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Relative Adrenal Insufficiency in Dogs with Sepsis

Jamie M. Burkitt, Steve C. Haskins, Richard W. Nelson, and Philip H. Kass

Background: A syndrome of relative adrenal insufficiency has been identified in septic humans, and is associated with hypotension and death. Relative adrenal insufficiency is generally associated with basal serum cortisol concentration within or above the reference range and a blunted cortisol response to adrenocorticotropic hormone administration. It is unknown whether relative adrenal insufficiency occurs in septic dogs.

Hypothesis: That relative adrenal insufficiency occurs in septic dogs, and that relative adrenal insufficiency is associated with hypotension and mortality.

Animals: Thirty-three septic dogs admitted to a small animal intensive care unit.

Methods: Dogs were included in the study if they had a known or suspected infectious disease and had systemic inflammatory response syndrome. Dogs were excluded if they had disease or medication history expected to affect the hypothalamic-pituitary-adrenal axis. Serum cortisol and endogenous plasma adrenocorticotropic hormone concentrations were measured before, and serum cortisol concentration measured 1 hour after, intramuscular administration of 250 μg of cosyntropin/dog. The change in cortisol concentration (Δ-cortisol) before and after cosyntropin administration was determined in each dog.

Results: Hypotension was associated with lower Δ-cortisol values (OR 1.3; CI 1.0–1.9; $P = .029$). Δ-Cortisol cutoff of 3.0 μg/dL was most accurate for predicting hypotension, survival to discharge, and 28-day survival. The rate of death in dogs with Δ-cortisol ≤3 μg/dL was 4.1 times that of dogs with Δ-cortisol >3 μg/dL (RR 4.1; CI 1.5–12.3; $P = .01$).

Conclusions and Clinical Relevance: Δ-cortisol ≤3 μg/dL after adrenocorticotropic hormone administration is associated with systemic hypotension and decreased survival in septic dogs.

Key words: Canine; Critical illness-related corticosteroid insufficiency; Hypotension; Septic; Systemic inflammatory response syndrome.

Sepsis is the invasion of microorganisms or their toxins into the bloodstream and the systemic response to it. Sepsis is manifested by a combination of clinical findings including abnormalities in body temperature, heart rate, respiratory rate, and leukocytes. Sepsis occurs in dogs, and has a reported survival rate of only 44–71%, even with intensive management.[1–4] Abnormalities of the hypothalamic-pituitary-adrenocortical (HPA) axis have been identified in humans with severe sepsis and septic shock. Relative adrenal insufficiency (RAI) has been reported in up to 77% of humans with septic and nonseptic critical illness.[5–14] It is generally characterized by basal serum cortisol concentration within or above the reference range and a blunted cortisol response after ACTH administration, suggesting that the adrenal cortex can make and release cortisol, but the quantity of cortisol produced is inadequate for the degree of physiologic stress.

Cortisol has important homeostatic effects on catecholamine production, adrenergic receptor function, and the immune system. Relative adrenal insufficiency has been associated with pressor-dependent systemic hypotension[5,15] and increased mortality[14,16–18] in humans with severe sepsis and septic shock. Treatment of septic humans with RAI by administration of low doses of hydrocortisone significantly improves survival.[5,7,14]

RAI has not been reported in dogs with sepsis. One study of 20 dogs admitted consecutively to an intensive care unit failed to demonstrate RAI in any dog; however, dogs were admitted to the intensive care unit for a variety of reasons, and only 3 of the dogs were diagnosed with a septic process.[19] The purpose of the current study was to determine whether RAI occurs in septic dogs and, if identified, to examine the association between RAI and pressor-dependent systemic hypotension and mortality. The authors hypothesized that RAI occurs in dogs with sepsis, and that dogs with RAI would have an increased incidence of pressor-dependent systemic hypotension and mortality, compared with dogs with an intact HPA axis.

Materials and Methods

This study was performed at the Veterinary Medical Teaching Hospital at the University of California, Davis, between October 2004 and November 2005. Dogs were included if they required intensive care and met the following criteria for sepsis: a confirmed or highly suspected infection, and evidence of systemic inflammatory response syndrome (SIRS). Infection was confirmed by culture or cytologic examination of appropriate samples for the presence of fungal elements or intracellular bacteria. Examples of situations in which infection was considered highly suspect included chemotherapy-associated SIRS; bite wounds; aspiration pneumonia (cranioventral pulmonary infiltrates on thoracic radiographs in a patient with witnessed emesis or radiographic evidence of megaesophagus); or endocarditis (development of a new murmur and demonstration of a vegetative lesion on a heart valve on echocardiogram). Systemic inflammatory response syndrome was considered present if dogs demonstrated at least 2 of the following 4 abnormalities at the time of study inclusion: (1) rectal temperature >103.0°F (>39.4°C) or <100.0°F (<37.8°C);

From the Department of Surgical and Radiological Sciences (Burkitt, Haskins), and the Department of Medicine and Epidemiology (Nelson), and the Department of Population Health and Reproduction (Kass), University of California, Davis, CA. *Previously presented in part at the 2005 International Veterinary Emergency and Critical Care Symposium in Atlanta, GA.*

Reprint requests: Dr Jamie M. Burkitt, Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California, Davis, One Shields Avenue, Davis, CA 95616; e-mail: jmburkitt@ucdavis.edu.

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(2) heart rate >120 beats per minute; (3) nonpanting respiratory rate >40 breaths per minute or PCO_2 (arterial or venous) <32 mmHg; and (4) total WBC count >16,000/μL, <6,000/μL, or >3% of the WBC count comprised of immature neutrophils.[1,20] The CBC had to be performed within the 24 hours of study inclusion.

Dogs were excluded if they had known or suspected hypoadrenocorticism or hyperadrenocorticism; if they had received glucocorticoid medications within 72 hours of inclusion; if they had received a long-acting glucocorticoid within the previous 6 weeks; if they had received a course of glucocorticoids lasting ≥7 days within the preceding 6 weeks; if the dog had received etomidate, ketoconazole, or any other drug known to affect the HPA axis within the previous 72 hours; or if they required anesthesia or were euthanized within the testing period. Dogs were also excluded if any blood sample was lost or mishandled, or if the primary clinician or owner refused inclusion. Owner informed consent was required for participation in the study.

Systemic blood pressure and endogenous adrenocorticotropic hormone (ACTH) concentration were measured, and an ACTH stimulation test was performed immediately after inclusion of the dog in the study. Blood pressure was determined either by indirect[a,b] or direct methods. Three milliliters of whole blood was collected for measurement of plasma endogenous ACTH concentration and 2 mL of whole blood was collected for measurement of baseline serum cortisol concentration. Blood for endogenous ACTH measurement was placed in a sterile plastic tube containing potassium EDTA anticoagulant. Blood for cortisol measurement was placed in a sterile glass tube containing no anticoagulant. Each dog received 250 μg cosyntropin[c] injected intramuscularly. One hour later, 2 mL of whole blood was collected into a sterile glass tube containing no anticoagulant for measurement of stimulated serum cortisol concentration. All blood samples were centrifuged within 30 minutes of collection and the plasma or serum stored in plastic tubes at −70°C until analysis. Cortisol concentration was determined by radioimmunoassay.[d] Endogenous ACTH concentration was determined by immunoradiometric assay.[e,f]

Presence of systemic hypotension, pressor dependence, survival to hospital discharge (considered recovery from sepsis), and 28-day survival were recorded for each dog. Hypotension was defined as a mean arterial pressure <60 mmHg or a systolic blood pressure <80 mmHg.[21] Each dog's baseline serum cortisol concentration was subtracted from its ACTH-stimulated serum cortisol concentration to determine the "Δ" cortisol value (Δ-cortisol). Twenty-eight-day survival was calculated using day of study entry (ACTH stimulation testing) as day 0. Dogs that died or were euthanized for grave illness or impending death were considered nonsurvivors. Dogs euthanized for poor long-term prognosis or financial reasons were censored from the survival analyses.

Sixteen dogs determined to be healthy by historical and physical examination findings were recruited as control subjects for HPA axis function testing. Control dogs were age- and weight-matched to the subject population. The same exclusion criteria applied to the control dogs as for subjects. This group of dogs underwent endogenous plasma ACTH concentration measurement and ACTH stimulation testing as for study subjects above.

Exact binary logistic regression was used to model the relationship between the Δ-cortisol value (as the predictive variable) and outcome (dead versus alive to hospital discharge), and hypotension (absent versus present) as the outcome variables. Fractional polynomials of Δ-cortisol were initially modeled to verify a linear functional relationship between Δ-cortisol and the respective outcomes. The model was then used to determine a value of Δ-cortisol that could be used as a cutoff to maximize the model's sensitivity and specificity. A binary variable was created with this cutoff for exact calculation of sensitivity and specificity (and their respective 95% confidence intervals). Cox proportional hazards regression models were also used to model the relationship between Δ-cortisol (both as a continuous and binary variable, using the cutoff determined above) and the rate of death. Regression results are presented as odds ratios (OR), which predict the probability of event occurrence in one population compared to another; rate ratios (RR), which predict the rate of event occurrence in one population compared to another; and 95% confidence intervals (CI). A Kruskal-Wallis analysis of variance was performed to determine any difference among Δ-cortisol values in controls, dead subjects, and subjects alive at discharge. To determine which groups were significantly different from each other, a Mann-Whitney test was performed. A P-value ≤.05 was considered significant.

Results

Eighty dogs met the inclusion criteria during the 14-month study period. Forty-seven of the 80 dogs were excluded from the study for the following reasons: known or suspected hyperadrenocorticism (7 dogs), prior glucocorticoid administration (24), ketoconazole administration (1), anesthetic procedure interfering with the testing period (6), euthanasia or death during the testing period (2), clinician refusal (3), client refusal (5), or mishandled blood samples (2). Three dogs had iatrogenic hyperadrenocorticism because of chronic, ongoing glucocorticoid administration, and therefore met more than 1 exclusion criterion.

The remaining 33 dogs were enrolled in the study. Median age was 7 years (range 0.75–13 years). There were 3 males, 14 castrated males, 5 females, and 11 spayed females. Median body weight was 29 kg (range 2–63 kg). Infection was confirmed by culture or cytology in 21 of 33 dogs. The septic source was aspiration pneumonia (4 dogs), intestinal perforation (2), uroabdomen with infected urine (2), bite wounds (2), mastitis (2), pyothorax (2), endocarditis (2), and systemic Salmonellosis, pyometra, perineal abscess, meningitis, and a septic joint in 1 dog each. The infection was bacterial in all dogs. A septic process was highly suspected in 12 dogs, with aspiration pneumonia (6 dogs); bite wounds (2); and multiple grass awn abscesses, intestinal perforation, infarction of the small intestines with no blood flow identified on Doppler ultrasonography, and severe typhlitis and colitis in 1 dog each.

Hypothermia and fever were identified in 11 and 13 dogs, respectively. Seventeen dogs had tachycardia. Twelve dogs were tachypneic, and 11 dogs were hypocapneic. Complete blood counts were available for all 33 dogs. Fourteen dogs had leukocytosis and 11 dogs had leukopenia. Thirty-two dogs had information regarding immature neutrophils reported on their CBCs. Twenty-seven dogs had an increased percentage of immature neutrophils. Seven dogs had hypotension refractory to fluid loading and required vasopressor therapy. Of these 7 dogs, 6 had persistent hypotension despite aggressive pressor therapy. All dogs with hypotension died or were euthanized for grave prognosis.

Sixteen of the 33 dogs were discharged from the hospital. Three dogs died and 11 were euthanized for

grave prognosis during hospitalization. At the time of euthanasia, 7 of these 11 dogs were hypoxemic (3 requiring mechanical ventilation), 5 were oliguric or anuric, 2 were hypothermic, 2 were stuporous to comatose, and 1 had severe hepatic failure. Three dogs were euthanized for poor long-term prognosis and were not gravely ill at the time of euthanasia; these dogs were excluded from the survival analyses. Thus, survival from sepsis to hospital discharge was 53%. Of the 16 dogs surviving to hospital discharge, 1 was euthanized on day 22 for intestinal neoplasia, and 1 was doing well on day 19 but was lost to follow-up before day 28.

Median endogenous plasma ACTH concentration was 4.9 pmol/L (range, 0–148.6 pmol/L; reference interval, 6.7–25.0 pmol/L). Median baseline serum cortisol concentration was 4.1 μg/dL (range, 0–14.8 μg/dL; reference interval, 0–6 μg/dL). Median ACTH-stimulated serum cortisol concentration was 9.4 μg/dL (range, 1.4–50 μg/dL; reference interval, 6–15 μg/dL). No dogs had hormonal changes consistent with primary hypoadrenocorticism (increased endogenous ACTH concentration and stimulated cortisol below the reference interval). The median Δ-cortisol value was 4.3 μg/dL (range, negative 2.3–37.6 μg/dL).

There was a significantly increased risk of hypotension as Δ-cortisol decreased (OR 1.3; CI 1.0–1.9; P = .029). There was no statistical association between survival to hospital discharge and Δ-cortisol value (OR 1.1; CI 0.98–1.3; P = .13). For every increase in the Δ-cortisol value by 1.0 μg/dL, the rate of death decreased by a factor of 0.91; this association was not statistically significant (RR 0.91; CI 0.82–1.1; P = .13).

A cutoff of Δ-cortisol of 3.0 μg/dL was most accurate for predicting hypotension, survival to hospital discharge, and 28-day survival. Fifteen of the 33 dogs had a Δ-cortisol of ≤3 μg/dL. Dogs with a Δ-cortisol of ≤3 μg/dL were significantly more likely to be hypotensive than those with a Δ-cortisol >3 μg/dL (OR 10.5; CI 1.0–551.1; P = .045). Six of 7 hypotensive dogs had a Δ-cortisol ≤3 μg/dL, and 17 of 26 normotensive dogs had a Δ-cortisol >3 μg/dL. The hypotensive dog with Δ-cortisol >3 μg/dL was enrolled in the study and underwent ACTH stimulation testing 1 week before the development of hypotension. The sensitivity, specificity, and overall accuracy of Δ-cortisol cutoff of 3 μg/dL for predicting hypotension were 86, 65, and 70%, respectively.

A Δ-cortisol value >3 μg/dL was associated with survival to discharge, but this association did not reach statistical significance (OR 5.1; CI 0.9–35.1; P = .07). The rate of death in dogs with Δ-cortisol ≤3 μg/dL was 4.1 times that of dogs with a Δ-cortisol >3 μg/dL (RR 4.1; CI 1.5–12.3; P = .01; Fig 1). Twelve of the 16 (75%) dogs that survived to hospital discharge had a Δ-cortisol of >3 μg/dL and 9 of 14 (64%) dogs that did not survive to discharge had a Δ-cortisol of ≤3 μg/dL. The sensitivity, specificity, and overall accuracy of Δ-cortisol cutoff of 3 μg/dL for predicting hospital discharge were 64, 75, and 70%, respectively.

The median Δ-cortisol for the 16 control dogs was 8.1 μg/dL (range, 5.7–12.9 μg/dL). There was no statistical difference between the Δ-cortisol values in subjects that survived to hospital discharge and control dogs (5.4 μg/dL versus 8.1 μg/dL; P = .12). The median Δ-cortisol value in patients that died was statistically significantly less than the median Δ-cortisol value in control dogs (2.6 μg/dL versus 8.1 μg/dL; P = .01).

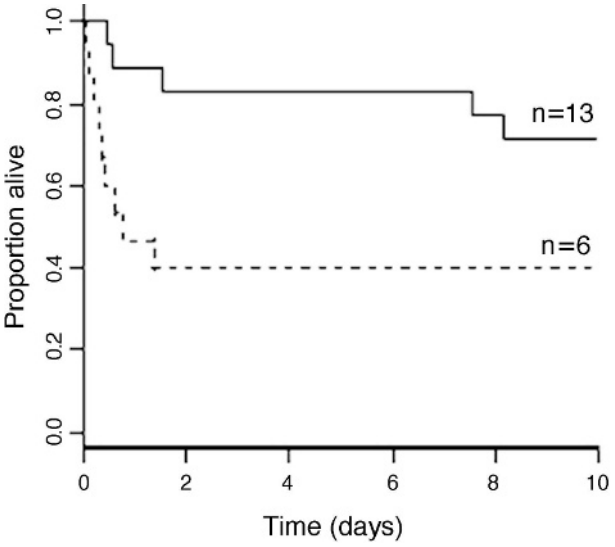

Fig 1. Kaplan-Meier survival curve depicting survival of dogs with Δ-cortisol >3 μg/dL (solid line) and those with Δ-cortisol ≤3 μg/dL (dashed line). Censored dogs are not included. By day 10, 13/17 dogs with Δ-cortisol >3 μg/dL were alive compared to only 6/13 dogs with Δ-cortisol ≤3 μg/dL. No dogs died of problems related to sepsis after day 10.

Discussion

Relative adrenal insufficiency is associated with hypotension and death in humans with severe sepsis, septic shock, and other critical illnesses.[5,10,14–18] Humans with RAI that receive short courses of low-dose hydrocortisone have improved blood pressure and survival.[5,7,10,11,13,22] This study identified RAI in a 48% of septic dogs, a prevalence similar to that seen in septic humans.[5–9,11,14] Although the importance of the syndrome in septic dogs is not known, the significant association between a Δ-cortisol value of ≤3 μg/dL and hypotension and decreased survival suggest that RAI is a marker of more severe illness, a detrimental physiologic change, or a combination of the two. The presence of a true RAI syndrome is supported by the statistical similarity between Δ-cortisol in survivors and control dogs, and the fact that nonsurvivors had significantly lower Δ-cortisol values than controls. It is unknown whether dogs with RAI would have improved blood pressure and survival with short course, low-dose hydrocortisone therapy as do humans.

More than half the septic dogs in this study had a Δ-cortisol value below the lowest Δ-cortisol found in the control population (median Δ-cortisol in septic dogs 4.3 μg/dL; range of Δ-cortisol in control dogs 5.7–12.9 μg/dL). Previous studies have found increased basal cortisol concentrations in dogs with nonadrenal illness,

those having undergone surgical procedures, and those subjected to repeated sublethal hemorrhage.[23,24] These findings suggest that stress and illness increase adrenal responsiveness. Although there are no data available regarding expected Δ-cortisol values in dogs with nonadrenal disease, 1 previous report found no difference in stimulated cortisol concentrations between healthy dogs and those with nonadrenal illness.[25] The findings of the current study, combined with information available in the literature regarding critically ill humans, suggest that during sepsis and other critical illness, adrenal function is impaired.

The pathophysiology of RAI is unknown, but it might be related to suppression of the HPA axis by cytokines such as tumor necrosis factor or interleukin-6, corticostatic substances circulating in sepsis, or adrenal microvascular thrombi and hemorrhage because of disseminated intravascular coagulation.[26–32] It has been proposed that RAI is associated with hypotension in people because cortisol is required for catecholamine production and proper adrenergic receptor function.[33,34] Why septic people with RAI have poor vascular responsiveness although some cortisol is circulating is unknown. It is theorized that although the adrenal cortices can produce and release cortisol, the quantity of cortisol produced is inadequate for physiologic needs in times of critical illness.

There is much debate in the human literature regarding the appropriate method for diagnosing RAI. The most accepted method is to determine Δ-cortisol from a standard 250-μg cosyntropin stimulation test.[35] This method is widely accepted and used in adult and pediatric humans with sepsis, in part because a study by Annane, et al (2002) showed an association between a Δ-cortisol ≤9 μg/dL and death, and an association between hydrocortisone treatment in human patients with Δ-cortisol ≤9 μg/dL and improved outcome.[5] However, other groups define RAI differently and there is currently no consensus for its diagnosis in humans.[36–38] We elected the Δ-cortisol method of diagnosis in the current study because of the strong evidence of its correlation with hypotension and mortality in people, and for its simplicity.

Dogs with highly suspected, but not proven, infections were included in the study population to maximize sample size. This approach may have allowed the inclusion of some dogs with SIRS that did not have an infectious underlying process. Alternately, dogs with infections may have had falsely negative cytologic and culture results if they had previously received antimicrobials, or if samples were excessively purulent. In some dogs, specific diagnostic procedures (such as bronchoalveolar lavage) were considered too risky for the anticipated benefit and the primary clinician elected not to perform the procedure that would have confirmed infection. We do not believe the inclusion of dogs with highly suspected infection is a study limitation because multiple studies have demonstrated the presence of RAI in nonseptic critically ill humans,[6,10,39] and the clinical syndrome of SIRS is the same whether the primary etiology is infectious or sterile.[40] Thus, the pathophysiologic consequences of SIRS (such as RAI) can be expected to be identical.

One drawback of the current study is the small sample size, which could have prevented the identification of a significant relationship between Δ-cortisol as a continuous variable and both hospital outcome and 28-day survival. Both of these analyses approached significance with P-values of .13. The authors suspect a type-II error (failure to reject the null hypothesis), in part because of the statistically significant association between a Δ-cortisol cutoff value of 3 μg/dL and survival.

A major limitation to subject inclusion was recent glucocorticoid administration. Many dogs had received large doses of glucocorticoids within 24 hours of arrival at our hospital. There is no evidence that large doses of glucocorticoids are beneficial in clinical sepsis, and the use of large glucocorticoid doses is currently discouraged in the human literature.[35,41–43] Studies involving large numbers of dogs with septic syndromes are needed to determine the benefit of low-dose glucocorticoids in canine sepsis. Until such studies are performed, glucocorticoids cannot be recommended for treatment of septic dogs.

Another limitation of the study was that only 1 ACTH stimulation test was performed in each dog at study enrollment. Only 1 Δ-cortisol value could be derived for each dog. For dogs that deteriorated in the days after ACTH stimulation testing, the Δ-cortisol value may have categorized them inaccurately as "responders," when they may have become "nonresponders" to ACTH by their worst day of illness. The mis-classification of nonsurviving dogs as responders, when by their worst clinical day they were nonresponders, would lead to poorer statistical association between low Δ-cortisol value and hypotension and mortality. The authors propose this problem as a second reason for the lack of an association between Δ-cortisol as a continuous variable and both hospital outcome and 28-day survival.

The authors conclude that relative adrenal insufficiency occurs in some septic dogs. Furthermore, a Δ-cortisol concentration of ≤3 μg/dL after ACTH administration is associated with an increased incidence of systemic hypotension and decreased survival in dogs with sepsis. It is unknown whether supplemental doses of hydrocortisone would improve blood pressure and outcome in septic dogs with Δ-cortisol values ≤3 μg/dL; further study is warranted.

Footnotes

[a] Dynamap 1846SX/P, Critikon Inc, Tampa, FL

[b] Cardell 9401 BP, Minrad International Inc, Buffalo, NY

[c] Cortrosyn, Amphastar Pharmaceuticals Inc, Rancho Cucamonga, CA

[d] Coat-a-Count, Diagnostic Products Corporation, Los Angeles, CA

[e] Allegro HS-ACTH, Nichols Institute Diagnostics, San Juan Capistrano, CA

[f] ACTH IRMA Immunoradiometric Assay, DiaSorin, Stillwater, MN

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