, and route of administration for anesthetic and analgesic medications.

Interestingly, serum aldosterone concentrations were below the limit of detection for most dogs at the beginning of the study. The reason was not apparent, but this could have been the result of dietary sodium intake because all dogs were fed the same diet.

Serum aldosterone concentrations increased in all dogs in the present study and increased significantly from before to after surgery. Activation of the renin-angiotensin system secondary to decreased blood pressure and, thus, renal perfusion likely contributed. Conversely, increases in sodium concentration as a result of administration of NaCl solution could have had a mild effect to decrease aldosterone secretion. The role of hypotension and sodium or potassium concentrations on stimulation of aldosterone secretion cannot be directly evaluated because neither blood pressure nor electrolyte concentrations were monitored. However, surgery causes significant increases in plasma concentrations of antidiuretic hormone in dogs, likely as a result of a decrease in blood pressure.[41,42] The significant inverse correlation found between the change in aldosterone concentration and total fluid volume administered per kilogram of body weight in the study reported here could further suggest that hypotension played a major role in causing aldosterone secretion. Fluids (NaCl solution) were administered IV to each dog at a standard rate; additional fluid boluses were administered if hypotension was suspected, as judged by the presence of persistent tachycardia. In other words, dogs with suspected hypotension would have received more fluid on a milliliter-per-kilogram basis. However, it cannot be ruled out that the inverse correlation between the change in cortisol concentration or change in aldosterone concentration and total fluid volume administered per kilogram of body weight was attributable to a dilutional effect.

Because postoperative cortisol and aldosterone concentrations as well as the change in cortisol concentration and change in aldosterone concentration were significantly and moderately correlated, additional mechanisms that induced an increase in aldosterone concentrations may have been similar to the mechanisms that influenced cortisol concentrations. Although ACTH does not play a major role in control of aldosterone secretion, it does have stimulatory effects. A correlation between postoperative cACTH and aldosterone concentrations or the change in cACTH and change in aldosterone concentration was not detected. However, it is possible that an early increase in cACTH concentration caused aldosterone secretion, but it was not detected because of the limitation of collecting only 2 samples (before and after surgery). Similarly, a correlation between the change in cortisol concentration and change in cACTH concentration was not detected. On the other hand, the increase in aldosterone and cortisol concentrations may have been independent but proportional for both to the degree of stress.

In the present study, postoperative cACTH concentrations were significantly higher than preoperative concentrations. Although a moderate correlation was detected between preoperative cortisol and cACTH concentrations, no correlation was detected between postoperative concentrations or between the change in cACTH concentration and the change in cortisol concentration. Use of a larger sample size would have increased statistical power, which may have led to detection of a significant relationship. On the other hand, cACTH concentration decreased in 6 of 32 (19%) dogs. Furthermore, the cACTH concentration decreased in 3 of 4 dogs in which cortisol concentration decreased. Dissociation may have been the cause, at least in part, for lack of a correlation between postoperative cortisol and cACTH concentrations.

To our knowledge, cACTH concentrations in dogs undergoing surgery have been evaluated in only 2 studies,[16,25] and there potentially was dissociation between cACTH and cortisol concentrations in both studies, but not until the postoperative period. Whether the change was significant was not stated, but mean cACTH concentrations decreased in the postoperative period, whereas mean cortisol concentrations did not. For the 6 dogs of the present study that had a lower postoperative cACTH concentration, the point during the course of surgery at which cACTH concentrations began to decrease could not be determined. Whether cACTH concentrations began to decrease intraoperatively was not evaluated in the other 2 aforementioned studies.[16,25]

Dissociation of ACTH and cortisol concentrations has been reported for humans in surgical studies[3–5] and has been associated with an increase in postoperative complications. Many factors could have caused cACTH concentrations to decrease during or after surgery, including a decrease in surgical or pain stimulus and duration of surgery. In addition, ACTH-independent mechanisms for sustained cortisol release (eg, autonomic nervous system stimulation or cytokine release) may have been present. The hypo-

thalamic-pituitary axis can be stimulated by IL-1, IL-6, and TNF-α (alone or in combination).[6] In humans, serum IL-6 concentrations are related to the magnitude of surgical trauma.[6] In dogs, IL-10 or TNF-α concentrations were not increased during cardiopulmonary bypass surgery[43]; however, IL-6 concentrations were significantly increased during cardiopulmonary bypass surgery and were significantly higher than concentrations in dogs undergoing ovariohysterectomy in that study.[43] A significant increase in IL-6 concentration was not detected in dogs undergoing cranial cruciate ligament repair[44] or mandibulectomy or maxillectomy[45]; however, each treatment group contained only 8 to 10 dogs, which limited the statistical power of those studies. Evaluation of results at additional time points throughout surgery as well as during the days following surgery is needed to determine the clinical importance of the dissociation between cortisol and ACTH concentrations in dogs.

A major limitation of the study reported here was that the dogs had been living in a kennel situation for different amounts of time and exposed to chronic stress,[46] which may have influenced their response to acute surgical stress. The dogs were judged to be healthy on the basis of results of a physical examination and a lack of abnormal behavior (ie, typical patterns of eating, drinking, urination, and defecation); however, routine hematologic analysis was not performed. Thus, findings of the present study must be interpreted cautiously with respect to applicability to clinical patients. A second limitation was that because of the confines of the veterinary student surgical laboratory, blood loss was not quantified and blood pressure was not monitored during surgery. As a result, the potential contribution of hypoxia and hypotension to changes in hormone concentrations cannot be evaluated. A third limitation was that measurement of serum potassium concentrations could have been helpful in the interpretation of aldosterone concentrations. However, previous studies[47,48] regarding aldosterone and potassium concentrations did not reveal that these analytes are typically strongly correlated. In addition, because hypotension would have been expected to affect aldosterone concentrations, trying to determine the contribution of the potassium concentration would have been impossible. Further studies are needed to assess the manner by which blood pressure and serum potassium concentrations each affect serum aldosterone concentrations. A fourth limitation was that surgical procedures were performed by numerous third-year veterinary students as part of a surgery laboratory. However, results of the present study likely reflected a maximum surgical stress response similar to that for complex invasive procedures often performed by board-certified veterinary surgeons.

In the present study, major abdominal surgery stimulated adrenocortical secretion of cortisol and aldosterone in dogs. The same mechanism may have been responsible, at least in part, for an increase in both cortisol and aldosterone secretion. Lack of correlation between the change in cACTH concentration and the change in cortisol concentration suggested that there were cACTH-independent mechanisms for increased postoperative cortisol concentrations, an early increase in cACTH concentration that caused a sustained cortisol release, or alterations in hormone clearance. Because the stress response may not be beneficial in surgical patients (adversely altering homeostasis, impairing tissue healing, increasing morbidity, and delaying postoperative recovery),[7,8] further research is needed to evaluate the endocrine response to other surgeries and to examine the cause for such changes to determine whether the stress response can be minimized.

Acknowledgments

This manuscript represents the degree research project (nonthesis option) performed by Dr. Skovira and submitted to the Department of Biomedical Sciences of Auburn University as partial fulfillment of the requirements for a Master of Science degree.

Presented in part as an abstract at the 2012 American College of Veterinary Internal Medicine Forum, New Orleans, May 2012.

Footnotes

a. Coat-a-Count cortisol assay, Siemens Medical Solutions Diagnostics, Los Angeles, Calif.
b. Coat-a-Count aldosterone assay, Siemens Medical Solutions Diagnostics, Los Angeles, Calif.
c. Scantibodies ACTH assay, Scantibodies Laboratory Inc, Santee, Calif.
d. SigmaPlot, version 12, Systat Software Inc, Chicago, Ill.
e. Carlson KJ, Behrend EN, Martin LG, et al. Optimization of a test protocol to assess aldosterone secretory capacity in dogs (abstr). *J Vet Intern Med* 2010;24:685.
f. Endocrine Diagnostic Laboratory, College of Veterinary Medicine, Auburn University, Auburn, Ala.

References

1. Desborough JP. The stress response to trauma and surgery. *Br J Anaesth* 2000;85:109–117.
2. Bornstein SR, Engeland WC, Ehrhart-Bornstein M, et al. Dissociation of ACTH and glucocorticoids. *Trends Endocrinol Metab* 2008;19:175–180.
3. Roth-Isigkeit A, Dibbelt L, Eichler W, et al. Blood levels of atrial natriuretic peptide, endothelin, cortisol and ACTH in patients undergoing coronary artery bypass grafting surgery with cardiopulmonary bypass. *J Endocrinol Invest* 2001;24:777–785.
4. Dimopoulou I, Tzanela M, Vassiliadi D, et al. Pituitary-adrenal responses following major abdominal surgery. *Hormones* 2008;7:237–242.
5. Cho YM, Kim SY, Cho BY, et al. Dissociation between plasma adrenocorticotropin and serum cortisol level during the early postoperative period after gastrectomy. *Horm Res* 2000;53:246–250.
6. Sido B, Teklote J-R, Hartel M, et al. Inflammatory response after abdominal surgery. *Best Pract Res Clin Anaesthesiol* 2004;18:439–454.
7. Roizen MF. Should we all have a sympathectomy at birth? Or at least pre-operatively? *Anesthesiology* 1988;68:482–484.
8. Hahnenkamp K, Herroeder S, Hollmann MW. Regional anaesthesia, local anaesthetics and the surgical stress response. *Best Pract Res Clin Anaesthesiol* 2004;18:509–527.
9. Williams GH. Aldosterone biosynthesis regulation and classical mechanism of action. *Heart Fail Rev* 2005;10:7–13.
10. Funder JW. Minireview: aldosterone and mineralocorticoid receptors: past, present, and future. *Endocrinology* 2010;151:5098–5102.

11. Brandt MR, Olgaard K, Kehlet H. Epidural analgesia inhibits the renin and aldosterone response to surgery. *Acta Anaesthesiol Scand* 1979;23:267–272.
12. Kouraklis G, Glinavou A, Raftopoulos L, et al. Epidural analgesia attenuates the systemic stress response to upper abdominal surgery: a randomized trial. *Int Surg* 2000;85:353–357.
13. Cochrane JP. The aldosterone response to surgery and the relationship of this response to postoperative sodum retention. *Br J Surg* 1978;65:744–747.
14. Fox SM, Mellor DJ, Lawoko CRO, et al. Changes in plasma cortisol concentrations in bitches in response to different combinations of halothane and butorphanol, with or without ovariohysterectomy. *Res Vet Sci* 1998;65:125–133.
15. Ko JCH, Mandsager RE, Lange DN, et al. Cardiorespiratory responses and plasma cortisol concentrations in dogs treated with medetomidine before undergoing ovariohysterectomy. *J Am Vet Med Assoc* 2000;217:509–514.
16. Benson GJ, Grubb TL, Neff-Davis C, et al. Perioperative stress response in the dog: effect of pre-emptive administration of medetomidine. *Vet Surg* 2000;29:85–91.
17. Väisänen M, Raekallio M, Kuusela E, et al. Evaluation of the perioperative stress response in dogs administered medetomidine or acepromazine as part of the preanesthetic medication. *Am J Vet Res* 2002;63:969–975.
18. Siracusa C, Manteca X, Cuenca R, et al. Effect of a synthetic appeasing pheromone on behavioral, neuroendocrine, immune, and acute-phase perioperative stress responses in dogs. *J Am Vet Med Assoc* 2010;237:673–681.
19. Mastrocinque S, Almeida TF, Tatarunas AC, et al. Comparison of epidural and systemic tramadol for analgesia following ovariohysterectomy. *J Am Anim Hosp Assoc* 2012;48:310–319.
20. Kim YK, Lee SS, Suh EH, et al. Sprayed intraperitoneal bupivacaine reduces early postoperative pain behavior and biochemical stress response after laparoscopic ovariohysterectomy in dogs. *Vet J* 2012;191:188–192.
21. Devitt CM, Cox RE, Hailey JJ. Duration, complications, stress, and pain of open ovariohysterectomy versus a simple method of laparoscopic-assisted ovariohysterectomy in dogs. *J Am Vet Med Assoc* 2005;227:921–927.
22. Imagawa VH, Fantoni DT, Tatarunas AC, et al. The use of different doses of metamizol for post-operative analgesia in dogs. *Vet Anaesth Analg* 2011;38:385–393.
23. Mastrocinque S, Fantoni DT. A comparison of preoperative tramadol and morphine for the control of early postoperative pain in canine ovariohysterectomy. *Vet Anaesth Analg* 2003;30:220–228.
24. Pekcan Z, Koc B. The post-operative analgesic effects of epidurally administered morphine and transdermal fentanyl patch after ovariohysterectomy in dogs. *Vet Anaesth Analg* 2010;37:557–565.
25. Rioja E, Dzikiti BT, Fosgate G, et al. Effects of a constant rate infusion of magnesium sulphate in healthy dogs anaesthetized with isoflurane and undergoing ovariohysterectomy. *Vet Anaesth Analg* 2012;39:599–610.
26. Slingsby LS, Murison PJ, Goossens L, et al. A comparison between pre-operative carprofen and a long-acting sufentanil formulation for analgesia after ovariohysterectomy in dogs. *Vet Anaesth Analg* 2006;33:313–327.
27. Almeida TF, Fantoni DT, Mastrocinque S, et al. Epidural anesthesia with bupivacaine, bupivacaine and fentanyl, or bupivacaine and sufentanil during intravenous administration of propofol for ovariohysterectomy in dogs. *J Am Vet Med Assoc* 2007;230:45–51.
28. Perez TE, Grubb TL, Greene SA, et al. Effects of intratesticular injection of bupivacaine and epidural administration of morphine in dogs undergoing castration. *J Am Vet Med Assoc* 2013;242:631–642.
29. Sibanda S, Hughes JML, Pawson PE, et al. The effects of preoperative extradural bupivacaine and morphine on the stress response in dogs undergoing femoro-tibial joint surgery. *Vet Anaesth Analg* 2006;33:246–257.
30. Romano M, Portela DA, Breghi G, et al. Stress-related biomarkers in dogs administered regional anaesthesia or fentanyl for analgesia during stifle surgery. *Vet Anaesth Analg* 2016;43:44–54.
31. Day TK, Pepper WT, Tobias TA, et al. Comparison of intraarticular and epidural morphine for analgesia following stifle arthrotomy in dogs. *Vet Surg* 1995;24:522–530.
32. Kona-Boun J-J, Cuvelliez S, Troncy E. Evaluation of epidural administration of morphine or morphine and bupivacaine for postoperative analgesia after premedication with an opioid analgesic and orthopedic surgery in dogs. *J Am Vet Med Assoc* 2006;229:1103–1112.
33. Leibetseder EN, Mosing M, Jones RS. A comparison of extradural and intravenous methadone on intraoperative isoflurane and postoperative analgesia requirements in dogs. *Vet Anaesth Analg* 2006;33:128–136.
34. Marcovich R, Williams AL, Seifman BD, et al. A canine model to assess the biochemical stress response to laparoscopic and open surgery. *J Endourol* 2001;15:1005–1008.
35. Naitoh T, Garcia-Ruiz A, Vladisavljevic A, et al. Gastrointestinal transit and stress response after laparoscopic vs conventional distal pancreatectomy in the canine model. *Surg Endosc* 2002;16:1627–1630.
36. Yoder B, Wolf JS Jr. Canine model of surgical stress response comparing standard laparoscopic, microlaparoscopic, and hand-assisted laparoscopic nephrectomy. *Urology* 2005;65:600–603.
37. Kemppainen RJ, Thompson FN, Lorenz MD. Use of a low dose synthetic ACTH challenge test in normal and prednisone-treated dogs. *Res Vet Sci* 1983;35:240–242.
38. Behrend EN, Weigand CM, Whitley EM, et al. Corticosterone- and aldosterone-secreting adrenocortical tumor in a dog. *J Am Vet Med Assoc* 2005;226:1662–1666.
39. Kemppainen RJ, Clark TP, Peterson ME. Preservative effect of aprotinin on canine plasma immunoreactive adrenocorticotropin concentrations. *Domest Anim Endocrinol* 1994;11:355–362.
40. Keller-Wood M. Fast feedback control of canine corticotropin by cortisol. *Endocrinology* 1990;126:1959–1966.
41. Hauptman JG, Richter MA, Wood SL, et al. Effects of anesthesia, surgery, and intravenous administration of fluids on plasma antidiuretic hormone concentrations in healthy dogs. *Am J Vet Res* 2000;61:1273–1276.
42. Höglund OV, Hagman R, Olsson K, et al. Intraoperative changes in blood pressure, heart rate, plasma vasopressin, and urinary noradrenalin during elective ovariohysterectomy in dogs: repeatability at removal of the 1st and 2nd ovary. *Vet Surg* 2014;43:852–859.
43. Mizuno T, Kamiyama H, Mizuno M, et al. Plasma cytokine levels in dogs undergoing cardiopulmonary bypass. *Res Vet Sci* 2015;101:99–105.
44. Cardozo LB, Cotes LC, Kahvegian MAP, et al. Evaluation of the effects of methadone and tramadol on postoperative analgesia and serum interleukin-6 in dogs undergoing orthopaedic surgery. *BMC Vet Res* 2014;10:194–200.
45. Martins TL, Kahvegian MA, Noel-Morgan J, et al. Comparison of the effects of tramadol, codeine, and ketoprofen alone or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol, and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy. *Am J Vet Res* 2010;71:1019–1026.
46. Hubrecht RC, Serpell JA, Poole TB. Correlates of pen size and housing conditions on the behaviour of kennelled dogs. *Appl Anim Behav Sci* 1992;34:365–383.
47. Reid LE, Behrend EN, Martin LG, et al. Effect of trilostane and mitotane on aldosterone secretory reserve in dogs with pituitary-dependent hyperadrenocorticism. *J Vet Intern Med* 2014;28:443–450.
48. Baumstark ME, Sieber-Ruckstuhl NS, Muller C, et al. Evaluation of aldosterone concentrations in dogs with hypoadrenocorticism. *J Vet Intern Med* 2014;28:154–159.