Relative adrenal insufficiency (RAI) can be caused by pathology associated with any component of the hypothalamic–pituitary–adrenal (HPA) axis and may occur secondary to cytokine production associated with critical illness. Normally, the stress of illness stimulates the HPA axis, causing the release of cortisol. The amount of cortisol released depends on the degree of stress. Patients in critical condition may have cortisol values that would be considered normal or elevated in a healthy patient but that are inappropriately low for the level of illness-induced stress they are experiencing. These patients may have decreased serum basal cortisol levels and subnormal responses to adrenocorticotropic hormone (ACTH) stimulation testing.

Cortisol, which is produced by the adrenal glands, has many systemic effects, such as maintaining vascular tone and dampening the inflammatory response. Hypotension and cytokine overproduction can develop secondary to inadequate cortisol levels, causing significant deleterious effects in patients in critical condition. RAI is typically seen in patients that remain hypotensive despite aggressive intravenous fluid and vasopressor therapy. Human medicine has demonstrated that RAI is prevalent among patients in the critical care setting and that the use of low-dose corticosteroids (300 mg/day of hydrocortisone) in patients with documented RAI has a positive effect on morbidity and mortality. Conversely, high-dose steroid therapy (30 mg/kg/day of methylprednisolone) has been shown to have a negative impact on morbidity and mortality. The significance of RAI in veterinary medicine is still emerging, as clinical trials are needed to further delineate its role in small animals.

ANATOMY, PHYSIOLOGY, AND PATHOPHYSIOLOGY

The adrenal glands are located in the retroperitoneal space cranial to the kidneys and are responsible for producing the glucocorticoid cortisol and the mineralocorticoid aldosterone. Gluco-
Cortisol regulates blood glucose during times of fasting and stress by increasing the catabolism of proteins into amino acids to form the substrates for glucose production and thereby stimulating hepatic gluconeogenesis.³ It likewise raises the production of the hepatic enzymes that convert amino acids into glucose.⁴ In addition, cortisol increases serum glucose levels by limiting glucose uptake and use by peripheral cells.

Cortisol also exerts cellular immunologic effects, including decreasing circulating lymphocyte levels, preventing migration of neutrophils into peripheral tissue, inhibiting macrophage release, and causing eosinophil apoptosis.³ It decreases the production of proinflammatory cytokines such as interferon-γ, IL-1, IL-2, IL-3, IL-6, TNF-α, and chemokines.³ Levels of IL-6, a potent stimulus of the HPA,³ are elevated in patients with RAI.⁶ Cortisol also increases production of antiinflammatory cytokines such as IL-10 and transforming growth factor β.³ It stabilizes lysosomal membranes and prevents the release of proteolytic enzymes to decrease capillary permeability and assist immune modulation.⁴ Furthermore, cortisol inhibits the cyclooxygenase pathway and the production of inducible nitric oxide synthase.³ By decreasing the production of nitric oxide, cortisol helps to prevent vasodilation. Cortisol also potentiates the effect of catecholamines to cause vasoconstriction by their effect on β-adrenergic receptor synthesis.⁷

Hypoadrenocorticism

Primary adrenal insufficiency, or hypoadrenocorticism (also known as Addison’s disease), is likely due to an autoimmune process. Clinical signs do not emerge until approximately 90% of both adrenal glands are affected.⁸ In most cases, production of cortisol and aldosterone is affected. Lack of cortisol results in gastrointestinal signs such as vomiting, diarrhea, and anorexia, as well as systemic problems due to hypoglycemia and hypotension. Decreased aldosterone levels result in hypotension due to hypovolemia and can lead to severe electrolyte abnormalities. Aldosterone deficiency causes hyperkalemia, which can be life threatening, and sodium:potassium ratios that are typically less than 27:1. Other biochemical abnormalities, including hypercalcemia, hypoglycemia, and metabolic acidosis, may be evident. Patients with hypoadrenocorticism also tend to lack a stress leukogram due to the absence of cortisol. Hypoadrenocorticism is more prevalent in mixed-breed female dogs, although standard poodles, Labrador
Hypoadrenocorticism is diagnosed using the ACTH stimulation test, in which blood samples are taken before and after the administration of synthetic corticotropin given IM or IV. For dogs, the dose is 250 µg; for cats, it is 125 µg. In dogs, the follow-up sample is taken 1 hour after corticotropin administration; in cats, follow-up samples are obtained 30 and 60 minutes postadministration. A lack of response to ACTH stimulation (i.e., cortisol levels of less than 1 µg/dL in both samples) is diagnostic for the disease. Treatment typically involves fluid replacement and administration of glucocorticoids and mineralocorticoids (fludrocortisone or prednisone and desoxycorticosterone pivalate).

**CLINICAL SIGNS**
RAI does not present similarly to hypoadrenocorticism. Sodium:potassium ratio abnormalities are uncommon in human RAI patients, but one study suggested that eosinophilia may be present. The lack of electrolyte abnormalities suggests that aldosterone deficiency is not present in RAI; however, these patients are typically on IV fluid therapy, which may mask the presence of sodium and potassium abnormalities. It is currently unclear whether hypokaldosteronism occurs in RAI in both human and veterinary medicine, but some human physicians recommend supplementation with mineralocorticoids.

It is difficult to differentiate precise clinical signs associated with RAI because they are nonspecific, and these patients usually have a severe critical illness as well. However, the salient sign in human patients (regardless of the critical illness) is hypotension refractory to aggressive IV fluid and vasopressor therapy. In humans, RAI is usually a transient phenomenon that resolves with recovery from the underlying illness.

**MECHANISMS**
RAI can result from pathology in any component of the HPA axis or from glucocorticoid receptor dysfunction. Primary RAI should be considered when decreased cortisol production is directly associated with dysfunction of the adrenal glands and steroidogenesis. Secondary RAI may develop when cortisol production is blunted due to injury to the hypothalamus or pituitary. The pathophysiology of RAI is still unclear and typically does not involve permanent damage to the HPA axis. However, a number of mechanisms have been proposed in the development of RAI.

**Primary Disease**
Primary RAI can occur after a direct insult to the adrenal glands, such as adrenal trauma resulting in bilateral hemorrhage or adrenal ischemia. One study in human medicine revealed that 30% of patients who succumbed to septic shock had bilateral adrenal necrosis and hemorrhage. Neoplasms can also render adrenal tissue nonfunctional. Another theory is that chronic illness-induced stress exhausts the body’s ability to produce cortisol by depleting the adrenal reserve.

Primary RAI can also be caused by drugs that affect steroidogenesis. Etomidate reversibly inhibits 11β hydroxylase, which is important for steroidogenesis and the conversion of cholesterol into cortisol. Etomidate decreases cortisol production, typically for a period of 24 hours, and has been widely studied in human medicine as a cause of adrenal insufficiency. A study found adrenal insufficiency in 76% of human patients with sepsis who received a single bolus of etomidate. Conversely, only 51% of patients with septic shock who did not receive etomidate had adrenal insufficiency (P = .0077). Other drugs that can decrease cortisol production include mitotane, megestrol, aminoglutethimide, trilostane, and ketoconazole.

**Secondary Disease**
Secondary RAI should be considered in any patient with pathology affecting the hypothalamus, pituitary, or cortisol receptors. Any traumatic, neoplastic, inflammatory, or infectious process affecting the hypothalamus or pituitary can result in decreased levels of CRH or ACTH, respectively. Prior therapy with glucocorticoids can suppress CRH and ACTH release, depending on the type, dose, and duration of therapy. Inflammatory mediators can also affect the HPA axis (Figure 2). IL-6, IL-2, IL-1, and TNF-α have been shown to increase ACTH secretion from the anterior pituitary, and IL-6 values are increased in patients with RAI. Some studies suggest that administration of subcutaneous exogenous IL-6 initially raises levels of cortisol and corticotropin for approximately 1 day but subsequently blunts the cortisol response. However, it is still unclear whether high levels of IL-6 are responsible for, or a consequence of, RAI.

Certain drugs (e.g., cyclosporine, clarithromycin, phenytoin, phenobarbital) can lead to secondary RAI by increasing cortisol metabolism and thereby decreasing circulating cortisol values. Therefore, the drug history of any patient suspected of having adrenal insufficiency should be closely scrutinized. Another potential mecha-
High-Dose Versus Low-Dose Stimulation Tests

Considerable controversy exists over the use of the high-dose ACTH stimulation test (HDST) versus the low-dose stimulation test (LDST) in human patients. Many physicians suggest that the supra-physiologic dose of ACTH (250 µg) used in the HDST may yield too many false-negative results by overriding the patient's resistance to ACTH; they therefore recommend the LDST (1 µg) as reflecting a more natural physiologic process. In one study comparing the use of the HDST with the LDST in human patients with sepsis,14 35% of the patients were found to have adrenal insufficiency with the HDST, whereas the LDST identified insufficiency in 67% of patients. Patients who responded appropriately to the HDST had poorer outcomes compared with those who responded to the LDST. Opponents of the LDST suggest that the amount of ACTH administered (1 µg) activates the adrenal gland for only 30 minutes, which is much less stimulation than would normally occur with a condition involving considerable stress.15 It has also been noted that cortisol levels in patients with stress due to sepsis are more variable than the levels obtained during the LDST. Additionally, diluting ACTH to 1 µg requires considerable time and attention to detail.15

The gold standard for evaluating the functional integrity of the adrenal glands in human patients is the insulin tolerance test (ITT). This involves administering insulin until hypoglycemia (glucose values <40 µg/100 mL) results, stimulating the HPA axis and cortisol production.12 The LDST and HDST have been compared with the ITT in healthy human controls, and the LDST was found to be comparable to, or even more sensitive than, the HDST.13 However, the ITT is not considered safe for patients in critical condition; therefore, it is not used to validate results of the LDST versus the HDST in these patients.

Low doses of cosyntropin were administered to healthy dogs in an attempt to identify the lowest dose necessary to cause the greatest cortisol secretion.16

Figure 2. Factors that can cause secondary RAI and their effect on the HPA axis.

nism for RAI is cortisol resistance at the receptor level, although this is less well defined.

DIAGNOSIS

There is still no consensus in human medicine about the most appropriate way to confirm RAI. Normal cortisol values in humans range from 5 to 24 µg/dL. These levels can increase sixfold during severe illness.13 Some physicians consider total cortisol values of less than 10 to 25 µg/dL in a patient in critical condition to be consistent with RAI. However, a cortisol level of 26 µg/dL may still be too low in a patient with critical illness. Therefore, most clinicians routinely perform ACTH stimulation testing. A posttest change in cortisol levels of less than 9 µg/dL is consistent with RAI in humans. It should be noted that ACTH stimulation does not address hypothalamus or pituitary dysfunction, but only evaluates adrenal production of cortisol.
Cosyntropin doses of 0.01, 0.05, 0.1, 0.5, and 1 µg/kg were administered IV, with blood samples subsequently obtained every 10 minutes for 1 hour, then at 2 and 4 hours. Postadministration cortisol levels were increased compared with baseline for all doses. Similar increases were seen with the 0.1-, 0.5-, and 1-µg/kg doses; the increases associated with the 0.01- and 0.05-µg/kg doses were less dramatic. However, the reliability of testing the HPA axis with low doses of cosyntropin remains to be determined in human and veterinary patients in critical condition.

Total Versus Free Cortisol Levels
Most human and veterinary studies have used total cortisol levels to assess adrenal corticosteroid production at baseline and after ACTH stimulation testing, thus measuring both protein-bound and free cortisol. In normal patients, cortisol bound to cortisol-binding protein (CBG) and albumin accounts for 90% of total cortisol, with only 10% remaining free and biologically active. Early in acute illness, the liver decreases production of CBG and albumin as part of the acute-phase response. The decreased levels of CBG and albumin may falsely decrease total cortisol levels while increasing free cortisol values. Therefore, measuring total cortisol levels may overestimate the number of patients with adrenal insufficiency.

One study looked at ACTH stimulation findings and total and free cortisol values in human patients receiving intensive care, 50% of whom were hypoproteinemic (serum albumin <2.5 g/dL) and 50% of whom had normal protein levels (albumin >2.5 g/dL). Total cortisol levels were decreased in patients who were hypoproteinemic, but free cortisol levels were the same in both groups and were three times higher than those in a healthy control population. About 21% of the study subjects had subnormal total cortisol levels after ACTH stimulation. All of these patients were hypoproteinemic, but their free cortisol levels were comparable with those of other patients receiving intensive care and of healthy controls. It would thus seem prudent to measure free cortisol levels in lieu of total cortisol levels, but free cortisol is not easily evaluated in most laboratories. These findings should be considered in hypoproteinemic patients (veterinary and human) that are being tested for RAI because total cortisol levels may not appropriately reflect the increase in free cortisol.

RESEARCH
Human Studies
Severe adrenal insufficiency characterized by circulatory shock was first noted in 1911 and 1918 in human patients whose adrenal glands were found to be non-functional as a result of hypoperfusion and hemorrhage due to severe sepsis. In the 1990s, a placebo-controlled, randomized, double-blind, parallel group trial used criteria that included documentation of infection, fever, tachycardia, hypotension despite IV fluid resuscitation and dopamine or epinephrine administration, and the need for mechanical ventilation to document RAI in patients with septic shock. The HDST was conducted in 299 eligible patients. Based on the results, RAI (i.e., change of <9 µg/dL before and after testing) was diagnosed in 77% of the subjects. Half of the patients with RAI were given corticosteroids, and half were given placebo. The patients who did not have RAI were divided similarly. The treatment group was given 200 mg of hydrocortisone IV and 50 mg of fludrocortisone PO daily. The daily hydrocortisone dose reflects the cortisol concentrations produced in healthy humans during intense exercise.

Among the patients with RAI, 70% of the placebo population died compared with 58% of the treatment group. There was no significant difference between placebo and treatment subjects who did not have RAI. In the patients with RAI, the median time to withdrawal of vasopressor therapy was 10 days in the placebo subjects versus 7 days in the treated subjects. Among those without RAI, the median time to vasopressor withdrawal was 7 days in the placebo group and 9 days in the treatment group. There were no significant differences between the two groups in terms of adverse corticosteroid effects. Patients were excluded from the analysis if they received etomidate within 6 hours of randomization.
Further analysis of these findings has shown that corticosteroids improved morbidity and mortality in patients with early acute respiratory distress syndrome (ARDS) and RAI. Patients who did not have ARDS had no improvement in outcome with corticosteroid use, regardless of whether they had RAI.12

RAI has been well documented in human patients with ARDS and septic shock, but recent studies have found that it also occurs in other critical illnesses. One study found a 47% prevalence of RAI in patients with hemorrhagic shock and trauma.4 The patients with RAI had high levels of IL-6 and required more IV fluid therapy, hetastarch, and vasopressor support.4

A study of traumatic brain injury (TBI)21 yielded a 53% occurrence of RAI, suggesting hypoperfusion of the HPA axis as a mechanism. However, ACTH stimulation testing was not performed in this study because it can underestimate secondary RAI due to hypothalamic pathology. Therefore, RAI was defined as two total cortisol levels of less than 15 µg/dL or one total cortisol level of less than 5 µg/dL. RAI was thought to be secondary in these patients. ACTH levels were low during periods of RAI. Corticosteroids were not administered; however, etomidate was commonly administered, and none of the patients were in septic shock. All of the patients with RAI had lower mean arterial pressures and needed more vasopressor therapy. The use of high-dose propofol or pentobarbital in these patients was found to be strongly associated with RAI (P = .001).

RAI has been documented in human patients requiring ventilator therapy. In one study,22 88% of patients with a normal adrenal reserve and 91% of patients with RAI receiving stress doses of hydrocortisone were weaned from ventilator therapy. However, only 68% of patients with RAI who did not receive hydrocortisone could be weaned from the ventilator, suggesting that patients in whom weaning is difficult should be screened and treated for RAI before ventilator withdrawal.

RAI has also been diagnosed in 72% of human patients with severe liver disease and patients who underwent liver transplantation without postoperative glucocorticoid therapy.21 Low levels of high-density lipoproteins (HDL) were a positive predictor for RAI in these patients. Because HDL is a precursor of cortisol, decreased HDL levels could cause RAI in this setting. The scenario of liver disease leading to RAI has been termed the hepatoadrenal syndrome. In this study, the mortality in patients who received glucocorticoid therapy was 26%; in patients with RAI who were not treated, it was 46%.

RAI has also been suspected of causing necrotizing pancreatitis in human patients. One study monitored serum cortisol, CBG, and serum ACTH levels in 109 patients with acute pancreatitis who did not receive glucocorticoids or etomidate.24 Free cortisol values were determined via calculation. Initially, cortisol and calculated free cortisol levels were increased and ACTH and CBG levels were decreased. After approximately 4 days, cortisol levels remained low while ACTH levels increased, especially in patients with necrotizing pancreatitis. The lack of endogenous cortisol may be due to adrenal gland exhaustion associated with chronic stress.

This results in an exaggerated inflammatory response that causes pancreatic acinar cell apoptosis, leading to pancreatic necrosis. However, it is not known whether RAI was the cause or the consequence of the necrotizing pancreatitis.

**Veterinary Studies**

The extent to which RAI exists within veterinary medicine remains controversial. There are few veterinary studies devoted to RAI. Additional studies are clearly required to determine whether patients will benefit from glucocorticoid replacement.

A rat study25 has demonstrated decreased adrenal reserve during the late stages of sepsis. Initially, the rats underwent cecal ligation and puncture (CLP). Twenty hours after the procedure, which was considered late sepsis, their plasma corticosterone (cortisol) and corticotropin levels were measured. An ACTH stimulation test was performed, and total corticosterone was remeasured 30 minutes later. This study also determined adrenal levels of cortisol and levels of insulin.
adrenal cAMP. A 75% increase in corticotropin was seen in the septic rats, but plasma corticosterone levels were similar between septic and control rats. Adrenal corticosterone levels were 42% lower in septic rats compared with control rats. Plasma corticosterone was reduced by 53% after cosyntropin stimulation in the CLP rats versus controls. Finally, cAMP levels after corticotropin administration decreased in the adrenal tissue of the septic rats. This study shows that baseline corticosterone levels can be elevated, within the reference range, or similar to those of controls, but ACTH stimulation testing reveals blunted corticosterone responses. The decreased adrenal corticosterone and cAMP levels suggested primary adrenal pathology during polymicrobial sepsis.25

A prospective study speculated that perhaps RAI is not common in veterinary medicine.26 Measurements were obtained for basal total plasma cortisol, HDST cortisol, and ACTH serum levels in 20 dogs under intensive care. All of these parameters were monitored daily until discharge or death. The dogs included in the study had a variety of diseases, including acute abdomen, neoplasia, sepsis, renal failure (acute and chronic), respiratory disorders, diabetic ketoacidosis, and congestive heart failure. Basal cortisol concentrations were elevated in 37% of patients and were within the reference range for the remainder. Cortisol levels after ACTH testing were within the reference range in 90% of the patients and high in 10%.26 When compared with those of healthy dogs, endogenous ACTH levels were normal in 54% of the patients, low in 35%, and high in 12%. There was no significant difference in basal cortisol concentrations, ACTH stimulation findings, or ACTH levels between the dogs that survived and those that died. The study also showed a lack of correlation between endogenous ACTH and cortisol levels: 35% of patients had low ACTH values and 12% had high values, despite normal basal cortisol levels.26 The study was limited by its small sample size, a population with a variety of illnesses, and failure to note hypotension or aggressive fluid and vasopressor therapy. No comment was made on differences between pre- and post-ACTH stimulation cortisol levels.

A retrospective study of 42 dogs27 identified RAI in four patients (9.5%). These four dogs had low baseline cortisol levels (<10 nmol/L) and blunted responses to ACTH stimulation (change in cortisol values of <9 nmol/L) and were diagnosed with RAI. All four died. Disorders in the dogs with RAI included severe bronchopneumonia, bacterial endocarditis, abdominal sepsis, and sepsis secondary to bite wounds.27 This study suggests that RAI does occur in critical veterinary patients.

Another study involved 20 cats admitted for intensive care.28 Basal cortisol levels were obtained, and each cat underwent ACTH stimulation testing (0.125 mg IV of cosyntropin) every other day until discharge or death. Ten healthy cats served as controls. This study revealed a lesser change in cortisol levels (difference between pre-
Nonresponders to ACTH stimulation testing included 20% of dogs with lymphoma and 19% with NHN. Basal cortisol concentrations and endogenous ACTH levels were not correlated.

**CONCLUSION**

RAI has been identified in human medicine, and patients thought to have this condition respond positively to stress doses of corticosteroids. Considerable research is still needed to clarify the role of RAI in the veterinary critical care setting. Specifically, clinical studies should focus on the incidence of RAI in patients on ventilators; in hemorrhagic or septic shock; in the post-traumatic period; with SIRS, liver disease, or pancreatitis; or with hypotension despite adequate fluid replacement and vasopressor therapy. Further studies must also be conducted to determine the most accurate methods of diagnosing RAI, both in veterinary and human medicine (e.g., total versus free cortisol, LDST versus HDST).

Veterinary patients that remain hypotensive despite appropriate measures should undergo ACTH stimulation testing, followed by stress doses of glucocorticoids. A positive clinical response to steroid replacement despite normal ACTH stimulation results does not necessarily warrant removal of therapy, as secondary RAI may be the culprit. Suggested dosages could include 0.4 mg/kg/day of prednisone or the equivalent dose of methylprednisolone or dexamethasone.

RAI is an important consideration for the veterinary clinician because it is often silent in presentation, without the electrolyte derangements typical of absolute adrenal insufficiency. However, as has been demonstrated in human medicine, its identification and treatment can promote a positive outcome for veterinary patients, decreasing morbidity and mortality in the intensive care setting.

**REFERENCES**

1. The HPA axis is not stimulated by
   a. hypoglycemia.
   b. IL-6.
   c. stress.
   d. cortisol.

2. RAI can result in
   a. hyperkalemia.
   b. eosinophilia.
   c. hyponatremia.
   d. hypertension.

3. Which of the following statements about primary adrenal insufficiency (Addison’s disease) is true?
   a. Clinical signs typically are not evident until more than 90% of the adrenal glands are affected.
   b. The sodium:potassium ratio is typically greater than 27:1.
   c. It is usually transient, only requiring glucocorticoid and mineralocorticoid replacement for about 6 months.
   d. Patients commonly have stress leukograms.

4. The pathophysiology of RAI
   a. is an autoimmune process.
   b. affects only the adrenal glands.
   c. typically involves permanent damage to the HPA axis.
   d. is currently unclear.

5. The most appropriate diagnostic test to evaluate for RAI in human or veterinary medicine is
   a. LDST.
   b. HDST.
   c. baseline free cortisol levels.
   d. There is currently no consensus within human or veterinary medicine on the most appropriate diagnostic test for RAI.

6. Which drug has not been shown to cause decreased levels of circulating cortisol?
   a. etomidate
   b. ketoconazole
   c. penicillin
   d. phenobarbital

7. Functionally, cortisol
   a. prevents eosinophil apoptosis.
   b. stimulates hepatic gluconeogenesis.
   c. increases the release of CRH and ACTH.
   d. increases the production of nitric oxide.

8. Which of the following statements about RAI is true?
   a. Therapy requires lifelong glucocorticoid supplementation.
   b. It usually resolves with recovery from an underlying critical illness.
   c. Patients present with signs similar to those of Addison’s disease.
   d. It is caused by increased levels of aldosterone.

9. A common sequela of stress-dose steroid replacement for patients with RAI is
   a. hyperglycemia.
   b. gastrointestinal bleeding.
   c. increased incidence of infection.
   d. reversal of hypotension associated with septic shock.

10. In veterinary medicine, RAI has not been documented in patients with
   a. neoplasia.
   b. sepsis and SIRS.
   c. hemorrhagic shock.
   d. bacterial endocarditis.