Acute Hypoadrenocorticism in a Dog

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Introduction

This report describes the clinical signs, diagnosis and treatment of an acute hypoadrenocortical crisis, or Addisonian crisis, in a dog. Hypoadrenocorticism is an uncommon disease that has been recognized more frequently in recent decades.[1] Known as the "great pretender" owing to its variety of symptoms and diagnostic findings that may mimic other diseases, the diagnosis and treatment of hypoadrenocorticism can be one of the greatest challenges faced by veterinary practitioners.[2,3] The practitioner must have a high index of suspicion, based on common signalment, history, physical examination and laboratory findings, to make the diagnosis of hypoadrenocorticism.[3] Definitive diagnosis of hypoadrenocorticism requires an appropriate choice of diagnostic endocrine tests which confirm the presence of adrenal insufficiency.[4-7] Expedient treatment is of foremost concern in cases where life threatening abnormalities are present and hypoadrenocorticism is suspected.[3] The use of intravenous (IV) fluid therapy, corticosteroids, and other medications to alleviate systemic abnormalities secondary to adrenal insufficiency generally ensures a successful outcome in acute cases.[3] With appropriate adrenal hormone replacement therapy, the long-term prognosis for animals with hypoadrenocorticism, once an adrenal crisis is controlled, is excellent.[2-7]

The underlying pathology in this disease is the lack of glucocorticoid and mineralocorticoid

production from the adrenal glands.[2-7] The paired adrenal glands are situated in the retroperitoneal space adjacent to the kidneys.[8] The adrenal glands are usually positioned craniomedially to the corresponding kidney and adjacent to the major vessels in the abdomen.[8] Each adrenal gland consists of two distinct parts, the outer cortex and inner medulla, which differ in endocrine function.[4,8] The cortex comprises approximately 75% of the adrenal gland mass and can be subdivided into three morphologically distinct zones: the outer zona glomerulosa, the middle zona fasciculata, and the inner zona reticularis.[4,8] Glucocorticoids (cortisol) and androgens (androstenedione and dehydroepiandrosterone) are produced by the zona fasciculata and zona reticularis, respectively.[4,6] Cortisol and androgen production are regulated by the release of adrenocorticotropic hormone (ACTH) from the pituitary gland.[4,6] ACTH secretion, in turn, is regulated by corticotropin-releasing hormone secreted by the hypothalamus.[4,6] A direct negative feedback mechanism, known as the hypothalamic-pituitary-adrenal axis, dictates the amount of corticotropin-releasing hormone and ACTH produced and thereby the amount of glucocorticoid production and release.[4]

Cortisol has numerous vital functions within the body, including stimulation of hepatic gluconeogenesis during fasting or starvation to maintain normal serum glucose levels, immune system and vascular endothelial support, erythrocytosis, control of blood pressure and volume, maintenance of a healthy gastric mucosal barrier by maintaining gastric mucosal blood flow and prostaglandin production, and water and electrolyte balance.[2,4-7] Hypoglycemia, hypotension, lethargy, gastrointestinal symptoms and the inability to respond to stress are seen when cortisol levels are low or absent.[2]

Aldosterone, a mineralocorticoid secreted by the zona glomerulosa, plays a primary role in the

maintenance of normal serum sodium and potassium concentrations as well as extracellular fluid volume.[4] Secretion of aldosterone is primarily regulated by the renin-angiotensin system and an elevated serum potassium level.[4] Extremely low sodium concentrations may also cause aldosterone release, while ACTH has a minimal role.[4] Renin is released from the juxtaglomerular cells in the kidney when the serum sodium level or renal perfusion is low.[2] Renin converts angiotensinogen into angiotensin I, which is converted into angiotensin II by angiotensin-converting enzyme found in the lungs.[2] Angiotensin II is a potent vasoconstrictor, resulting in increased arteriolar blood pressure, stimulation of thirst, and aldosterone secretion.[4] Aldosterone acts primarily in the distal renal tubule to increase sodium reabsorption and excretion of potassium, but also has effects in the gastrointestinal tract and salivary glands for the same purpose.[4] Negative ions such as chloride are reabsorbed along with sodium due to electrical potentials which cause water to be reabsorbed passively as it follows concentration gradients created by movement of sodium and chloride.[6] Lack of aldosterone results in hyponatremia, hypochloremia, hypovolemia, and hyperkalemia.[2,6]

There are two general categories of hypoadrenocorticism: primary, also known as Addison's disease, and secondary.[9] Naturally occurring primary hypoadrenocorticism is more common and is usually caused by immune-mediated destruction of all three layers of the adrenal cortex, resulting in both glucocorticoid and mineralocorticoid deficiency.[2,6] Approximately 80-90% of the adrenal cortex must be destroyed before clinical signs of hypoadrenocorticism occur.[2,6] An estimated five to ten percent of dogs with primary hypoadrenocorticism will have normal sodium and potassium levels, a condition referred to as atypical primary hypoadrenocorticism.[10,11] This has conventionally been attributed to sparing of the zona

glomerulosa and, thus, maintained aldosterone production, distinguishing them from the dog with typical primary hypoadrenocorticism.[2,10,12] Aside from immune-mediated destruction of the adrenal cortex, less common causes of primary hypoadrenocorticism include infiltrative fungal or granulomatous disease, neoplasia, amyloidosis, infarction, hemorrhage due to trauma or coagulopathy, or iatrogenic causes such as the sudden stoppage of chronic glucocorticoid therapy or misuse of mitotane or trilostane in the treatment of hyperadrenocorticism. [2,6,13] Secondary hypoadrenocorticism, a rare condition in which the pituitary gland produces inadequate amounts of ACTH or the hypothalamus produces inadequate amounts of corticotropin-releasing hormone, can be caused by chronic steroid therapy or less commonly by tumors, trauma, or congenital defects of the pituitary gland.[3,6] Secondary hypoadrenocorticism is always atypical as the lack of ACTH or corticotropin-releasing hormone causes atrophy of the zona fasciculata and zona reticularis with a secondary decrease in cortisol production, while the zona glomerulosa and mineralocorticoid production remain intact.[2,6,13]

Hypoadrenocorticism is most often diagnosed in young to middle-aged female dogs, which are more prone to immune-mediated disease and constitute approximately 70% of documented cases.[2,3] A known genetic predisposition for the development of hypoadrenocorticism is found in some breeds such as the Nova Scotia Duck Tolling Retriever, Standard Poodle, Bearded Collie, Leonberger and Portuguese Water Dog.[4,14-16] The mode of inheritance in these breeds appears to be an autosomal recessive gene, although the mode of inheritance in the Bearded Collie is unclear.[14-16] Specifically, hypoadrenocorticism occurs in one percent of Nova Scotia Duck Tolling Retrievers, a rate ten times the normal dog population, with an estimated 18% of the population being carriers for the gene.[16] It occurs at an earlier age and tends to affect all

siblings around the same time in this breed.[16] Other breeds, such as the Great Dane, West Highland White Terrier, Saint Bernard, Airedale Terrier, Bassett Hound, German Shepherd, Soft-coated Wheaton Terrier, and Rottweiler, are commonly affected although a genetic predisposition to the disease has not been shown.[6,11]

Clinical signs of hypoadrenocorticism are often vague and variable as dogs present in different stages of the disease.[2,4,6] Common presenting complaints include a history of lethargy, inappetence, and weight loss, or waxing and waning gastrointestinal signs that temporarily resolve with supportive care such as fluid therapy, glucocorticoids, and rest.[2] Other symptoms may include vomiting with or without hematemesis, diarrhea with or without melena or hematochezia, polyuria, polydipsia, shaking, seizures, weakness or muscle cramping, and abdominal pain.[2] Diarrhea may be classified into two types based on the location of origin, small intestine or large intestine.[17] In general, the pattern of small intestinal diarrhea includes normal to increased volume, lack of hematochezia except in cases of hemorrhagic gastroenteritis syndrome, lack of tenesmus, dyschezia or mucus, and normal urgency.[17] The pattern of large intestinal diarrhea includes normal to decreased volume and increased urgency, often with mucus, hematochezia and dyschezia.[17] The pattern of diarrhea is often non-specific in cases of hypoadrenocorticism.[6]

In approximately 30% of cases, perhaps due to a non-recognition of earlier subtle clinical signs by the owner, dogs will present in an acute hypoadrenocortical crisis with signs of hypovolemic shock, including obtundation or collapse, bradycardia or tachycardia, weak pulses, hypothermia, and increased capillary refill time.[2,4,6,13] Occasionally, dogs without electrolyte abnormalities, as in cases of secondary hypoadrenocorticism, rare cases of primary

hypoadrenocorticism or emerging primary hypoadrenocorticism in which the zona glomerulosa is not yet affected, will exhibit a longer duration of signs consistent with cortisol insufficiency, possibly due to lack of recognition by the clinician.[2,11]

A database including a complete blood count, biochemistry profile, urinalysis, electrocardiogram, and diagnostic imaging is usually obtained by the clinician at the time of presentation due to the nonspecific clinical signs or in cases of critical illness. Unfortunately, routine laboratory findings are not specific for hypoadrenocorticism but certain abnormalities or the lack of anticipated changes in the complete blood count should raise suspicion for the presence of the disease.[2] Theoretically, a stress leukogram, often seen in sick or stressed dogs and characterized by neutrophilia, lymphopenia, monocytosis, and eosinopenia, will not be present in dogs with hypoadrenocorticism, while the overall leukocyte numbers may be unremarkable.[2,6,18,19] The term *stress* refers to the increased release of cortisol from the adrenal glands secondary to anxiety, severe disease, pain, dehydration, hyperthermia, or hyperadrenocorticism, and its variable effects on leukocyte populations.[19] The hallmark of a stress leukogram is lymphopenia as cortisol causes retention of lymphocytes in lymphoid organs and lymphocyte lysis.[19] A recent study found that dogs with hypoadrenocorticism have a significantly higher lymphocyte count, or lack of lymphopenia, than dogs without hypoadrenocorticism, even though the majority of dogs in the study had a normal lymphocyte count.[18] Lymphocyte counts greater than 2 x 10^3/uL in sick or stressed dogs had a sensitivity of 58% and a specificity of 85% as a marker for the presence of hypoadrenocorticism.[18] This finding is due to the lack of cortisol in dogs with hypoadrenocorticism when compared to sick or stressed dogs without hypoadrenocorticism.[18] It is hypothesized that the lymphocyte count is

the variable most indicative of cortisol activity compared to other leukocytes, which may be influenced by other factors.[18]

The chronic systemic effects of cortisol insufficiency, including gastrointestinal ulceration and blood loss or bone marrow suppression, may cause a normocytic, normochromic, non-regenerative anemia.[2,7] A reticulocyte count is needed to define an anemia as regenerative or non-regenerative.[20] Variations in the red cell distribution width, a quantitative measure of the heterogeneity of the red cell population (anisocytosis), may be used along with mean corpuscular volume (the average volume of red cells) and hemoglobin concentrations to further define an anemia.[21] An increase or decrease in the red cell distribution width is indicative of a regenerative or non-regenerative anemia, respectively.[21] An increase in the volume of red blood cells is suggestive of a regenerative anemia, whereas a normal to decreased volume of red bloods cells may indicate a non-regenerative anemia.[21] An increased, normal, or decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration are used to define a hyperchromic, normochromic, or hypochromic anemia, respectively.[22] Decreased gastrointestinal motility, poor tissue perfusion due to hypovolemia, and a compromised mucosal barrier may lead to gastrointestinal ulceration and bleeding in the absence of cortisol, particularly in times of stress when ulcers are more likely to form.[23] A mild anemia tends to resolve with the treatment of hypoadrenocorticism and gastroprotectant medications such as antacids, but, in rare cases, a severe anemia may require treatment with a blood transfusion.[23]

The classic and most common biochemistry abnormalities in dogs with hypoadrenocorticism include hyperkalemia, hyponatremia, and azotemia, although these abnormalities are not pathognomonic for the disease.[5,6,24] Dogs with early primary hypoadrenocorticism, atypical

hypoadrenocorticism or secondary hypoadrenocorticism in which mineralocorticoid production is still adequate will not have the classic abnormalities of hyperkalemia and hyponatremia.[2] However, hyponatremia may develop in cases of atypical or secondary hypoadrenocorticism in which cortisol secretion is diminished while mineralocorticoid function is normal.[9] A sodium: potassium ratio less than 27:1 should raise suspicion of hypoadrenocorticism (sensitivity 70%, specificity 94%) while a sodium: potassium ratio less than 24:1 is highly suggestive of hypoadrenocorticism (sensitivity 62%, specificity 96%).[24,25] The electrolyte abnormalities are the result of aldosterone deficiency which causes sodium and water loss with increased potassium and hydrogen ion reabsorption.[2] Dehydration and a metabolic acidosis ensue, which may be worsened by decreased renal perfusion and hypotension causing hypoperfusion and lactic acidosis.[2]

Metabolic acidosis is characterized by an increase in hydrogen ions; a decrease in blood bicarbonate (HCO_3) and total carbon dioxide (TCO_2), which reflects the serum bicarbonate quantity; a decrease in blood pH; a negative base excess in the extracellular fluid (BE, ECF), defined as the amount of strong acid needed to titrate one liter of blood to a pH of 7.4 at 37^oC while pCO_2 is held constant at 40 mmHg; and a decrease in plasma carbon dioxide tension (pCO_2) due to secondary hyperventilation.[26] Metabolic acidosis causes movement of potassium out of cells as cells exchange potassium ions for hydrogen ions, further exacerbating the hyperkalemia.[2,25] Other potential causes of hyperkalemia and hyponatremia may include acute or chronic renal failure, gastrointestinal disease, parasitic (whipworm) infections, urinary obstruction, congestive heart failure, chronic blood loss or chronic effusion with repeated drainage, and diabetes mellitus.[3,27,28] A recent study examining the acid-base and electrolyte

abnormalities in dogs with gastrointestinal foreign bodies found that hyponatremia and hypochloremia were present in 20.5% and 51.2% of the patients, respectively.[29] In contrast to hypoadrenocorticism, hypokalemia and a metabolic alkalosis were noted in dogs with a gastrointestinal obstruction.[29] Therefore, electrolyte and blood gas levels can influence the differential diagnoses list in an acutely ill patient with a history of vomiting or anorexia.

The serum sodium concentration is an indication of the amount of sodium relative to the amount of water in the extracellular fluid but provides no direct information about total body sodium content.[30] Hyponatremia may be classified according to hydration state, plasma osmolality, or plasma volume status.[31] Plasma osmolality, which ranges from 290 to 310 mOsm/kg in healthy dogs, is defined as the number of solute particles per kilogram, or the concentration, of a solvent and may be calculated by the formula:

$$\text{Calculated plasma osmolality (mOsm/kg)} =$$
$$2(Na^{+}\,[\text{mEq/L}]) + [\text{Blood urea nitrogen (mg/dL)}/2.8] + [\text{Glu (mg/dL)}/18].^{30,31}$$

The osmolality of the extracellular fluid and serum sodium concentration are regulated by adjusting water balance, which is mediated by antidiuretic hormone release (water output) or thirst (water intake).[30] A decreased serum sodium concentration generally, but not always, implies hypoosmolality.[30] A reduction in plasma osmolality may or may not cause movement of water between the extracellular and intracellular compartments.[30] The ability of water to move between the extracellular and intracellular space, known as tonicity or effective osmolality, is dependent on the concentration of impermeant solutes, such as sodium and glucose.[30] If these serum solutes are decreased with a low plasma osmolality, water will move from the

extracellular space to the intracellular space, resulting in hypovolemia.[30] Circulating volume depletion stimulates the release of antidiuretic hormone, resulting in increased free water absorption by the kidney and dilution of plasma sodium concentrations.[9,30] Additionally, cortisol deficiency also seems to play an important role in the development of hyponatremia.[9] Cortisol has inhibitory effects on antidiuretic hormone release.[9] In any form of hypoadrenocorticism, the inhibitory effect of cortisol on antidiuretic hormone release is lost, resulting in further dilution of plasma sodium concentrations.[9] Volume depletion through diarrhea, vomiting, and renal sodium loss associated with aldosterone deficiency also contributes to or exacerbates the degree of hyponatremia.[9]

The brain is the organ most affected by changes in serum sodium concentration.[31] The clinical signs of hyponatremia, such as weakness, incoordination, seizures and coma, are related more to the rapidity of the onset than the severity of the associated plasma osmolality.[30,31] If the serum sodium concentration acutely drops to less than 120-125 mEq/L, the decrease in plasma osmolality is more rapid than the brain's ability to compensate for the shift of water into the neurons, resulting in cerebral edema and water intoxication.[30,31] During chronic hyponatremia, the cells in the brain synthesize sodium-potassium adenosine triphosphate pumps within two or three days of the onset of hyponatremia to maintain the osmotic gradient between the extracellular and intracellular fluid.[32,33] Clinical signs are often absent with mild hyponatremia.[31]

Azotemia is generally prerenal as a result of dehydration, hypovolemia, or gastrointestinal hemorrhage.[2] However, renal azotemia may occur in rare cases.[2] Hyponatremia may lead to medullary washout, a decrease in the hyperosmolarity of the renal medulla due to sodium and chloride loss, and the inability to concentrate the urine.[13,34] Therefore, the urine specific gravity

cannot be used to assess renal function or differentiate pre-renal from renal azotemia because many dogs with hypoadrenocorticism will have a low urine specific gravity regardless of dehydration or hypovolemia.[2,6,13,34] In addition, polyuria and polydipsia secondary to medullary washout may be present, further complicating the differentiation between hypoadrenocorticism and renal failure.[2]

Additional biochemistry abnormalities noted in dogs with hypoadrenocorticism may include hypoglycemia, hypercalcemia, hypoproteinemia due to hypoalbuminemia, hypocholesterolemia, and elevated liver enzymes (alanine aminotransferase or aspartate aminotransferase), although these abnormalities are not present in all dogs with the disease.[2] Hypoglycemia, which may be the only biochemistry abnormality in cases of atypical or secondary hypoadrenocorticism, is the result of glucocorticoid deficiency, impaired gluconeogenesis and glycogenolysis.[3] Although the exact cause of hypercalcemia in hypoadrenocorticism is unclear, hemoconcentration, decreased calciuresis from glucocorticoid deficiency, and increased intestinal and bone calcium reabsorption due to the lack of glucocorticoid inhibition on Vitamin D, are thought to play a role.[35,36] In contrast to hypercalcemia, decreased total and ionized calcium levels may occur in hypoadrenocorticism.[36,37] Hypoalbuminemia decreases the amount of protein-bound calcium; the ionized calcium, the unbound, biologically active form of calcium, may form a complex with compounds, such as acid oxalate, lactate, sulfate, and citrate, in uremic acidosis.[36,37] Hypoalbuminemia can occur from gastrointestinal hemorrhage, protein-losing enteropathy, or decreased albumin synthesis in the liver.[2,38] If hypoalbuminemia is present, the calcium may be corrected by using the formula:

Corrected calcium = serum calcium- serum albumin + 3.5.[37]

Hypocholesterolemia, combined with hypoproteinemia and hypoalbuminemia, may mimic protein-losing enteropathy in dogs with hypoadrenocorticism, or may be secondary to concurrent liver disease.[39] Protein-losing nephropathy and vasculitis, which may also lead to hypoalbuminemia, may be suspected if significant proteinuria is noted on the urinalysis or if focal to diffuse signs of inflammatory disease, such as skin petechia and ecchymoses, pitting edema, dermal ulceration, and fever are noted, respectively.[40,41] Decreased tissue perfusion and hypoxia are thought to cause elevated liver enzymes in cases of hypoadrenocorticism, although a primary hepatopathy, suspected to be a part of an immune mediated complex of diseases which may cause or contribute to adrenal cortex destruction, is possible.[2,6]

As the serum potassium concentration increases, electrocardiogram (ECG) changes occur due to the effect of hyperkalemia on atrial and ventricular depolarization and repolarization.[9] At rest, an electrical gradient is maintained across the cardiac cell membrane such that the inside of the cell is negative compared to the extracellular fluid.[42] This is due to fixed negative charges within the cell, likely from intracellular proteins or polypeptides too large to diffuse out of the cell, which attract positively charged potassium ions and impair their movement out of the cell.[42] Additionally, the cardiac cell membrane is relatively impermeable to sodium and permeable to potassium, leading to higher concentrations of potassium within the cell and higher concentrations of sodium outside of the cell.[42] Proteins within the cell membrane function as selective ion channels, opening or closing in response to depolarization and allowing sodium and potassium to move into and out of the cell, respectively.[42] Once depolarization occurs, the sodium-potassium adenosine triphosphatase pump in the cell membrane is

activated which restores the resting membrane potential by expelling three sodium ions and pumping in two potassium ions for each hydrolyzed adenosine triphosphate molecule.[42] Over time, hyperkalemia reduces the resting concentration gradient between intracellular potassium and extracellular sodium, resulting in a less negative resting membrane potential and eventually closing the sodium-potassium channels.[2] The result of retained intracellular potassium is a prolonged cardiac action potential and ECG abnormalities.[2,42]

In experimentally-induced hyperkalemia in healthy animals, an increased T-wave amplitude was seen when the serum potassium was 5.5-6.5 mEq/L.[43] A decreased R wave amplitude, prolonged QRS intervals, prolonged P-R intervals, and S-T segment depression were seen when serum potassium was 6.6-7.0 mEq/L.[43] When serum potassium reached 7.1-8.5 mEq/L, decreased P wave amplitude, increased P wave duration, and a prolonged Q-T interval were noted.[43] Absent P waves and a sinoventricular rhythm occurred when the serum potassium level reached 8.6-10 mEq/L.[43] When serum potassium reached a level greater than 10.1 mEq/L, widened QRS complexes and ventricular flutter, fibrillation, or asystole were seen.[43] ECG abnormalities may not occur in proportion to the degree of hyperkalemia, nor do ECG changes follow a specific pattern; other abnormalities which may be present in dogs with hypoadrenocorticism, such as acidemia, hyponatremia, hypocalcemia, hypochloremia and decreased tissue perfusion, may also exacerbate ECG changes.[44] In contrast, hypercalcemia, which occurs in 30% of dogs with hypoadrenocorticism, and hypernatremia can counteract the effects of hyperkalemia on cardiac conduction.[3,9,27]

Radiographic findings in dogs that present with untreated hypoadrenocorticism, particularly dogs suffering from an adrenal crisis, may include signs associated with hypovolemia including

decreases in the size of the heart, liver, caudal vena cava, and cranial lobar pulmonary artery.[2,45] In one study, 81.8% of dogs considered to have moderate to severe adrenal crises had one or more of these radiographic changes, while only 18.2% of dogs in the same clinical state did not have any radiographic abnormalities.[45] Megaesophagus, thought to arise from muscle weakness due to a deficient cortisol level or altered membrane potentials secondary to the hyponatremia and hyperkalemia associated with an inadequate aldosterone level, is a rare finding in dogs with hypoadrenocorticism; it should not be considered a dependent radiologic abnormality if the disease is suspected.[4,45,46] Diseases that may cause an increase in the size of the heart and lobar vessels include right- and left-sided cardiomyopathies (volume overload), myocardial failure, thromboembolic disease, heartworm disease and iatrogenic fluid overload.[47]

Definitive diagnosis of hypoadrenocorticism requires demonstration of inadequate adrenal reserve characterized by a low resting serum cortisol concentration combined with a subnormal or negligible response to exogenous ACTH administration.[44] Synthetic ACTH, or cosyntropin, is most commonly used and is available in two formulations in one milliliter vials: a 0.25 mg sterile powder that requires reconstitution with a diluent and a 0.25 mg/ml liquid that does not need to be reconstituted.[2] Studies have shown that either of these formulations are equally effective when administered IV or intramuscularly (IM) in ACTH testing, although IV administration is recommended in a hypovolemic dog to avoid the possibility of poor absorption.[2,48,49] Compounded ACTH gel preparations are also available but are not recommended as they must be given intramuscularly, even in cases of poor perfusion, and do not produce reliable ACTH stimulation results.[50] Previously, ACTH stimulation testing was considered cost prohibitive as the recommended dose of cosyntropin was 250 micrograms (mcg), an entire vial, regardless of

the patient's weight.[2] A recent study documented that a 5 mcg/kg dose of cosyntropin was equally effective in diagnosing hypoadrenocorticism compared with the standard 250 mcg dose for any weight.[51] It was also found that cosyntropin can be frozen in plastic syringes, as it adheres to glass, and stored for up to six months without any detrimental effect on efficacy when thawed and administered IV.[52] The lower dose and ability to use the entire vial reduce expense for the clinician and owner, thereby making ACTH stimulation testing a more viable option.[2]

Greater than 90% of dogs with hypoadrenocorticism will have pre- and post-ACTH cortisol levels less than 2 mcg/dL, while the majority of cases will have values much less than 1 mcg/dL.[4] A standard protocol for ACTH stimulation testing includes drawing a venous blood sample for baseline cortisol measurement, administering cosyntropin 5 mcg/kg IV, then drawing a second venous blood sample for cortisol measurement one hour after cosyntropin administration.[2,3,25,44] With the exception of dexamethasone, exogenous glucocorticoids can falsely elevate cortisol tests so the administration of these medications should be avoided until after ACTH stimulation testing is performed.[2] If glucocorticoids other than dexamethasone have been given, it is recommended to stop the therapy, or change to dexamethasone, for a period of at least 24 hours before ACTH testing is performed.[2,4] A much longer washout period of several weeks is required to ensure accurate test results if the patient has been receiving chronic glucocorticoid treatment.[2]

A basal or resting serum cortisol level has been shown to be a reliable screening test for dogs with symptoms compatible with hypoadrenocorticism.[2] Although cortisol is secreted intermittently throughout the day and serum cortisol levels may fluctuate, one study revealed

that all dogs with hypoadrenocorticism had basal cortisol levels less than 2 mcg/dL, whereas only 21.8% of dogs with nonadrenal illness had cortisol levels less than 2 mcg/dL.[53] The study determined that a resting cortisol level less than 2 mcg/dL was highly sensitive (100%) and specific (78.2%) for the presence of the disease.[53] The high specificity, or the ability of the test to correctly identify those without the disease, allows the assumption that dogs with basal cortisol levels greater than 2 mcg/dL do not have hypoadrenocorticism, while dogs that have basal cortisol levels less than 2 mcg/dL are likely to have hypoadrenocorticism; an ACTH stimulation test is required to confirm the diagnosis.[2,53] The benefits of this screening test is that it is fast, inexpensive, and may allow the elimination of hypoadrenocorticism from the differential diagnosis list prior to the more expensive ACTH stimulation test.[2,53]

An ACTH stimulation test does not differentiate between primary and secondary hypoadrenocorticism in cases where electrolytes are normal.[2] In primary hypoadrenocorticism, endogenous ACTH is high due to the lack of negative feedback of cortisol on secretion of ACTH and corticotropin-releasing hormone from the pituitary and hypothalamus, respectively.[4,6] Endogenous ACTH is low due to decreased release from the pituitary gland in secondary hypoadrenocorticism.[2] Therefore, measurement of endogenous ACTH is the primary method to differentiate between the two forms of hypoadrenocorticism and allows the clinician to determine the level of electrolyte monitoring that will be required in an Addisonian patient with normal electrolytes.[2] Furthermore, a cortisol-to-ACTH ratio may be performed which, in a recent study, was shown to have a diagnostic sensitivity of 100% and a specificity of 99% in the diagnosis and differentiation of primary or secondary hypoadrenocorticism.[54] Dogs with primary typical and atypical hypoadrenocorticism will have low cortisol-to-ACTH ratios, due to

low cortisol levels and high ACTH levels, while dogs with secondary hypoadrenocorticism will have high cortisol-to-ACTH ratios, due to low cortisol and ACTH levels.[2,54] As with the ACTH stimulation test, it is important that samples for endogenous ACTH be collected prior to the administration of glucocorticoids, except for dexamethasone, as glucocorticoids may normalize ACTH levels within a few hours in dogs with primary hypoadrenocorticism.[2] An endogenous ACTH level can be difficult to run for the clinician due to very specific and meticulous handling requirements. Endogenous ACTH, a labile substance, has a half-life of 25 minutes in fresh whole blood so it dissipates quickly.[2] Samples must be collected in siliconized tubes containing ethylenediaminetetraacetic acid, which prevents adherence to glass and coagulation, then immediately frozen and submitted to the closest lab that runs the test before the sample thaws.[2,6]

Additional diagnostic testing in cases of hypoadrenocorticism with normal electrolytes may include an aldosterone level and an aldosterone-to-renin ratio.[13,55] In typical primary hypoadrenocorticism, the aldosterone level will be low due to destruction of the zona glomerulosa with resultant hyperkalemia and hyponatremia.[4,55] In atypical primary hypoadrenocorticism and secondary hypoadrenocorticism, aldosterone secretion remains intact due to sparing of the zona glomerulosa.[4,55] A recent study analyzing aldosterone concentrations in animals diagnosed with hypoadrenocorticism, animals with diseases mimicking hypoadrenocorticism, and healthy dogs showed that aldosterone concentrations were low or undetectable in most dogs with hypoadrenocorticism compared to the other groups and independent of sodium and potassium levels.[55] Therefore, normal sodium and potassium concentrations in dogs diagnosed with hypoadrenocorticism may not reflect a

normal function of the zona glomerulosa.[55] Possible mechanisms allowing a normal potassium balance without aldosterone may include a higher renal tubular flow rate with higher delivery of potassium to the collecting duct through maintained sodium intake and extracellular fluid volume, an increased sensitivity of the tubule to aldosterone caused by up-regulation of the receptor, or both.[55,56] Some of the published cases of atypical hypoadrenocorticism in the literature developed electrolyte abnormalities in the follow-up period, likely due to the eventual destruction of the zona glomerulosa or the failure of the mechanisms that allow potassium homeostasis in the absence of aldosterone.[11,55] It could therefore be argued that almost all dogs diagnosed with primary hypoadrenocorticism would benefit from mineralocorticoid supplementation independent of their electrolyte concentrations.[55] However, segmental sparing of the zona glomerulosa with atrophy of the zona fasciculata and zona reticularis has been documented in dogs.[55]

The plasma renin level will be high if the aldosterone level is low as aldosterone deficiency results in hyponatremia and renin release.[57] Accordingly, the aldosterone-to-renin ratio will be low in cases of primary hypoadrenocorticism; whereas, in cases of secondary hypoadrenocorticism, aldosterone and renin levels will be normal with a normal aldosterone-to-renin ratio.[57] The measurement of renin levels would allow the clinician to completely assess the function of the zona glomerulosa but, unfortunately, aldosterone-to-renin ratios are not generally available to the clinician as most commercial laboratories do not measure renin levels.[57]

During an acute hypoadrenocortical crisis, rapid assessment of the clinical state of the patient is critical for the successful reversal and treatment of the typical physiologic and biochemical

abnormalities that are generally present.[3] Based on age, breed, sex, and history provided by the owner, an intuitive clinician may suspect that a critically ill dog with signs of bradycardia, increased capillary refill time, hypothermia, and shock is suffering from a hypoadrenocortical crisis without a definitive diagnosis of the disease.[25] Restoration of tissue perfusion and acid-base balance, correction of hypovolemia, hypotension and electrolyte abnormalities, identification and treatment of arrhythmias, and correction of hypoglycemia if present are the primary goals of treatment during a hypoadrenocortical crisis**.**[2,9] This is accomplished primarily through the appropriate use of aggressive fluid therapy.[2,9] Intravenous fluids will rectify hypotension and hypovolemia by increasing intravascular volume.[2,9] Intravenous fluids also help to eliminate hyperkalemia through dilution while increasing renal elimination of potassium via increased renal perfusion and glomerular filtration.[2,9] Rapid intravascular volume replacement also helps to correct acidosis by causing a transcellular shift of potassium into cells, thereby decreasing serum potassium concentrations as the blood pH increases.[9,27] Therefore, the initial treatment protocol is predominantly focused on correcting identified abnormalities, including shock, which may be caused by numerous diseases.[2,4,6,25]

Shock is defined as a state of inadequate cellular energy production or the inability of the body to supply cells and tissues with oxygen and nutrients and remove waste products.[58] Hypovolemic or circulatory shock is the most common type of shock seen in small animal practice and is caused by decreased intravascular volume.[59] Possible causes of hypovolemic shock include hemorrhage, severe dehydration, endocrine disease such as hypoadrenocorticism, and hypoproteinemia.[59] Cardiogenic shock results predominately from a failure of adequate forward blood flow and may be caused by congestive heart failure,

myocardial abnormalities such as dilated cardiomyopathy in dogs, and cardiac arrhythmias.[59] Clinical signs associated with both hypovolemic and cardiogenic shock include tachycardia, pale mucous membranes, increased capillary refill time, poor pulse quality, and hypothermia.[59] Distributive shock results from an abnormal, usually decreased, systemic vascular resistance, which causes a maldistribution of blood flow.[59] Sepsis and conditions which cause obstructions to blood flow, such as gastric dilatation-volvulus, caval syndrome secondary to heartworm disease, and pericardial effusion may result in distributive shock.[59] Other causes of distributive shock include systemic inflammatory response syndrome (SIRS), anaphylaxis and heat stroke.[59] Bright red mucous membranes, tachycardia, decreased capillary refill time, and a normal to increased temperature are associated with distributive shock.[59] Hypoxic shock is caused by decreased blood oxygen content and may occur secondary to anemia, hypoventilation, or pulmonary parenchymal disease.[59] Deranged cellular metabolism that, as in all shock states, leads to decreased cellular energy production may cause metabolic shock.[59] Hypoglycemia and cytopathic hypoxia of sepsis are major causes of metabolic shock.[58] The categories of shock are not mutually exclusive, and one type of shock may progress into or cause another type of shock.[59] In addition to shock, SIRS or sepsis may be considered if the patient has an abnormal temperature (<38^{o}C or >39^{o}C), an abnormal heart rate (>120 beats/min), an abnormal respiration rate (>20 breaths/min), or a change in leukocyte numbers (leukocytosis, leukopenia, or > 3% bands).[59] Sepsis is highly suspected when two to three of the criteria are met.[60]

The recommended crystalloid resuscitation volume to administer in dogs in shock is 90 ml/kg/hr, which is equivalent to replacing one blood volume per hour.[2,4,9] When large quantities of intravenous crystalloids are rapidly administered, an immediate increase in

hydrostatic pressure and extravasation of fluid into the interstitial space occurs.[4] The lymphatics will return the excess fluid to the vascular space to be excreted by the kidneys.[4] The brain and lungs are major organs which may collect fluid or fail if the capacity of the lymphatics is surpassed.[4] Extreme care must be taken when treating hypovolemia and perfusion deficits with crystalloids alone in an animal with suspected pathology in these organs, or if there is impaired renal function.[4] To alleviate this concern, it is recommended to administer 20-30 ml/kg boluses of crystalloids, equal to one quarter to one third of the shock dose, every 15 minutes while continually monitoring the patient's perfusion status.[9] Heart rate, capillary refill time, blood pressure, mentation and urine output are generally monitored, while blood lactate concentrations and base deficit may also be evaluated.[61] Hemodynamic stability is reached when these parameters, considered end points of resuscitation, stabilize or return to normal levels.[61] Once the signs of shock have been resolved and the goals of resuscitation have been met, boluses of intravenous fluids are discontinued and fluids may be administered at a calculated rate which accounts for maintenance, rehydration and ongoing losses until hydration, electrolytes, renal values, or other physiological or biochemical abnormalities return to normal.[2] Complete recovery and normalization of vital parameters may occur within 48-72 hours in a typical hypoadrenocortical crisis with appropriate fluid therapy.[34]

The use of colloids reduces the volume of crystalloids needed to treat signs of shock, correct hypovolemia, and achieve hemodynamic stability.[62] Colloids contain high molecular weight particles which increase intravascular colloid oncotic pressure and more efficiently hold fluid within the intravascular space.[62] Natural colloids include whole blood, plasma, or concentrated albumin.[61] Synthetic colloids include dextrans and hydroxyethyl starches.[62] Hydroxyethyl

starches, such as hetastarch and tetrastarch used in the United States (pentastarch is available in Europe and Canada), are commonly used in veterinary medicine because they are readily available, inexpensive, and have fewer potential side effects compared to natural colloids.[62,63] The differences in the synthetic colloids are the average molecular weight, or size, of the particles and the degree of glucose unit substitution with a hydroxyethyl group on the molecule, both of which determine the exerted colloid oncotic pressure and degradation time.[62] Synthetic colloids with higher molecular weights and hydroxyethyl group substitution persist longer in the intravascular space, eventually being degraded by enzymes and eliminated through the kidneys.[62] Hetastarch has the highest molecular weight (450 kDa) and degree of substitution (0.7), lasting for 24 hours after administration, while tetrastarch has the lowest molecular weight (130 kDa) and degree of substitution (0.4), lasting for 12 hours after administration.[62] Hetastarch and tetrastarch contain 77 mEq/L and 154 mEq/L of sodium, respectively.[63] The standard dose for hetastarch and tetrastarch is 20 ml/kg/day and may be bolused in 5-10 ml/kg increments followed by 1-2 ml/kg as a continuous rate infusion to achieve a 20 ml/kg/day dose depending on the hemodynamic status of the patient.[63]

The rationale and protocol for the use of colloids in veterinary medicine has largely been extrapolated from human guidelines where studies have shown that acute kidney injury, coagulopathies and pathologic tissue uptake may occur with colloid use.[64,65] Although clinical evidence of coagulation abnormalities secondary to the use of hetastarch has not been reported in veterinary medicine, it is believed that the higher molecular weight products at doses greater than 20 ml/kg/day may directly decrease factor VIII and von Willebrand factor, cause platelet dysfunction, and decrease fibrin clot stabilization.[62,66] Other contraindications for

the use of colloids may include patients with fluid overload, cases of pulmonary edema secondary to cardiac failure, and severe hypernatremia or hyperchloremia.[63] Because of this, the lower molecular weight and shorter acting tetrastarch may be regarded as a safer colloid for use in patients with clinical signs of shock, hypovolemia or dehydration where these diseases cannot be initially ruled out.[67] In addition, tetrastarch has been dosed at 50 ml/kg/day in human studies with significant reduction in adverse effects on the kidneys or coagulation systems, as well as a reduction in tissue storage.[67] Assuming similar pathophysiology in dogs as in humans, with the realization that species variation may exist, tetrastarch doses higher than 20 ml/kg for larger molecular weight colloids in dogs may be considered.[67] Hypersensitivity reactions are also possible but are very rare.[63]

If a patient remains hypotensive once euvolemia has been achieved either with or without the use of colloids, the use of pressor medications should be considered.[68] Commonly used pressors, administered for their alpha agonist effects and vasoconstriction properties, include dopamine, epinephrine, norepinephrine and phenylephrine.[68] Vasopressin, a hormone traditionally used in the treatment of diabetes insipidus, has, in recent years, been shown to be effective in the treatment of hypotension which may be non-responsive to traditional pressor medications.[69] Dobutamine, a beta agonist and positive inotrope, may also be considered in cases where decreased cardiac contractility is suspected as the cause of hypotension.[68] All of these medications are generally administered through constant rate infusions (CRI) and are titrated to effect.[68]

Lactate production is traditionally considered an anaerobic event secondary to tissue hypoxia.[70] However, even in aerobic conditions, some lactate is produced.[70] Skeletal muscle and the

gastrointestinal tract are the major sites of lactate production in the body; other tissues and cells, including the brain, skin, and erythrocytes, also contribute to lactate production.[70] In the presence of sustained tissue hypoxia, anaerobic metabolism generates lactate more rapidly than it can be metabolized, resulting in hyperlactatemia.[70] Lactate production results in hydrogen ion production, resulting in metabolic acidosis during periods of prolonged anaerobic metabolism.[70] The use of lactate measurement in cases of an acute hypoadrenocortical crisis can provide helpful diagnostic and prognostic information, gauge response to treatment, and provide a resuscitation endpoint.[70] Normal lactate concentrations for dogs vary slightly but lactate concentrations above 2.5 mmol/L are considered to be normal in unstressed patients.[70] Lactate concentrations of 2.5 to 4.9 mmol/L are deemed mild elevations, while concentrations of 5 to 7 mmol/L are regarded as moderate elevations and are usually associated with acidemia.[70] Lactate concentrations greater than 7 mmol/L are considered severe elevations and may carry a worse prognosis.[70] One study examining lactate concentrations in critically ill and injured dogs found significantly higher lactate concentrations in nonsurvivors than in survivors.[70,71] A recent study looking at lactate levels in dogs with babesiosis illustrated the increased prognostic value in conducting serial lactate measurements rather than a single lactate measurement.[70,72] As with most conditions, treating hyperlactatemia involves treating the underlying cause.[70]

Although metabolic acidosis is common in an acute hypoadrenocortical crisis, accurate characterization of the acid-base status facilitates assessment of the patient's overall condition, early detection of complications, orientation for treatment, and identification of complications associated with treatment.[73] Acid-base disorders are divided into two types: metabolic and

respiratory.[26] Each primary metabolic or respiratory acid-base disturbance is accompanied by a secondary change in the opposing system, returning the pH of the system toward, but not completely to, normal.[26] A mixed acid-base disturbance is characterized by the presence of two or more separate acid-base abnormalities in the same patient and should be suspected whenever the secondary or adaptive response exceeds or falls short of that which is expected.[26] If a mixed acid-base abnormality is present, the effect on the blood pH is additive.[73] The traditional approach for assessing acid-base balance focuses on how pCO_2 and HCO_3^- interact through the carbonic acid-bicarbonate equation (Henderson-Hasselbach equation):

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

which shows that the HCO_3^- and the CO2 levels have a direct correlation to each other.[26,74] If an acute respiratory acidosis is suspected, the expected change in HCO_3^- concentration may be calculated through the formula:

$$\text{Expected } HCO_3^- = 22 + ((pCO_2 - 35) \times 0.15) +/- 2 \text{ mEq/L}$$

to determine if compensation is adequate.[26]

Additionally, serum chloride and HCO_3^- concentrations have an inverse relationship and change reciprocally in response to an increase or decrease of the other.[26,75] Changes in water balance and the presence of unmeasured anions disturb the inverse relationship between serum chloride and HCO_3^- concentrations, affecting accurate interpretation of acid-base status.[76] Serum chloride concentrations must be corrected to account for changes in plasma free water.[76] A corrected chloride is calculated using the formula:

$$[Cl^-] \text{ corrected} = [Cl^-] \text{ measured} \times 146 / [Na^+] \text{ measured}$$

where 146 reflects the mean value for serum sodium in dogs.[76] Corrected chloride levels range from 107-113 mEq/L in dogs.[76] A corrected hyperchloremia is associated with acidosis (hyperchloremic acidosis) and hypovolemia.[76] Hyperchloremia may result from excessive sodium loss relative to chloride (small bowel diarrhea), excessive chloride gain relative to sodium (exogenous intake), or renal chloride retention (renal failure or renal tubular acidosis, hypoadrenocorticism, diabetes mellitus, and chronic respiratory alkalosis).[76]

The anion gap, the difference between unmeasured cations and unmeasured anions, may be a useful tool in determining electroneutrality.[26] The anion gap may be calculated using the formula:

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-).[77]$$

The equation states that every time there is a decrease in HCO_3^-, chloride, or other unmeasured anions, must increase to maintain a normal electroneutrality.[26] The anion gap in normal dogs ranges from 12-24 mEq/L and is heavily influenced by the net negative charge of albumin.[77] A normal anion gap with hyperchloremia may occur secondary to diarrhea, renal tubular acidosis, hypocapnic acidosis, and rapid sodium chloride ingestion.[77] An increased anion gap acidosis may result from toxicosis, such as ethylene glycol ingestion, or lactic acidosis.[77] Uremic acidosis and hypoadrenocorticism may cause either a normal or increased anion gap acidosis.[77] The anion gap may be corrected for changes in albumin concentration using the formula:

$$\text{Anion gap (adjusted for albumin)} = \text{Anion gap} + 4.2 \times (3.77 - [\text{albumin}]).[77]$$

Even though electrolyte abnormalities generally resolve with fluid therapy secondary to dilution, increased renal perfusion, and correction of acidosis, immediate treatment of hyperkalemia-induced cardiotoxicity is necessary if life threatening ECG changes are present.[9] ECG changes usually begin when the serum potassium level rises above 7 mEq/L with life threatening arrhythmias developing around 9 mEq/L.[9,25] Since previously mentioned factors other than hyperkalemia may influence ECG changes, the decision to institute emergency treatment for hyperkalemia should be based on the severity of the ECG changes and not on the serum potassium value.[25] The administration of 10% calcium gluconate 0.5-1.0 ml/kg IV to effect over five to ten minutes antagonizes the cardiotoxic effects of hyperkalemia by reestablishing the normal gradient between resting cell membrane and threshold potential but does not directly reduce the potassium level.[2,43] The effects of calcium gluconate are instantaneous and short lived, only lasting for approximately 30-60 minutes, so its use is often beneficial in patients with life- threatening arrhythmias caused by hyperkalemia that require immediate stabilization until additional therapy can be given.[2] Continuous ECG monitoring is warranted as the infusion should be stopped once ECG abnormalities have resolved, new arrhythmias appear, or the heart rate drops dramatically.[2,9]

In addition to aggressive fluid therapy, IV dextrose and insulin promote the movement of potassium from the extracellular space to the intracellular space and should be considered if severe ECG changes secondary to hyperkalemia are present.[9,25] Dextrose promotes the excretion of endogenous insulin from the pancreas which promotes glucose and potassium uptake via stimulation of sodium-potassium adenosine triphosphate activity in skeletal muscle; the administration of iatrogenic insulin adds to this effect.[2,6,56] A bolus of 50% dextrose 0.5-1.0

ml/kg diluted 1:1 with saline is generally administered initially.[2,3] The use of dextrose has been shown to decrease the serum potassium level by 0.5 to 1.5 mEq/L within one hour with effects lasting up to six hours.[3,9,27] Additionally, dextrose may be required to treat hypoglycemia which occurs in 20% of dogs with hypoadrenocorticism.[3,9] If insulin is used in the treatment of hyperkalemia, a continuous rate infusion of dextrose, generally a 5% solution administered for six hours following insulin administration, is needed to prevent iatrogenic hypoglycemia.[5] Dextrose supplementation should be gradually tapered and discontinued as determined by serial blood glucose measurements, usually checked every hour for six hours after insulin administration.[3]

Ultrasonography has become a useful tool in the assessment of a critical patient at presentation.[78] Focused assessment with sonography for trauma (FAST) may be used as an initial diagnostic test for the assessment of free fluid in the peritoneal, pleural, and pericardial spaces in unstable patients where trauma or other abnormalities are suspected.[78] To differentiate thoracic FAST from abdominal FAST, the two have been referred to as TFAST and AFAST, respectively.[78] The sensitivity and specificity of a FAST examination for detection of free fluid remains high even when performed by nonradiologists.[78] An experienced sonographer may be able to determine the site of disease or trauma, assess for evidence of diffuse disease that may not be obvious on radiographs, or, in some instances, obtain a definitive diagnosis through ultrasound alone within minutes of presentation. Ultrasonographic signs of hepatic neoplasia or parenchymal disease, such as focal or diffuse masses or nodules, changes in parenchymal echogenicity, irregular serosal contour, or a reduction in hepatic size may be noted.[79] Changes to the gastrointestinal tract, such as alterations in normal gastric or intestinal

wall layering and thickness, disruption of normal wall delineation, mucosal speckling or dilated lacteals may indicate inflammatory, infiltrative, or protein-losing gastrointestinal disease.[80,81,82] The lumen of the stomach and small intestines may be evaluated for signs of an obstructive pattern or fluid stasis which may indicate metabolic or mechanical ileus.[80,81] The abdominal lymph nodes may be assessed for changes in size, shape, and echogenicity.[83] The size, contour, structure and echogenicity of the spleen may be evaluated for signs of focal or diffuse disease.[84]

The urinary bladder may be evaluated for signs of rupture or blockage.[85] Kidney size is judged primarily by subjective evaluation as there is marked variation of kidney length and volume among normal dogs with similar body weights.[85] The normal relationship of the echogenicity, or the intensity of the echo produced by the sound waves, of the kidney to that of the liver and spleen is important for recognizing abnormalities.[85] In normal dogs, the kidneys are less echogenic than the spleen and less than or equal to the echogenicity of the liver.[85] Acute renal disease or insult may result in swollen kidneys with either increased or decreased echogenicity but normal appearance; chronic renal disease generally results in loss of renal volume, decreased kidney size, loss of normal renal architecture and margination, and increased echogenicity.[85]

An experienced sonographer may include an echocardiogram in the TFAST to assess for myocardial failure, cardiac tamponade, chamber enlargement, or hypovolemia.[78] The most commonly used index of left ventricular function is the fractional shortening.[86] Fractional shortening has been reported to be between 25-45% in normal dogs.[86] The distance between the ventricular septum and the maximal initial opening of the mitral valve (E point) is inversely related to left ventricle stroke volume which, combined with heart rate, is indicative of cardiac

output.[86] This measurement, known as the mitral E point to septal separation (EPSS) has also been used as a practical and easily reproducible clinical index of left ventricular function.[86] Decreased preload may lead to reduced atrial and ventricular diastolic volume, decreased stroke volume, and decreased cardiac output.[86,87]

The thin-walled left atrium will dilate in response to both pressure and volume overloads.[86] The left atrium is generally compared in size to the aortic root.[86] The aortic root to left atrium ratio is usually less than 1.3 to 1.4 and is often close to 1.0 in a normal dog.[86] The most accurate method to evaluate the internal short-axis widths of the two structures is in the right parasternal short axis view.[86] In the absence of acute regurgitation of the aortic or mitral valves, such as with acute aortic valve endocarditis or chordae tendinae rupture, both of which may cause high left ventricle end diastolic pressure without chamber enlargement, the left atrium must be significantly enlarged for congestive heart failure to occur.[86] Right heart enlargement and myocardial failure may either be cardiogenic or secondary to respiratory or systemic disease.[88] In cases of suspected right-sided heart failure, abdominal ultrasound may be performed to detect characteristic dilatation of the caudal vena cava and hepatic veins, hepatomegaly, and ascites.[86]

In addition to FAST, ultrasonography has become a useful tool in evaluating the size of the adrenal glands in suspected cases of hypoadrenocorticism.[1,89,90] Since there is no linear relationship between adrenal gland thickness and body weight as there is with adrenal gland length and body weight, the greater difference in thickness between affected and healthy adrenal glands is considered more significant in assessing for possible adrenal insufficiency.[89,90] A maximal width or thickness of 0.74 cm has been used as the upper limit of adrenal gland

diameter in normal dogs.[91] However, a recent study showed that adrenal gland width in normal dogs may be correlated with body weight such that reference intervals for adrenal gland width were proposed for different weight categories.[92] The lower limit of adrenal gland size has not been established.[91] Subjective criteria, including the shape and contour of the adrenal glands, may also help identify aberrant adrenal glands when the width measurements are not obviously abnormal [89,91]

Theoretically, the bilateral adrenal glands will be symmetrically shorter and thinner, and thus flatter in appearance, than in healthy dogs of similar body weight in cases of autoimmune destruction of the adrenal cortices.[89] In one recent study, the length and width of the left adrenal gland of dogs with hypoadrenocorticism was compared to previously established standards for length and width of the left adrenal gland in healthy dogs.[89] The length and thickness of the left adrenal gland in dogs with hypoadrenocorticism was significantly less than that of healthy dogs.[89] Specifically, the length of the left adrenal gland was 25% less than the length in a healthy dog while the thickness of the left adrenal gland was 42% less than the width in a healthy dog.[89] It is possible that the appearance, length, and width of the adrenal glands in dogs with hypoadrenocorticism will fall within the reference range for body weight.[90] Thus, the use of ultrasound may be considered a viable screening test for hypoadrenocorticism, especially in emergency cases of an acute Addisonian crisis.[89]

Glucocorticoid therapy should be instituted as soon as possible and concurrent with fluid resuscitation if an adrenal crisis is suspected.[2,3,9,25] The administration of glucocorticoids helps maintain blood pressure, blood glucose concentrations, and intravascular volume in glucocorticoid deficient patients.[9] Dexamethasone is the glucocorticoid of choice as it is fast

acting, may be given intravenously, does not suppress the hypothalamic-pituitary-adrenal axis, and will not interfere with corticotropin stimulation testing used to definitively diagnose hypoadrenocorticism.[2,3,9] Dexamethasone has eight to ten times more glucocorticoid activity than prednisone and has a biological half-life of 48 hours.[2,25,93] Doses for dexamethasone vary, ranging from 0.1-4 mg/kg q 12-24h.[3,9,25] The wide range of reported dexamethasone doses lies in the rationale that lower doses reduce the risk of complications associated with higher doses of dexamethasone, such as gastrointestinal hemorrhage in a hypovolemic patient in a state of shock, while higher doses may protect the blood brain barrier and reduce the risk of permanent neurologic damage, which will be discussed later.[9] Other glucocorticoids, such as prednisone, prednisolone, and hydrocortisone, may falsely elevate the serum cortisol level and should be avoided before completion of corticotropin stimulation testing to definitely diagnose hypoadrenocorticism.[25]

Of these, intravenous hydrocortisone, in addition to fluid therapy at conservative rates, was shown to be more beneficial in the acute management of hypoadrenocorticism in a recent study.[94] Hydrocortisone has equipotent glucocorticoid and mineralocorticoid activity compared to prednisone, which has four times the glucocorticoid activity and four-fifths the mineralocorticoid activity of hydrocortisone, and dexamethasone, which has thirty times the glucocorticoid activity of hydrocortisone with no mineralocorticoid activity.[94] The use of hydrocortisone at 0.5-0.625 mg/kg/hr continuous rate infusion (CRI) in the study resulted in normalization of potassium in 68.4% and 100% of cases by 12 and 24 hours, respectively, with a median hospitalization time of two days.[94] Additionally, hydrocortisone may lessen the risk of gastrointestinal hemorrhage in hypovolemic patients, as well as other deleterious side effects

of glucocorticoids, due to its decreased glucocorticoid activity compared to other steroids.[94] Therefore, treatment of a suspected hypoadrenocortical crisis with hydrocortisone and appropriate fluid therapy may be considered when ACTH stimulation testing is not readily available.

Even though a metabolic acidosis is corrected by fluid and glucocorticoid therapy in most instances of a hypoadrenocortical crisis, the use of sodium bicarbonate in cases of a severe acidosis (pH <7.2) may be considered.[44] The bicarbonate deficit, or total dose of bicarbonate, may be calculated using the formula:

Deficit in mEq = (body weight in kg) x 0.5 x (base deficit).[44]

Twenty-five percent of the calculated deficit is given in the IV fluids over the initial six to eight hours of treatment, at which time the acid-base status is reevaluated.[44] The use of sodium bicarbonate is contraindicated in cases of hypochloremia secondary to vomiting, congestive heart failure, nephrotic syndrome, and oliguria.[95] Sodium bicarbonate should not be used in patients with compromised ventilation, as the HCO_3^- will be converted into CO_2 and will result in hypercapnia, increased respiratory acidosis, hemodynamic instability and potential cardiac arrest.[73,95]

Additional treatments may be aimed at alleviating possible gastrointestinal ulceration secondary to hypovolemia and hypocortisolemia. Injectable gastroprotectants, such as a proton pump inhibitor, are strongly recommended, as well as antiemetics if vomiting is present.[2] Omeprazole, or similar medications in the proton pump inhibitor class of gastroprotectants, have been shown to be superior to histamine H2-receptor blockers, such as famotidine, for

increasing gastric pH and the prevention or treatment of gastric ulceration.[96,97,98] Maropitant is an effective antiemetic as it mimics the structure of substance P, a key neurotransmitter in the stimulation of vomiting, and binds to neurokinin 1 (NK1) receptors so they cannot bind substance P, thus decreasing stimulation of the emetic center.[99]

Broad spectrum antibiotics are also indicated owing to possible breakdown of the gastrointestinal barrier that may result in bacterial translocation.[2] A recent study showed that the most common anaerobic isolate from the gastrointestinal tract in dogs is Clostridium perfringens which showed low resistance to amoxicillin-clavulanate.[100] Ampicillin-sulbactam may be considered when oral amoxicillin-clavulanate treatment is not viable or when large parenteral doses are desired in cases of sepsis, pneumonia, other severe infections or surgical prophylaxis.[101] Ampicillin-sulbactam is also effective against a variety of aerobic and anaerobic bacteria such as Escherichia coli, Pasteurella spp, Staphylococcus spp, Streptococcus spp, Salmonella spp.[101]

Reported complications associated with acute adrenal insufficiency treatment include acute renal failure and central pontine myelinosis.[25,32] Acute renal failure may occur due to renal ischemia as a result of prolonged hypotension, hypovolemia, impaired myocardial effusion, and possible colloid use.[25,65] Myelinolysis is a symmetrical, non-inflammatory demyelination of central pontine regions within the brain associated with rapid correction of chronic hyponatremia with intravenous fluids.[33,102] Expeditious treatment of hyponatremia, in which the plasma becomes hypertonic to surrounding extracellular and intracellular spaces, draws fluid out of the adapted brain cells, leading to osmotic shrinkage of axons and severing their connections with the surrounding myelin sheaths.[9,33] Degeneration of oligodendrocytes, glial

cells that produce myelin, also occurs.[32,33] Neurologic signs from myelinolysis generally arise several days after resuscitation and are indicative of brainstem dysfunction.[32] Weakness, marked ataxia, muscle tremors, head pressing, dysphagia, decreased sensory perception, and quadraparesis are reported with this condition and are generally considered to be untreatable and irreversible, although some documented cases of myelinolysis showed gradual improvement in neurologic signs over several weeks.[9,33] This condition may be underrepresented in the veterinary literature as clinical signs may be attributed to adrenal insufficiency itself.[25] Magnetic Resonance Imaging may be used to visualize characteristic lesions within the pons for diagnosis confirmation, although lesions may not be detectable for up to four weeks.[9] Therefore, negative magnetic resonance imaging results do not rule out myelinolysis in the early stages of the disease.[9]

Experimental studies in dogs and clinical experience in humans suggest that the degree of change in sodium concentration over 24 hours is more important than the change that occurs over a given hour or period of hours.[9,103] The accepted rate of sodium correction in a hyponatremic patient is no more than 12 mEq/L in 24 hours, or less than or equal to 0.5 mEq/L/hr, to prevent myelinolysis.[2,25,104] The expected rate of sodium change using any fluid per liter can be calculated using the formula:

(Fluid Na+ - Serum Na+) / (Total Body Water +1)

where Total Body Water equals body weight in kg x 0.6.[105]

Once the expected change in sodium per liter of fluid is known, the clinician can calculate the rate at which serum sodium concentrations will increase using a particular rate of fluid

administration and, therefore, keep the rate of sodium administration under the recommended 0.5 mEq/L/hr rate. The fluid rate is determined by calculating metabolic fluid requirements while estimating dehydration, hypovolemia, or monitoring ongoing fluid losses.[62] The calculation of resting energy expenditure:

REE = ml water = (30 x body weight (kg)) + 70,

where metabolism of 1 kcal of energy equals 1 ml of water consumed, allows the determination of the daily water requirements of a patient in a 24-hour period, although other formulas may be used.[62] Replacing fluid loss secondary to dehydration, hypovolemia , or ongoing losses (vomiting, diarrhea, or renal loss) may be calculated using the formula:

Dehydration (%) x body weight in kg x 1000 = ml fluid deficit.[62]

This deficit is generally replaced over a six to 24-hour period, depending on a patient's stability and ability to handle the volume administered.[62] There is no absolute correct method of replacing an animal's fluid deficits, as long as the deficit is calculated in the amount of fluids that need to be administered to a dehydrated or hypovolemic patient.[62] Frequent weighing or monitoring urine, vomit, or diarrhea fluid output allow the clinician to determine whether a patient's maintenance and fluid deficit needs are being met.[62]

Traditionally, 0.9% sodium chloride (154 mEq/L of sodium) has been the preferred sole intravenous fluid for resuscitation during a hypoadrenocortical crisis as it improves hyponatremia by providing sodium without adding potassium.[2,62] Many clinicians advocate the use of other balanced crystalloid solutions with lower sodium concentrations, such as Lactated Ringers solution (130 mEq/L of sodium) or Normosol-R (140 mEq/L of sodium), for resuscitation

even though they contain small amounts of potassium.[2,6,7,9,62] This allows a slower sodium correction rate while any added potassium in the hyperkalemic patient is eliminated through increased renal perfusion and excretion through the collecting duct.[7] The use of 0.9% sodium chloride is not without benefit, however, as some clinicians prefer to use a 20-30 ml/kg bolus of 0.9% sodium chloride during the initial one to two hours of treatment, especially if neurologic abnormalities that may be secondary to severe hyponatremia are present.[2] The goal of administering a bolus of 0.9% sodium chloride is to acutely raise the sodium concentration to 120 mEq/L, a level which resolves clinical signs of hyponatremia, while also treating ECG changes secondary to hyperkalemia.[30] Once the bolus is finished, an isotonic fluid with a lower sodium concentration will be used for further resuscitation.[2]

Lifelong therapy for primary typical hypoadrenocorticism consists of glucocorticoid and mineralocorticoid supplementation.[2] Glucocorticoid supplementation is generally provided by giving a physiologic dose of 0.1-0.2 mg/kg/day per os (PO) of prednisone or prednisolone.[2,6,34] The dose of glucocorticoids may be tapered to the lowest effective dose to prevent symptoms of chronic glucocorticoid use, including polyuria, polydipsia, polyphagia and panting; or increased two to ten times the dose in times of stress, such as surgery or illness, to prevent a hypoadrenocortical crisis.[2]

Mineralocorticoid supplementation is provided by either injectable desoxycorticosterone pivalate (DOCP) or oral fludrocortisone acetate.[2] DOCP is a long acting mineralocorticoid that has no glucocorticoid effect, thus a glucocorticoid is required with its use.[106] The initial dose is 2.2 mg/kg IM or SQ as a microcrystalline depot for slow dissolution into the circulation which allows a therapeutic effectiveness of approximately 25 days.[106] Normal electrolytes should be

present at 2 weeks post administration of DOCP and most patients are well controlled on 1.65-2.2 mg/kg IM or SQ every 21-30 days.[106] Electrolyte levels should be checked two, three and four weeks after starting DOCP to determine the duration of action, dose, and dosing interval.[2] If mild hyperkalemia and hyponatremia persist, the dose should be increased by 5-10% at the next administration.[2,6] Conversely, the dose may be decreased by 5-10% if hypokalemia and hypernatremia are seen.[2] Once the dose and dosing interval have been established, electrolytes should be checked every three to six months.[2] Side effects with the use of DOCP are rare and tend to be dose- or disease-related but may include polyuria, polydipsia, and injection site reactions.[106] Polyuria and polydipsia may arise from the effects of concurrent glucocorticoids with DOCP, but it is thought that the mineralocorticoid effects of DOCP at higher doses may increase renal blood flow and glomerular filtration through an increase in blood pressure.[7] Additionally, long term use of DOCP, especially in large dogs, may be cost prohibitive.[2] A recent study indicated that lower initial and maintenance doses of DOCP, ranging from 0.36-2.19 mg/kg IM, did not result in hypoadrenocortical crises, reduced survival times, or persistent or severe electrolyte abnormalities.[107] Although close monitoring of electrolytes is needed with lower doses of DOCP, this knowledge may promote better owner compliance in the treatment of hypoadrenocorticism in larger dogs or in cost prohibitive cases.[107]

Mineralocorticoid replacement using DOCP during an acute hypoadrenocortical crisis is controversial as there have been no objective, evidence based studies that prove an advantage to using a mineralocorticoid prior to increasing perfusion and correcting electrolyte abnormalities.[2] Administration of a mineralocorticoid prior to restoring adequate perfusion may decrease the absorption of the medication as it may only be given subcutaneously (SQ) or

IM.[2] Additionally, use of a mineralocorticoid in dogs with profound hyponatremia may result in a rapid rise in the sodium level and subsequent neurologic derangements.[2] However, other studies have demonstrated no harm or toxicity, with only transient increases in serum sodium concentrations, when large amounts of a mineralocorticoid were given to healthy dogs over an extended time period; a recent paper surmised that there is no medical disadvantage to giving a mineralocorticoid during a hypoadrenocortical crisis.[108,109] Some clinicians still choose to administer a mineralocorticoid during the initial crisis once perfusion parameters have stabilized, as absorption and effects of the medication are slow acting, while the correction rate of sodium is more dependent on the fluid choice and rate of administration rather than mineralocorticoid administration.[2,9,103]

Fludrocortisone acetate is an oral mineralocorticoid alternative to DOCP which also has some glucocorticoid activity.[110] The recommended starting dose is 0.01 mg/kg PO q12h but may be adjusted by 0.05-0.1 mg/day based on serial electrolyte monitoring.[111] Electrolyte levels should be checked weekly until they stabilize, then checked monthly for three to six months followed by indefinite electrolyte monitoring every three to four months.[2,111] In many dogs receiving fludrocortisone, the daily dose required to maintain normal electrolytes increases over the first year of treatment, often reaching a dose of 0.02-0.03 mg/kg/day.[2,7,110] In the initial treatment of hypoadrenocorticism, both fludrocortisone and prednisone should be used, as approximately 50% of dogs will require prednisone despite the glucocorticoid activity of fludrocortisone.[2,6] Polyuria, polydipsia, weight gain, hypercholesterolemia, hypertriglyceridemia, and relative resistance are the primary side effects with the use of fludrocortisone.[2,7] These signs, which are compatible with iatrogenic hyperadrenocorticism, are generally the result of glucocorticoid

excess when prednisone and fludrocortisone are given together but are also seen with the use of fludrocortisone alone.[2] In dogs that develop signs associated with hyperadrenocorticism, even when hyponatremia and, less frequently, hyperkalemia persist, the addition of sodium chloride 0.1 g/kg/day may be useful to reduce the dose of fludrocortisone, while maintaining normal serum sodium.[111] As with DOCP, fludrocortisone is also quite expensive, especially in larger dogs.[2] Plasma renin levels were significantly higher in dogs treated with fludrocortisone than those treated with DOCP.[57]

Dogs diagnosed with atypical or secondary adrenal insufficiency require only glucocorticoid replacement.[2,4,10,11] A daily physiologic dose of 0.1-0.2 mg/kg of prednisone is usually sufficient, except in times of stress.[110] However, if a primary pituitary ACTH deficiency has not been confirmed, the clinician must monitor serum electrolyte concentrations on a regular basis while the owner must monitor for clinical signs associated with a mineralocorticoid deficiency at home.[110] As stated earlier, many dogs with atypical primary hypoadrenocorticism, originally showing normal electrolyte levels, will subsequently develop electrolyte abnormalities and require mineralocorticoid replacement.[11,55]

The long-term prognosis for dogs with hypoadrenocorticism, whether diagnosed with stable clinical signs or after recovery from an adrenocortical crisis, is excellent.[3] With appropriate glucocorticoid and/or mineralocorticoid replacement therapy, most dogs should be expected to live a normal life.[3] The owners of a patient with hypoadrenocorticism must be well informed as to the importance of consistent medication administration, increasing glucocorticoid supplementation during stressful times, periodic monitoring of electrolytes, and expected costs of lifelong treatment of the disease.[3,25]

Clinical Report

A three-year-old spayed female Labrador Retriever mix presented for severe lethargy, collapse, vomiting, and diarrhea. The owner reported a gradual decrease in activity level and appetite in the week prior to presentation. Sporadic vomiting and consistent diarrhea started as the appetite declined. The owner described the vomiting as initially occurring two times a day and containing mostly large amounts of food. Small amounts of bilious vomiting with an increased frequency of four to five times a day were observed as appetite declined and the dog's condition worsened. Diarrhea developed at approximately the same time as the vomiting and was consistent in frequency and appearance, occurring two to three times a day with normal volume, urgency, and lacking mucous or blood. Collapse was not witnessed but the owner found the dog in a recumbent state and could not get the dog to stand. The clinical signs developed after application of an over-the-counter topical flea medication containing etofenprox, S-methoprene, and piperonyl butoxide, one week before presentation. The owner fed a balanced diet and did not report any known dietary indiscretion. Normal urination was described by the owner up until the day of presentation. No other relevant medical history was reported. The dog had received all pertinent vaccinations two months prior to the onset of clinical signs. A heartworm test was performed at the time of vaccinations and was negative. The dog received a monthly oral heartworm preventative but was not on any other medications.

At presentation, the dog was obtunded and recumbent. On physical examination, her mucous membranes were pale pink in color and dry with a capillary refill time of greater than two

seconds. Increased skin tenting was present. No evidence of pain, trauma or a foreign body was noted on orolaryngeal examination and a gag reflex was present. Moderate dental calculus and gingivitis was noted mostly on the right and left upper premolars and molars. Examination of the eyes revealed normal pupil size with no nystagmus, strabismus, enophthalmos, or signs of Horner's syndrome. Palpebral reflexes were intact in both the right and left eyes. Direct and consensual pupillary light reflexes were present in both eyes. The external ear canals were pale pink with minimal ceruminous debris. The skin and hair coat were normal in appearance. The abdomen was non-distended in size and soft on palpation with no palpable abnormalities or evidence of intra-abdominal effusion. Assessment of possible proprioceptive deficits in the forelimbs or hind limbs was difficult due to the inability to stand or ambulate. No signs of external trauma were found. Patellar, sciatic, and cranial tibial reflexes, along with pain sensation and a withdrawal reflex, were intact and normal in both rear limbs. Severe bradycardia and mild bradypnea were noted on thoracic auscultation. The heart rate was bradycardic at 40 beats per minute (110-120 beats per minute), while the respiration rate was 14 breaths per minute (15-30 breathes per minute).[112] A heart murmur was not detected. Femoral pulse quality was weak. The initial oscillometric mean arterial pressure[a] (MAP) obtained from the right forelimb in a lateral position was decreased at 70 mmHg (85-120 mmHg).[113] Auscultation of the left and right lung fields revealed normal inspiratory and expiratory movement of air in the lungs with no auditory crackles or wheezes. The dog's body temperature was 34.4^{o}C (37.5^{o}C-39.2^{o}C), consistent with hypothermia.[112] The dog's weight was 29.5 kg with a body condition score of 5/9.[114]

Based on the history and physical examination, the initial problem list included inappetence or anorexia, vomiting, diarrhea, weakness and altered consciousness, severe bradycardia, hypoventilation, hypotension, hypothermia, dehydration and shock. Many of the causes of anorexia and vomiting are similar: disorders of the gastrointestinal tract such as inflammatory disease, intestinal foreign bodies and obstruction, intussusception, parasitic or viral infections, bacterial disease or overgrowth including Helicobacter spp., ulceration, obstipation or neoplasia, and abdominal disorders such as pancreatitis, peritonitis, hepatobiliary disease, or non-gastrointestinal neoplasia.[115,116] Other causes of anorexia or vomiting include metabolic or endocrine disorders such as anemia, hypoadrenocorticism, diabetes mellitus, hepatic disease, electrolyte or acid-base disorders, intoxicant ingestion, or dietary intolerance.[115,116] Potential causes of small intestinal diarrhea include maldigestive or malassimilation disorders, inflammatory disease, dietary indiscretion, abrupt diet change, a gastrointestinal foreign body or obstruction, parasitic or infectious organisms, toxin ingestion and various diseases involving the endocrine or non-gastrointestinal organ systems.[17]

The patient was weak with a decreased consciousness and differential diagnoses for this state include various abnormalities of the cardiovascular or pulmonary systems, electrolyte abnormalities such as hyperkalemia and severe hyponatremia, neurologic disease including typical or atypical seizures, musculoskeletal afflictions, metabolic myopathies or myositis, hypoglycemia and neoplasia.[117] Structural or arrthymogenic cardiac disease, a severe vasovagal response, hypothermia, hypoglycemia, endocrine disease and secondary electrolyte abnormalities such as hyperkalemia, neurological disease, toxin ingestion and neoplasia may cause bradycardia.[118] Hypoventilation may result from cardiovascular or pulmonary disease,

hypothermia, endocrine disease and secondary electrolyte disturbances such as hyperkalemia, acidosis, shock, airway obstruction, abnormal central or peripheral neurologic function, and toxicosis.[119]

Hypotension was noted as the MAP was 70 mmHg (85-120 mmHg) and the femoral pulse quality was weak.[68,113] Hypotension may result from numerous diseases that may cause hypovolemia, decreased venous return, decreased cardiac function, or decreased vascular tone.[68] Hypovolemia may arise secondary to hemorrhage, effusions, gastrointestinal fluid loss, or hypoadrenocorticism.[68] Causes of decreased venous return include pericardial effusion and cardiac tamponade, restrictive pericarditis, severe pneumothorax, gastric dilatation-volvulus, and heartworm disease.[68] Cardiomyopathies, arrhythmic cardiac disease, electrolyte abnormalities, acid-base disturbances, severe hypoxia, and SIRS or sepsis may decrease cardiac function and vascular tone.[68] Differential diagnoses for hypothermia include cardiovascular disease and secondary decreased peripheral perfusion, central nervous system disease, dehydration, hypoglycemia, electrolyte imbalances such as hyperkalemia, or toxicant exposure.[120]

The degree of dehydration was estimated to be between 5-10% which was based on the presence of dry mucous membranes, increased skin tenting, weak femoral pulses and hypotension.[62] Possible causes for mild dehydration include decreased fluid intake as a result of the many causes of anorexia, normal fluid loss secondary to typical urine output and evaporation from the lungs, and increased fluid loss from vomiting or diarrhea.[121]

Due to the presence of obtundation, bradycardia, hypoventilation, weak femoral pulses,

hypotension and pale mucous membranes with an increased capillary refill time, the dog was considered to be in a state of shock.[58] An 18-gauge over the needle catheter[b] was placed in the right cephalic vein with collection of a small venous blood sample. A 22.5 ml/kg IV (664 ml) bolus of an isotonic crystalloid replacement fluid[c] and a 5 ml/kg IV (148 ml) dose of a low molecular weight tetrastarch[d] were administered over the initial 15 minutes of treatment. A 3-lead electrocardiogram[e] (ECG) was placed and continuous Lead II monitoring confirmed the presence of bradycardia with a heart rate of 38 beats per minute (110-120 beats per minute).[111] The ECG also showed a regular rhythm with consistent atrial standstill characterized by the absence of P waves prior to ventricular depolarization.[42] Decreased R wave and increased to tall T wave amplitudes were also observed. Differential diagnoses for the presence of atrial standstill and the respective changes in R and T waves include the loss of normal atrial myocardium, severe hyperkalemia and other electrolyte abnormalities including hyponatremia and hypocalcemia, or acidosis.[9,118]

A blood gas, electrolyte, and metabolite analysis[f] (Table 1) was performed in-house immediately after obtaining the venous blood sample. Numerous abnormalities were present on the initial panel which warranted a refined problem list. Decreases in cerebral tissue oxygen saturation (cSO_2), HCO_3^-, TCO_2, venous pH, base excess in extracellular fluid (BE, ECF), and electrolytes including sodium, chloride, ionized calcium, and glucose were present. Significant increases in potassium and creatinine levels, along with a mildly increased hematocrit, were also observed. The decreased venous pH was consistent with an acidemia.[26] The decreased HCO_3^-, the decreased TCO_2, and the negative base excess in the extracellular fluid were indicative of a metabolic acidosis.[26]

Table 1: Initial venous blood gas, electrolyte, and metabolite analysis, Day 1 presentation (**Bold** indicates outside of reference range)

Analyte	Result	Reference Range	Units
pO_2	25.8	24.0-54.0	mmHg
cSO_2	**34.0**	40.0-90.0	**%**
pCO_2	41.9	30.0-47.0	mmHg
Bicarbonate	**15.8**	16.0-28.0	mmol/L
$cTCO_2$	**17.1**	18.0-28.0	mmol/L
pH	**7.184**	7.360-7.460	
BE, ECF	**-12.5**	-5.0-5.0	mmol/L
Sodium	**115**	140-151	mmol/L
Potassium	**8.6**	3.5-5.0	mmol/L
Chloride	**94**	106-127	mmol/L
Calcium, ionized	**0.98**	1.13-1.42	mmol/L
Anion gap	14	5-22	mmol/L
Lactate	1.20	0.6-3.0	mmol/L
Creatinine	**5.43**	0.4-1.5	mg/dL
Glucose	**33**	63-124	mg/dL
HCT	**58**	36-55	**%**

Once a metabolic acidosis was noted, the respiratory component of the acid-base balance was considered. The pCO_2 level was consistent with a respiratory acidosis.[26] Potential causes of a mixed metabolic and respiratory acidosis include hypoadrenocorticism, hypoadrenocorticism-like syndrome in dogs with gastrointestinal disease, low output heart failure with pulmonary edema, thoracic trauma with hypovolemic shock, advanced septic shock, gastric dilatation-volvulus, and acute tumor lysis syndrome.[73]

When considering the other aberrant values on the panel, abnormalities that may result in a decreased cSO_2 include any disease that may result in decreased blood flow or oxygen delivery to tissues, such as hypotension or cardiac disease; decreased oxygenation of the blood, such as pulmonary disease or injury; or decreased oxygen carrying capacity of the blood, such as anemia or internal hemorrhage.[122] Plasma osmolality was most likely low or normal due to the degree of hyponatremia and hypoglycemia.[30] Common causes of hyponatremia with low to normal plasma osmolality in the presence of possible hypovolemic shock include gastrointestinal loss via vomiting or diarrhea, third space loss as with uroabdomen, cavitary effusions, pancreatitis or peritonitis, and hypoadrenocorticism.[28] An unremarkable lactate level was present. The anion gap was normal and consistent with a normal anion gap acidosis, despite the low serum chloride and sodium concentrations.[77] A corrected hyperchloremia was calculated which may occur secondary to renal tubular acidosis and hypovolemia.[76]

Possible diseases that may cause severe hyperkalemia include those that may cause decreased urinary excretion of potassium, such as hypoadrenocorticism; anuric or oliguric renal failure; urethral or ureter obstruction and urinary bladder rupture; or redistribution of potassium from

the intracellular to extracellular space, such as metabolic acidosis.[123] Other rare or less likely potential causes of hyperkalemia included high numbers of whipworms (pseudohypoadrenocorticism), massive tissue damage as with tumor lysis syndrome or trauma, severe infections or significantly elevated white blood cell counts greater than 100,000 cells/uL, thromboembolism, or hyperkalemia periodic paralysis.[123]

Acute or chronic renal failure and subsequent metabolic acidosis may cause an increase in acid oxalate, lactate, sulfate and citrate, all compounds which may form complexes with calcium; the result is a decrease in ionized calcium.[36] Other potential causes of the decreased ionized calcium included parathyroid gland disorders, intestinal malabsorption, hypovitaminosis D, hypomagnesemia, soft tissue trauma or rhabdomyolysis, or tumor lysis syndrome.[37]

The elevated creatinine was compatible with prerenal azotemia, renal azotemia, or postrenal azotemia.[124] Differential diagnoses for prerenal azotemia include any process that decreases renal blood flow, including dehydration, hypovolemia, hypotension, heart failure, hepatic failure, various forms of shock, or hypoadrenocorticism.[124] Differential diagnoses for renal azotemia include causes of chronic renal failure, such as glomerulonephritis, pyelonephritis, or renal dysplasia, and causes of acute renal failure, such as toxicosis, infectious disease, severe dehydration, or neoplasia.[124] Urinary tract obstruction or urinary tract rupture are the primary causes of postrenal azotemia.[124]

Hypoglycemia may result from hepatic insufficiency or failure, neoplasia (specifically an insulinoma), sepsis, hypoadrenocorticism, or anorexia.[125] The mildly elevated hematocrit was consistent with a relative erythrocytosis secondary to dehydration and was not elevated to a

degree where absolute polycythemia was considered.[126]

Aggressive fluid therapy and treatment were continued with monitoring of vital signs every 15 minutes during the first hour of treatment (Table 2). After assessment of the vital signs following the initial 15 minutes of treatment, bradycardia, hypotension, hypothermia and blood pressure were improving but still below normal limits. A second dose of the tetrastarch colloid 5 ml/kg IV (148 ml) was given over another 15 minutes. For the immediate treatment of the severe hyperkalemia, several medications were used. A dose of 10% calcium gluconate[g] 0.5 ml/kg IV (1475 mg) was administered over 20 minutes on a syringe pump[h]. The ECG was closely monitored during calcium gluconate infusion for the development of new arrhythmias or decreases in heart rate, which were not observed. Atrial standstill was no longer present on the ECG by the time the calcium gluconate infusion was finished. A single dose of regular insulin[i] 0.25 U/kg IV (7.4 U) was administered. Following the injection of insulin, 50% dextrose[j] 1 ml/kg IV (500 mg) diluted 1:1 with the isotonic replacement fluid was given.

Following the bolus of the isotonic crystalloid replacement fluid, a balanced electrolyte fluid[k] was administered at 3.4 ml/kg/hr (100 ml/hr) to provide daily fluid requirements and correct both dehydration and hyponatremia over a 24-hour period. The tetrastarch colloid 0.8 ml/kg/hr (24 ml/hr) was continued as a CRI after the initial 10 ml/kg dose was infused for a total fluid rate of 4.2 ml/kg/hr (124 ml/hr). In order to continue to treat potential hypoglycemia from the administration of insulin, a 5% Dextrose CRI was added to the liter of the balanced electrolyte solution. Ampicillin-sulbactam[l] 15 mg/kg IV (443 mg) q8h was chosen as a prophylactic antibiotic. Maropitant[m] 1 mg/kg IV (29.5 mg) q24h and famotidine[n] 1 mg/kg IV (29.5 mg) q24h

Table 2: Vital signs, initial 60 minutes following presentation, Day 1 (**Bold** indicates outside of reference range)

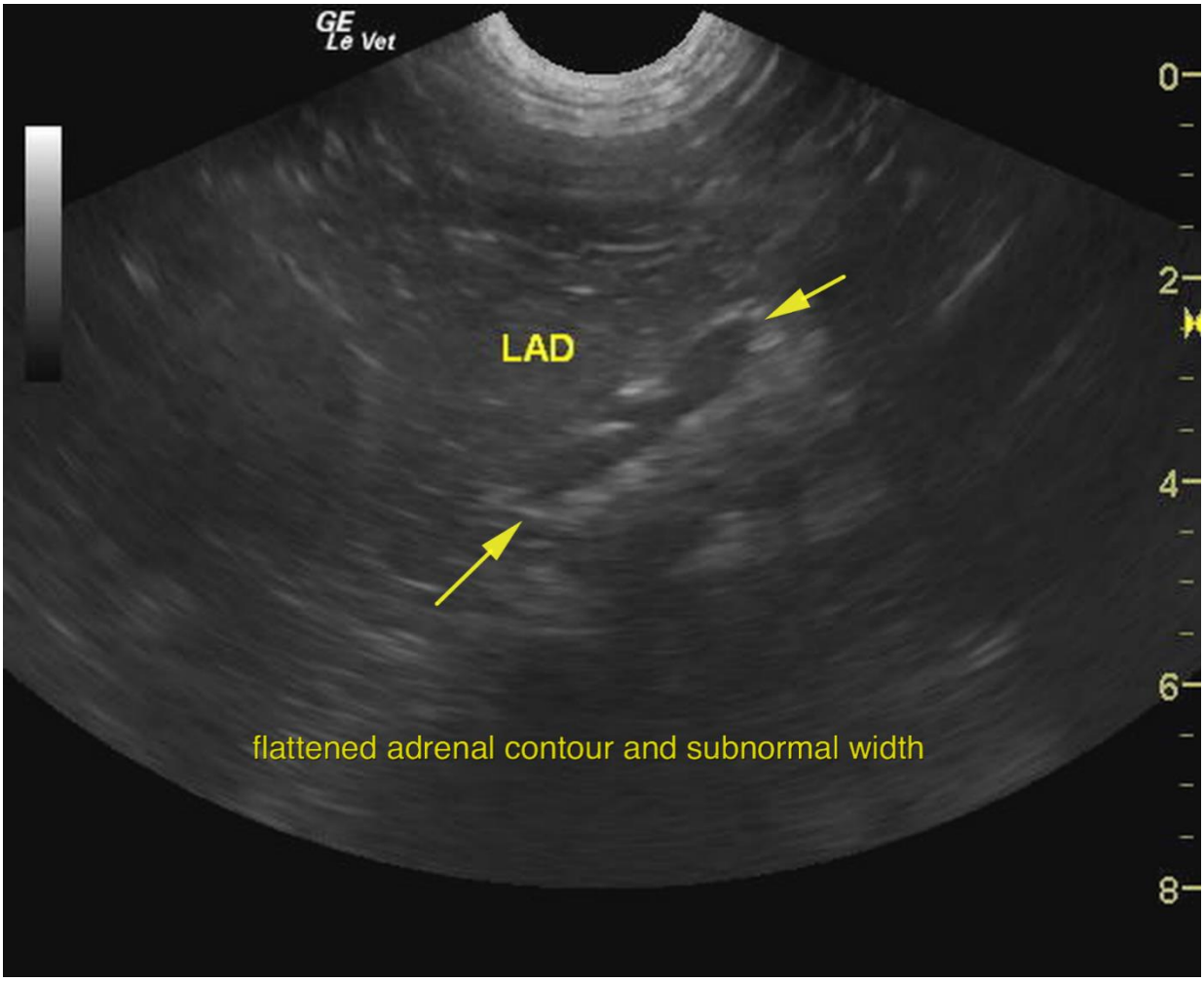
	Presentation (fluid bolus)	15 min (fluid bolus)	30 min	45 min	60 min	Reference range[112,113]
Heart rate (beats/min)	**40**	**90**	110	120	**130**	110-120
Resp. rate (breaths/min)	**14**	24	**32**	30	**32**	15-30
Body temp (^{o}C)	**34.4**	**34.9**	**36.4**	**36.8**	**37.4**	37.5–39.2
MAP (mmHg)	**70**	90	110	120	**135**	85-120

were also given. All initial treatments were given within 30 minutes of the onset of resuscitation.

Within 15 minutes of the initiation of treatment, the dog was more alert, able to raise its head, and move its limbs. After 30 minutes of treatment, the dog was able to lie sternally and attempted to stand. At the end of the initial hour, the dog was able to sit and move about the cage. The continuous ECG showed normal complexes with resolution of atrial standstill and was discontinued. Cranial nerve and peripheral nerve function were rechecked and found to be normal. The body temperature remained slightly below normal limits but was trending upward. Mild tachycardia was now present, and the mean arterial pressure was slightly elevated. The respiration rate varied between a normal rate of breathing and mild tachypnea. Normal inspiratory and expiratory movement of air in the lungs with no auditory crackles or wheezes was noted on lung auscultation.

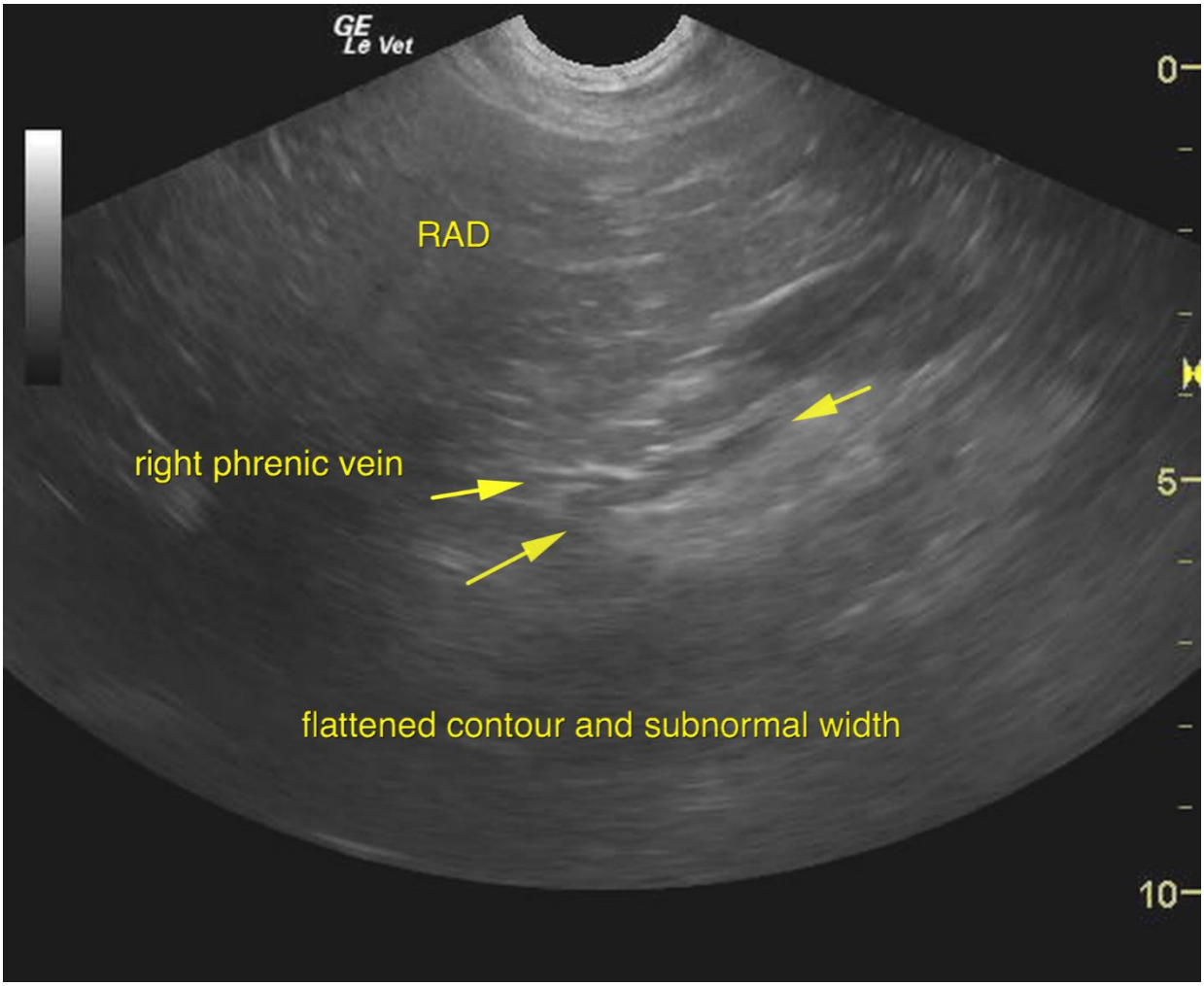
An AFAST^{o} (Figures 1 and 2) was performed approximately 30 minutes after presentation. No enlarged abdominal or retroperitoneal lymph nodes were found. The urinary bladder was mild to moderately full with anechoic urine. The walls of the urinary bladder were intact and normal in appearance. The bilateral kidneys were subjectively normal in size and margination with normal echotexture and architectural distinction. The bilateral adrenal glands in the dog were flattened in shape and contour with decreased width based on body size. Both adrenal glands measured less than or equal to 0.4 cm in width with the right adrenal gland smaller in size. The liver and spleen were normal in size, structure, and contour. Intact wall layering and normal wall thickness were noted in the stomach and small intestine. The lumen of the stomach and small intestine was empty and free of static fluid. The caudal vena cava, aorta and portal vein

Figure 1



Sagittal view of the left adrenal gland (LAD) on Day 1.

Figure 2



Sagittal view of the right adrenal gland (RAD) on Day 1.

appeared to be subjectively normal in size with an approximate 1:1:1 ratio.[127] Normal laminar flow was present in the three vessels on color flow Doppler with no evidence of thrombosis. No evidence of peritoneal effusion was found.

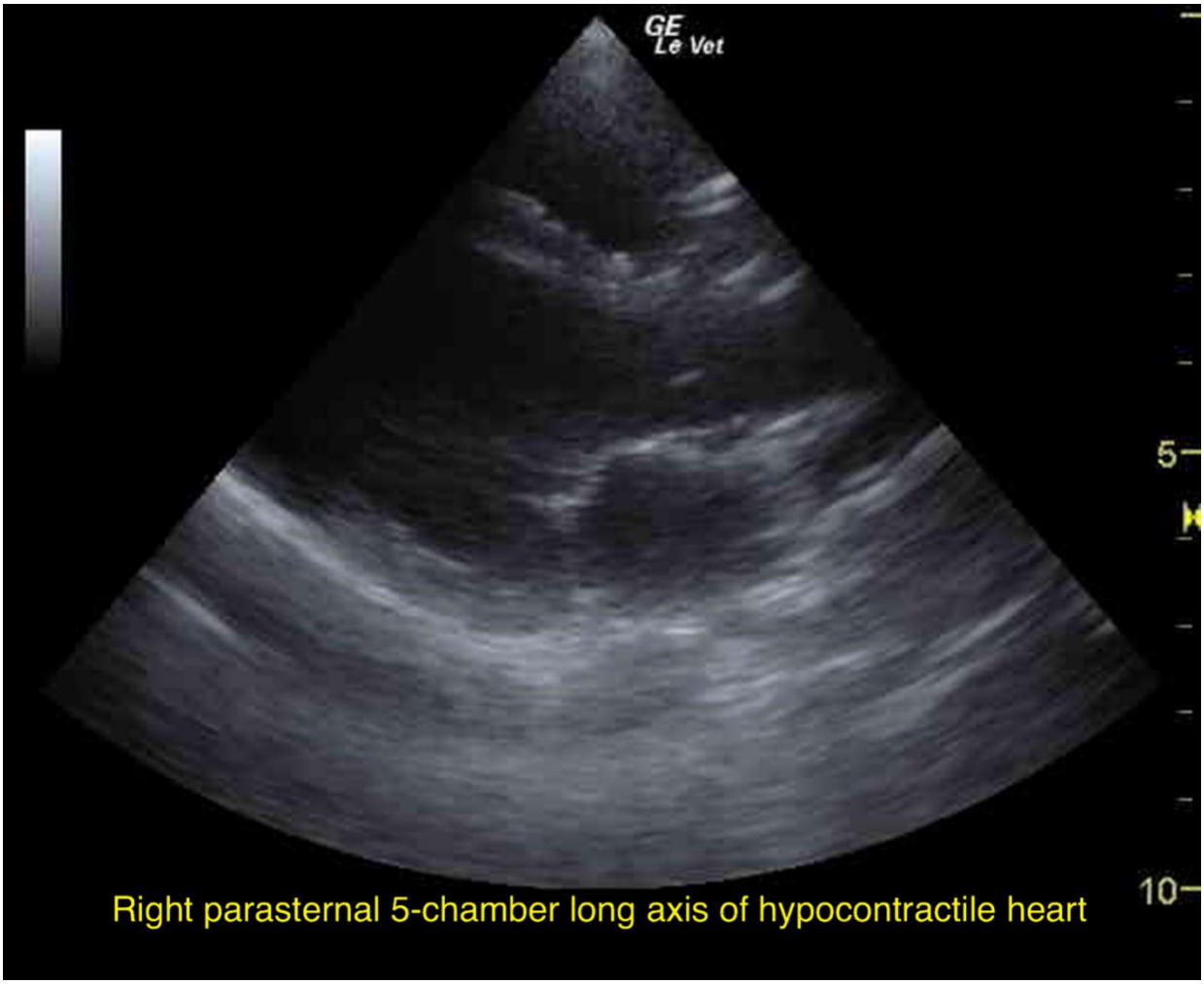
A TFAST and echocardiogram (Table 3, Figures 3 and 4) were performed following the abdominal ultrasound. The size of the left atrium was normal to slightly small for body weight with a left atrium to aorta ratio of approximately 1:1 despite aggressive fluid therapy.[86] The chordae tendinae were intact. The left atrial myocardium appeared to be intact and symmetrical. Left ventricle measurements in both systole and diastole were within normal parameters for the dog's body weight.[86,128] The fractional shortening or contractility of the left ventricle was mildly decreased.[128] The right atrium and ventricle were normal in size and appearance. All of the valves exhibited normal thickness, echogenicity, and range of motion. The sternal lymph nodes were not enlarged. No pleural effusion, pericardial effusion or evidence of cardiac, mediastinal, pulmonary neoplasia was present.

Thoracic radiographs[p] (Figures 5 and 6) were obtained. The cranial mediastinum, which was similar to the width of the vertebra in the ventrodorsal view, was unremarkable in appearance.[129] The thoracic spine, ribs, and diaphragm were intact with no evidence of trauma. The margins of the lungs were directly adjacent to the ribs with no pleural effusion or evidence of a pneumothorax. A diffuse, mild, unstructured interstitial pattern was present primarily around the carina and in the caudal lungs in the right lateral view and around the heart in the ventrodorsal view.[130] The vertebral heart score (Table 4) was 9.1 (9.2-10.2).[131] The major lobar vessels were normal in size.[47]

Table 3: Echocardiographic M-mode measurements, Day 1 (**Bold** indicates outside of reference range)[128]

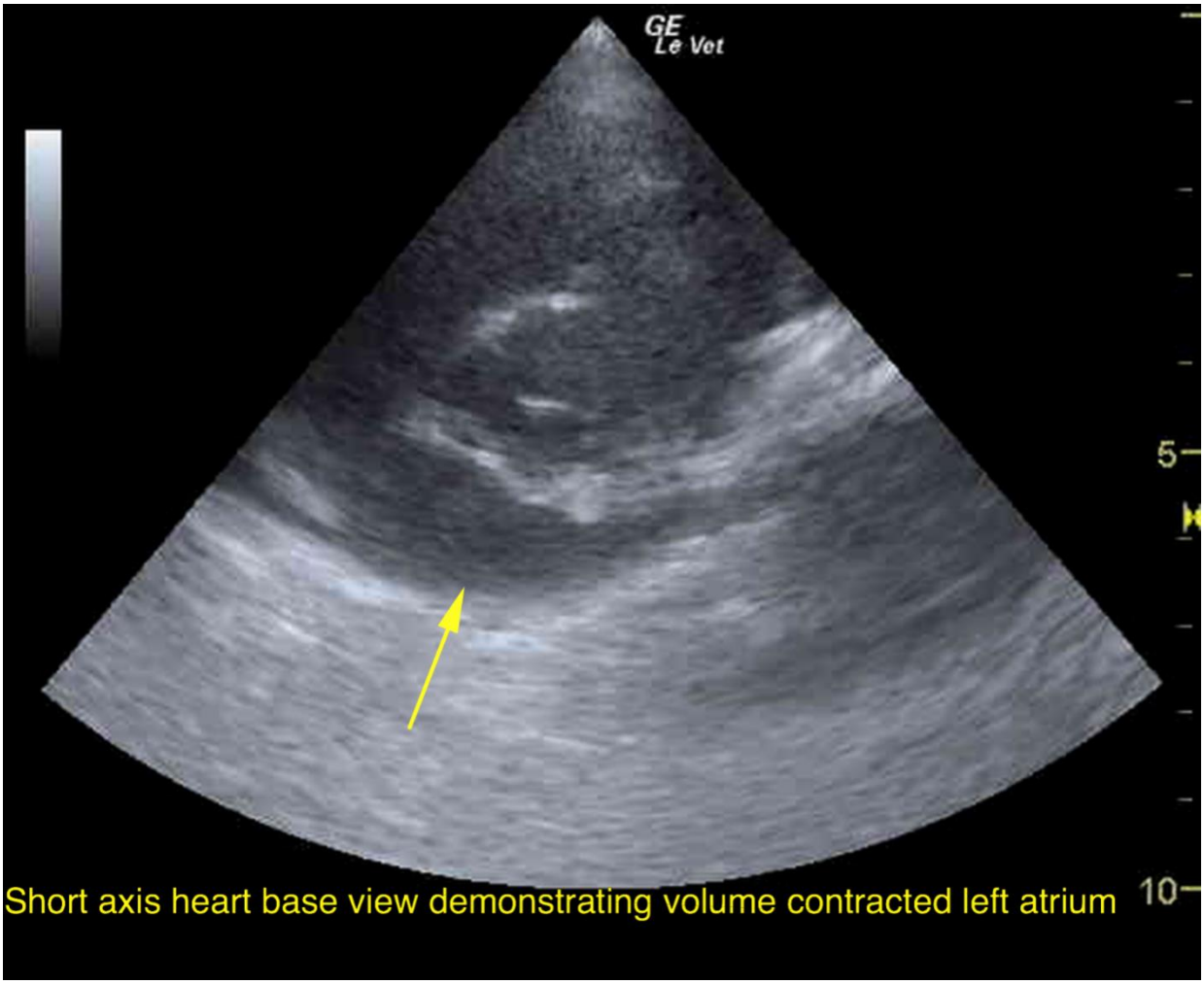
IVSd- 1.1 cm (1.01-1.12 cm)	IVSs- 1.65 cm (1.54-1.66 cm)
LVIDd- 3.4 cm (3.17-4.34 cm)	LVIDs- 2.4 cm (1.86-2.88 cm)
LVPWd- 0.85 cm (0.82-0.91 cm)	LVPWs- 1.35 cm (1.31-1.43 cm)
FS- **30%** (33-46%)	EPSS- 0.35 cm (0.03-0.77 cm)
LA- 2.2 cm (2.10-3.63 cm)	HR-115
Aorta- 2.1 cm (1.66-3.03 cm)	
LA/Aorta Ratio- 1.0 (0.8-1.3)	

Figure 3



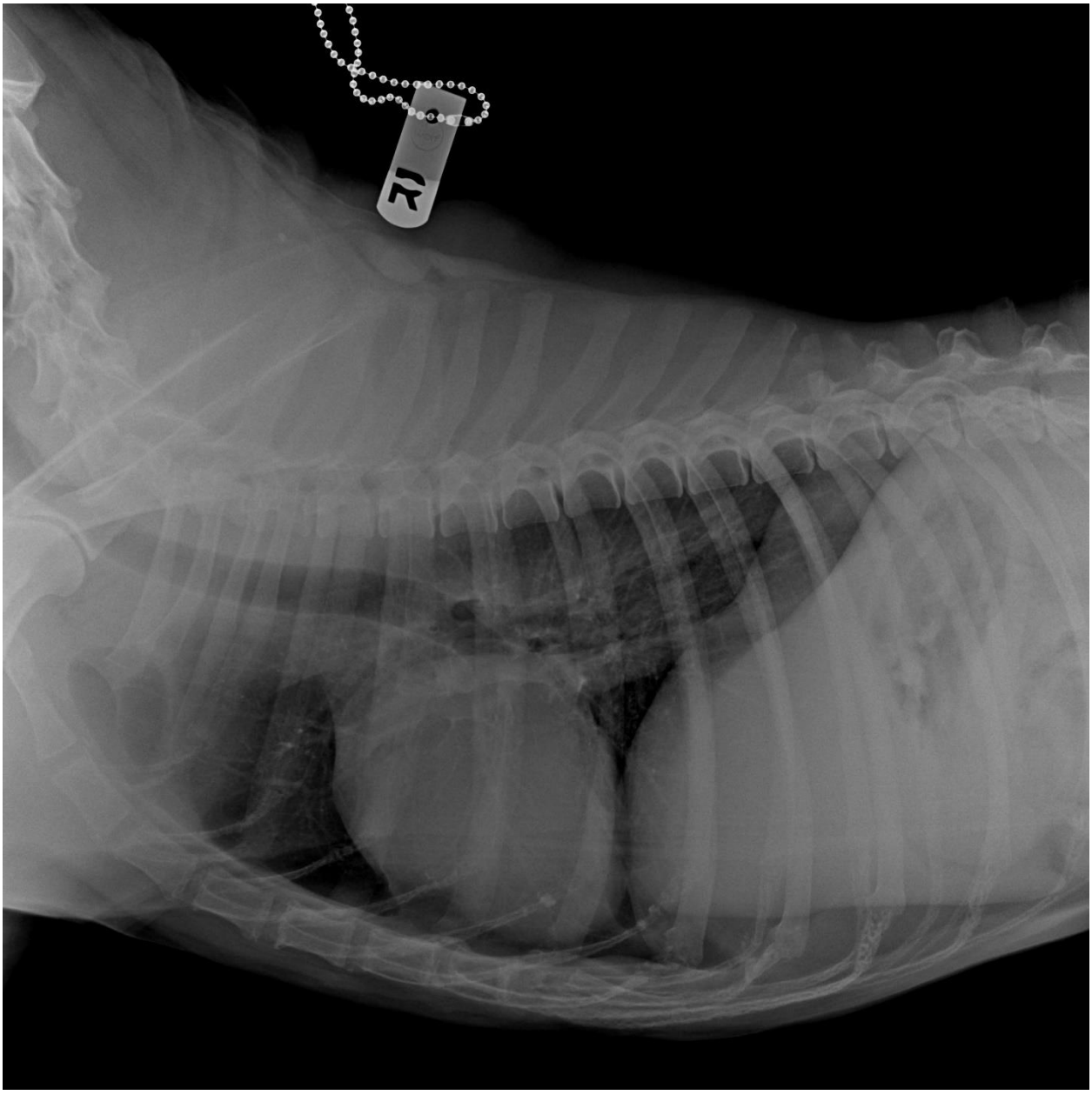
Right parasternal long axis left ventricular outflow view of the heart on Day 1.

Figure 4



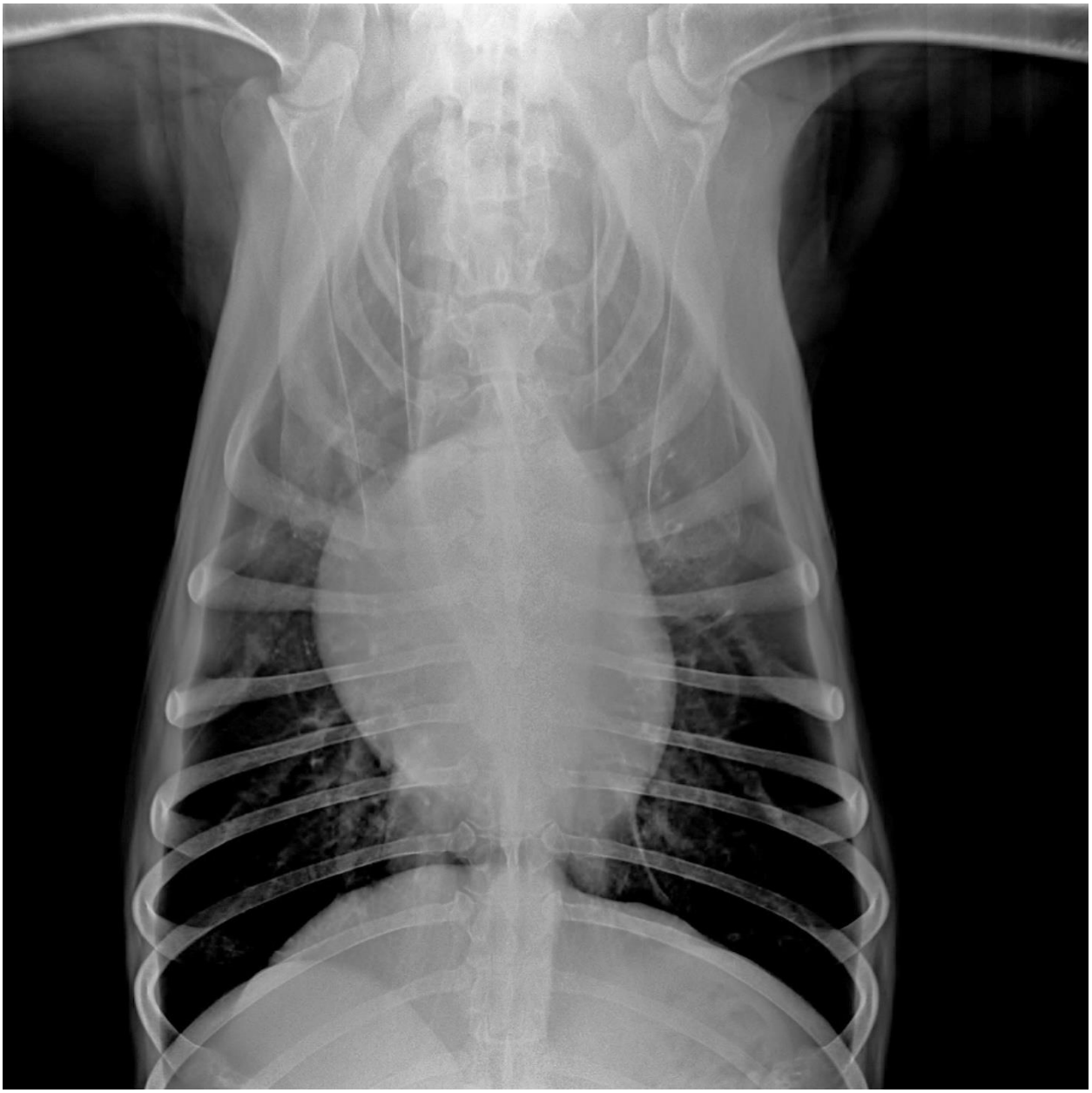
Right parasternal transverse view of the heart base on Day 1.

Figure 5



Right lateral radiographic view of the thorax on Day 1.

Figure 6



Ventrodorsal radiographic view of the thorax on Day 1.

Table 4: Vertebral Heart Score, Day 1 (**Bold** indicates outside of reference range)

Measurement	Measurement sum	Reference Range (Canine)[131]
Long axis: 5 vertebra Short axis: 4.1 vertebra	**9.1**	9.7 ± 0.5

A refined master problem list after diagnostic imaging included a flattened contour and subnormal widths of both adrenal glands; a mild diffuse, unstructured interstitial pattern in the lungs; and mild microcardia. The primary differential diagnosis for the reduced adrenal gland size was hypoadrenocorticism.[1,89,90] Possible causes of a diffuse interstitial pattern include an artifact, such as underexposure or end expiratory exposure, or pneumonitis secondary to viral, parasitic, metabolic (uremia or septicemia), inhalant or toxic insults.[130] An absolute decrease in cardiac size may occur secondary to hypovolemia, atrophic cardiomyopathies, or hypoadrenocorticism.[47] Due to the appearance of the bilateral adrenal glands, dexamethasone sodium phosphate[q] 0.2 mg/kg IV (6 mg) was administered.[3,9,93]

Approximately 90 minutes after presentation, a second venous blood sample and a sample of urine through ultrasound-guided cystocentesis were obtained for an in-house complete blood count[r] with an automated and manual differential (Table 5), chemistry panel[s] (Table 6), and urinalysis[t] (Table 7). A fecal analysis[u] following centrifugation (Table 8) was also performed after obtaining a fecal sample using a fecal loop[v]. The complete blood count was generally unremarkable with a normal white blood cell count, normal white blood cell distribution, and normal hematocrit. The hematocrit had dropped to 49.4% from 58% on the initial blood gas, electrolyte, and metabolite panel. A stress leukogram or degenerative left shift were not present. The red cell distribution width percentage was slightly elevated while the average red cell distribution width and mean corpuscular volume were normal. The platelet count was adequate with no evidence of thrombocytopenia. The manual white blood cell differential generally followed the percentages from the automated differential. Band neutrophils or intracellular bacteria were not found.

Table 5: Complete blood count, Day 1 (**Bold** indicates outside of reference range)

Analyte	Result	Reference range	Units
WBC	13.2	6.0-17.0	10^3/uL
Lymphocytes	3.0	0.9-5.0	10^3/uL
Monocytes	0.9	0.3-1.5	10^3/uL
Granulocytes	9.3	3.5-12.0	10^3/uL
Lymphocyte %	23.4		%
Monocyte %	5.6		%
Granulocyte %	71.0		%
Hematocrit	49.4	37-55	%
MCV	63.2	60.0-72.0	fl
RDWa	48.5	35.0-65.0	fl
RDW %	**19.5**	12.0-17.5	**%**
Hemoglobin	17.9	12.0-18.0	g/dl
MCHC	36.2	32.0-38.5	g/dl
MCH	22.9	19.5-25.5	pg
RBC	7.81	5.5-8.5	10^6/uL
PLT	298	200-500	10^3/uL
MPV	8.4	5.5-10.5	fl
Manual diff			
Neutrophils	69		%
Lymphocytes	25		%
Monocytes	4		%
Eosinophils	2		%
Bands	0		%
Bacteria	None		None

Table 6: Chemistry Panel, Day 1 (**Bold** indicates outside of reference range)

Analyte	Result	Reference Range	Units
BUN	**115.7**	9.0-29.0	mg/dl
Creatinine	**2.5**	0.4-1.4	mg/dl
BUN/Crea ratio	**46.2**		
Phosphorous	**14.1**	1.9-5.0	mg/dl
Calcium	**8.5**	9.0-12.2	mg/dl
Corr Calcium	10.3	9.0-12.2	mg/dl
Total Protein	**3.9**	5.5-7.6	g/dl
Albumin	**1.7**	2.5-4.0	g/dl
Globulin	2.2	2.0-3.6	g/dl
Alb/Glob ratio	0.8		
Glucose	**238**	75-125	mg/dl
Cholesterol	**61**	120-310	mg/dl
ALT	70	0-120	U/l
ALP	25	0-140	U/l
GGT	<10	0-14	U/l
Total Bilirubin	0.1	0.0-0.5	mg/dl
Sodium	**118**	141-152	mEq/l
Potassium	**6.5**	3.8-5.3	mEq/l
Chloride	**91**	102-120	mEq/l
Na/K ratio	**18**	>27	
Est Osm	283		mOsm/l

Table 7: Urinalysis, Day 1 (**Bold** indicates outside of reference range)

Urinalysis	Result	Reference Range[132]
pH	6.0	5.5-7.5
Protein	Trace	Negative
Glucose	Negative	Negative
Ketones	Negative	Negative
Blood	Negative	Negative
Bilirubin	Negative	Negative to 1+
Urobilinogen	Normal	Negative
Leukocytes	Negative	0-3
Nitrites	Negative	Negative
SG	1.035	1.015-1.050
Bacteria	None seen	None
Epi Cell	None seen	0-3
Mucus	Negative	Negative
Casts	None seen	None
Crystals	None seen	None
Urobilinogen	Negative	Negative

Table 8: Fecal analysis following centrifugation, Day 1

Test	Result	Reference Range
Microscopic analysis of a feces sample following centrifugation	Negative for parasite ova	The detection of parasite ova is consistent with parasitism. No detection of ova indicates that parasites are not present.

The chemistry panel revealed new abnormalities in addition to previously noted abnormalities on the initial blood gas, electrolyte and metabolite panel. Blood urea nitrogen (BUN) and phosphorous were elevated while the creatinine dropped from a level of 5.43 mg/dl to 2.5 mg/dl. Hypocalcemia and hypoproteinemia, including hypoalbuminemia and a low normal globulin level, were present. Hyperglycemia, as opposed to hypoglycemia on the initial panel, and hypocholesterolemia were also evident. The serum potassium level was still elevated but improved, dropping from 8.6 mEq/L on the initial panel to 6.5 mEq/L. The serum sodium level was still decreased but improved from the initial panel, increasing 3 mEq/L in 90 minutes, while the serum chloride level was slightly decreased from the initial panel. The corrected chloride level was within normal limits.[76] The estimated plasma osmolality was low but the calculated plasma osmolality was normal.[30] The sodium: potassium ratio improved to 18 but remained low. The urinalysis and urine sediment were unremarkable. The fecal analysis was negative for parasite ova.

Continued refinement of the master problem list was warranted. The primary differential diagnoses for the mildly elevated red cell distribution width percentage was anisocytosis or an artifact.[21] Elevations of BUN and creatinine, when combined with an adequately concentrated urine specific gravity on the urinalysis, were consistent with a prerenal azotemia.[124] Dehydration and shock were the primary differentials for the prerenal azotemia.[133] Prerenal azotemia seemed the most likely cause of the significant hyperphosphatemia, as the dog was fed a balanced diet with no vitamin D supplementation.[134] Excessive bone resorption could not be ruled out but seemed less likely.[134] Differential diagnoses for the decreased serum calcium level included an acute renal insult, metabolic acidosis, or hypoalbuminemia.[36,37] Other

potential causes of hypocalcemia, such as primary or secondary parathyroid gland abnormalities, hypomagnesemia, or malabsorptive gastrointestinal disease, could not be ruled out but were considered to be less probable.[37] Differential diagnoses for the hypoalbuminemia with a low normal globulin level included hypoadrenocorticism or protein-losing enteropathy while hepatic insufficiency, protein-losing nephropathy, and vasculitis were considered unlikely.[40,41,135]

The hyperglycemia was most likely caused by the intravenous administration of 50% dextrose at presentation followed by the administration of 5% dextrose solution via continuous rate infusion. Differential diagnoses for the hypocholesterolemia included anorexia while protein-losing enteropathy could not be ruled out.[136] When considered together, the probable cause of the electrolyte abnormalities was hypoadrenocorticism or acidosis while gastrointestinal disease could not be ruled out.[2-7,9] Trichuriasis was considered to be less likely based on the fecal results.

An ACTH stimulation test was performed and sent to an outside laboratory[w]. A sample of venous blood was obtained, followed by an injection of cosyntropin[x] 5 mcg/kg IV (0.15 mg), and collection of a second venous blood sample one hour after the injection of cosyntropin. After the ACTH stimulation test was finished, DOCP[y] 2 mg/kg (59 mg) IM was administered. Prednisone[z] 0.17mg/kg (5 mg) PO q24h was also prescribed and administered. A small amount of a bland diet[aa] was offered and eaten with good appetite.

Continued treatment focused on supportive care and correcting bloodwork abnormalities while monitoring vital signs. Vital signs (Table 9) were monitored hourly following the initial

Table 9: Vital signs, 2-24 hours following presentation, Day 1 (**Bold** indicates outside or reference range)

Hour	2	3	4	5	6	9	12	15	18	21	24	Normal[112,113]
Heart rate (beats/min)	120	110	120	120	120	110	**104**	**104**	**108**	112	130	110-120
Resp. rate (breaths/min)	28	30	**32**	30	**32**	**32**	**32**	30	**32**	**36**	**36**	15-30
Body temp (^{o}C)	39	38.5	38.7	38.8	38.9	38.8	38.9	38.7	38.6	38.6	38.7	37.5–39.2
MAP (mmHg)	**135**	**135**	**130**	**132**	**130**	**125**	**130**	**124**	**125**	**125**	**130**	85-120
Weight (kg)	29.9		30.2		30.0		30.3		30.2		30.2	

stabilization period. After vital signs remained stable during the initial six hours of treatment, vital signs were monitored every three hours for the first 24 hours of hospitalization. Due to the glucose level on the chemistry panel, the 5% dextrose CRI was discontinued and a 2.5% dextrose solution was made. The fluid rate was maintained at a 4.2 ml/kg/hr (124 ml/hr) rate which included the colloid CRI. The MAP rose to a maximum of 135 mmHg during the second and third hour of treatment but decreased to a range of 120-130 mmHg, slightly above the normal range of 85-120 mmHg, for the remainder of the initial 24 hours of treatment. Aside from the initial blood pressures obtained in a lateral position prior to improved mentation and mobility, the mean arterial pressures were obtained in a sitting position from the right forelimb. Possible causes of the consistent mild hypertension included excessive intravenous fluid and colloid administration, patient anxiety or stress, elevated blood pressure secondary to positioning or technique, or a combination of these.[137,138]

An ECG performed six hours after presentation confirmed a consistent heart rate of approximately 120 beats per minute, a normal sinus rhythm, and no signs of atrial standstill reoccurrence. The dog was weighed every two hours during the initial six hours of treatment to monitor for weight gain until urination was noted. A large amount of urine was produced when the dog was walked outside six hours after presentation. Weight was monitored every six hours once urination was observed and remained stable with no evidence of fluid retention. Mentation remained normal with no signs of ataxia or decreased proprioception when the dog was walked outside.

Venous blood gases, electrolytes, and select metabolites were analyzed to reassess the previous abnormalities at six and 24 hours after presentation (Table 10). The six-hour panel

Table 10: Recheck blood gas, electrolyte, and metabolite analysis, Day 1, 6 and 24 hours post presentation (**Bold** indicates outside of reference range)

Analyte	Result	Result	Reference Range	Units
	6 hours	24 hours		
pO_2	38.3	45.0	24.0-54.0	mmHg
cSO_2	66.6	82.1	40.0-90.0	%
pCO_2	37.7	35.3	30.0-47.0	mmHg
Bicarbonate	18.1	21.4	16.0-28.0	mmol/L
$cTCO_2$	19.3	22.3	18.0-28.0	mmol/L
pH	**7.289**	7.363	7.360-7.460	
BE, ECF	**-8.5**	0.6	-5.0-5.0	mmol/L
Sodium	**122**	**135**	140-151	mmol/L
Potassium	**5.5**	4.7	3.5-5.0	mmol/L
Chloride	**94**	**104**	106-127	mmol/L
Calcium, ionized	**1.08**	1.18	1.13-1.42	mmol/L
Anion gap	15.4	14.3	5-22	mmol/L
Lactate	1.78	1.52	0.6-3.0	mmol/L
Creatinine	**2.82**	**1.84**	0.4-1.5	mg/dL
Glucose	**190**	**154**	63-124	mg/dL
HCT	53	48	36-55	**%**

showed normalization of cSO_2, HCO_3^-, and TCO_2 levels. The venous pH and base excess levels were improved but still mildly decreased, indicating a continued mild acidemia and mild metabolic acidosis, respectively. The calculation of expected HCO_3^- change showed that the HCO_3^- was higher than normal which indicated the pCO_2 level was higher than normal.[26] Electrolyte abnormalities were still present, although improvement was observed in the levels of hyponatremia and hyperkalemia. The sodium level had increased 7 mEq/L in the initial six hours of fluid therapy, equal to a sodium change rate of 1.2 mEq/hr. The lactate level of 1.78 mmol/L remained within the reference range but increased from the initial value of 1.2 mmol/L. The level of hypochloremia remained the same but the corrected chloride level was normal.[76] The serum creatinine level was improved from the initial panel but similar to the chemistry panel. The ionized calcium level had also slightly improved.

The 24-hour panel showed that the serum potassium level had normalized, while serum sodium and chloride levels were still decreased but gradually improving. The sodium had increased by 20 mEq/L over 24 hours of fluid administration, or 0.8 mEq/hr. The corrected chloride remained normal.[76] The venous pH, HCO_3^- level, and base excess were within normal limits. The expected HCO_3^- level fell within the +/- 2 mEq/L margin of error.[22] The creatinine level had improved to slightly above normal limits. Mild hyperglycemia was present but the serum glucose level had decreased from the chemistry panel and the six-hour panel. The lactate level decreased from 1.78 mmol/L to 1.52 mmol/L and remained within the reference range.

On the second day of hospitalization, the dog was quiet, alert, and responsive. On physical examination, the mucous membranes were pink in color and moist with a capillary refill time of less than two seconds. Vital signs were stable with a temperature of 38.7°C (37.5°C-39.2°C), a

heart rate of 130 beats per minute (110-120 beats per minute), a respiration rate of 36 breaths per minute (15-30 breathes per minute) and a mean arterial pressure of 130 mmHg (85-120 mmHg).[112,113] A normal sinus rhythm was noted on heart auscultation. Normal inspiratory and expiratory movement of air in the lungs with no auditory crackles or wheezes continued to be present on thoracic auscultation. Abdominal palpation was soft with no palpable abnormalities. No neurologic deficits were present. A larger amount of bland diet was offered and eaten with good appetite. Normal amounts of urine were produced when the dog was walked outside**.** Since vital sign parameters remained stable with correction of fluid deficits and a consistently elevated MAP, the colloid CRI was discontinued after the full dose of 30 ml/kg/day was completed. The balanced electrolyte solution rate was reduced to 1.4 ml/kg/hr (41 ml/hr), or the previously calculated metabolic water requirement, while free choice water was offered. The 2.5% Dextrose was also discontinued since the dog was eating normally and hyperglycemia was present on the 24-hour panel. Ampicillin-sulbactam 15 mg/kg (443 mg) IV q8h was continued pending the results of the ACTH response test. Maropitant was discontinued as the dog was eating with a good appetite and drinking small amounts of water with no vomiting. Famotidine was discontinued and omeprazole[bb] 0.68 mg/kg (20 mg) PO q24h was administered. Prednisone 0.17mg/kg (5 mg) PO q24h was continued.

The ACTH response test result (Table 11) was received during the second day of hospitalization and confirmed hypoadrenocorticism. After 24 hours of treatment, the majority of the metabolic abnormalities that were diagnosed at presentation had returned to normal. The mixed metabolic and respiratory acidosis, decreased plasma osmolality, life threatening hyperkalemia and secondary cardiac arrhythmias, hypovolemia and hypovolemic shock had resolved. By

Table 11: ACTH Response Test, Day 2 (**Bold** indicates outside of reference range)

ACTH stimulation test	Serum cortisol levels	Reference Range	Units
Pre-cosyntropin	**0.2**	2-6	ug/dL
Post-cosyntropin	**0.3**	6-18	ug/dL

design, mild hyponatremia was still present along with mild hypochloremia and a slightly elevated serum creatinine. The corrected chloride was normal while the creatinine level was trending toward the normal reference range. Aside from minimal hypertension, which may be due to several factors, vital signs remained strong and consistent while neurologic, gastrointestinal, and urinary function appeared to be normal after stabilization. A definitive diagnosis of hypoadrenocorticism had been reached and treatment for the disease had been instituted. The balanced electrolyte fluid rate was maintained at the metabolic requirement rate of 1.4 ml/kg/hr while heart rate, respiration rate, temperature, mean arterial pressure and weight were evaluated every four hours (Table 12). Small amounts of a bland diet were offered every six hours with free choice water to subjectively observe intake. A regular frequency and volume of urine was produced when the dog was walked. Neither defecation nor diarrhea were observed. Ampicillin-sulbactam was discontinued.

On the third day of hospitalization, the dog remained bright, alert and responsive. Vital signs remained stable with a temperature of 38.2^{o}C (37.5^{o}C-39.2^{o}C), a heart rate of 120 beats per minute (110-120 beats per minute), a respiration rate of 42 breaths per minute (15-30 breathes per minute) and a mean arterial pressure of 120 mmHg (85-120 mmHg).[112,113] The dog continued to have a normal appetite, drink free choice water, and urinate with routine frequency. Based on its current stable clinical appearance, the dog was discharged with instructions to monitor closely at home for similar signs that were existent prior to presentation; or, although unlikely, the development of neurologic abnormalities, such as ataxia or obtundation, that may occur secondary to rapid hyponatremia correction. The previously prescribed prednisone 0.17 mg/kg (5 mg) PO q24h was sent home with the owner to

Table 12: Vital signs, 24-48 hours following presentation, Day 2 (**Bold** indicates outside of reference range)

Hour	**24**	**28**	**32**	**36**	**40**	**44**	**48**	Normal[111,112]
Heart rate (beats / min)	**130**	110	100	110	100	120	120	110-120
Resp. rate (breaths/min)	**36**	30	**32**	30	**32**	**32**	**42**	15-30
Body temp (°C)	38.7	38.6	38.5	38.4	38.4	38.2	38.2	37.5–39.2
MAP (mmHg)	**128**	**125**	**132**	**130**	**125**	**122**	120	85-120
Weight (kg)	30.2	30.1	30.0	30.0	30.1	30.1	30.1	

give as directed. Omeprazole 0.68 mg/kg (20 mg) PO q24h was also prescribed for the owner to give for seven days. The owner was directed to increase the dose of prednisone two to ten times the dose in times of stress.[2] The owner was advised that electrolyte levels will be rechecked two, three, and four weeks after discharge to determine the duration of action, dose, and dosing interval for DOCP. A follow up phone conversation with the owner on the third day following discharge indicated that the dog was doing well at home with no reported abnormalities.

The patient was examined again on days 14, 21, and 28 after discharge. Venous blood gases, electrolytes, and select metabolite panels were performed to assess electrolyte levels (Table 13). The owner reported that the dog had been doing well at home with normal appetite, water intake, urination, and defection. No signs of neurologic abnormalities were described by the owner. The owner had been giving the prescribed prednisone as directed. On the recheck panels, all parameters, except for glucose on day 14, were within normal limits. The mild hyperglycemia was most attributable to anxiety or stress, the ingestion of a recent meal, or the use of glucocorticoids.[125] The owner was advised that injections of DOCP would be required every 28 days for the remainder of the dog's life but administration intervals could vary. Periodic monitoring of electrolytes, such as prior to receiving the DOCP injection every 28 days, would be needed to monitor control of the hypoadrenocorticism and make appropriate dose changes of the DOCP. Prednisone would also be given for the remainder of the dog's life, but the dose may vary based on weight changes and during times of stress. Instructions were given to have the dog rechecked if physical abnormalities signaling the possible early effects of abnormal electrolyte levels, such as lethargy, inappetence, vomiting, or diarrhea, were

Table 13: Vital signs and recheck blood gas, electrolyte, and metabolite analysis, Day 14, 21, and 28 post DOCP (**Bold** indicates outside of reference range)

Vital sign / Analyte	Result	Result	Result	Normal[112,113] / Reference Range	Units
	Day 14	Day 21	Day 28		
Heart rate	120	116	118	110-120	Beats/min
Resp rate	28	28	26	15-30	Breaths/min
Temperature	38.6	38.8	39	37.5-39.2	^{o}C
MAP	112	108	110	85-120	mmHg
Weight	30.2	30.2	30.3		
pO_2	49.0	48.6	48.8	24.0-54.0	mmHg
cSO_2	84.5	83.9	84.3	40.0-90.0	%
pCO_2	34.2	38.4	36.9	30.0-47.0	mmHg
Bicarbonate	19.1	23.3	21.9	16.0-28.0	mmol/L
cTCO2	20.2	24.5	23.1	18.0-28.0	mmol/L
pH	7.392	7.419	7.378	7.360-7.460	
BE, ECF	3.2	2.3	0.6	-5.0-5.0	mmol/L
Sodium	148	149	144	140-151	mmol/L
Potassium	3.9	3.8	4.5	3.5-5.0	mmol/L
Chloride	124	121	116	106-127	mmol/L
Calcium, ionized	1.20	1.24	1.29	1.13-1.42	mmol/L
Anion gap	8.9	8.5	10.7	5-22	mmol/L
Lactate	1.31	1.28	1.19	0.6-3.0	mmol/L
Creatinine	1.1	0.9	1.2	0.4-1.5	mg/dL
Glucose	**132**	110	105	63-124	mg/dL
HCT	48	49	52	36-55	**%**

observed at home. The long term prognosis was considered to be good assuming that the owner was diligent in monitoring electrolytes and medication was administered as directed.

Discussion

The definitive diagnosis of primary hypoadrenocorticism in this case was made by showing an inadequate adrenal reserve with an ACTH stimulation test. At presentation, however, several signs compatible with an acute hypoadrenocortical crisis were present on physical examination and in the initial blood tests. The dog's age and sex are included in the most common demographic of dogs to be affected with hypoadrenocorticism.[2-4,6] The clinical state of the dog upon arrival, when combined with the vague, waxing and waning history provided by the owner in the week leading up to the acute presentation for lethargy, collapse and gastrointestinal signs, was highly suspicious for hypoadrenocorticism.[2-4,6] The presence of atrial standstill and bradycardia were the first indications that severe hyperkalemia was present.[42] The severe hyponatremia and hyperkalemia, with a sodium to potassium ratio of 13.4 at presentation, was considered to be a classic electrolyte irregularity seen with a mineralocorticoid deficiency.[3] The lack of a stress leukogram or lymphopenia on the complete blood count pointed to an inability of the dog to respond to stress in acute sickness and was indicative of a glucocorticoid insufficiency.[18] The presence of hypoglycemia was considered to be possibly related to inadequate glucocorticoid level, decreased gluconeogenesis and increased glycogenolysis as the owner reported a gradual decrease in appetite, not prolonged anorexia.[2]

The other physiologic and metabolic abnormalities may have been caused by numerous diseases and could not be directly associated with hypoadrenocorticism. The pattern of

diarrhea was considered to be acute and was suspected to be originating from the small intestine.[17] Based on the presence of obtundation, decreased mucous membrane color, increased capillary refill time, hypothermia, bradycardia, and weak femoral pulses, the dog was considered to be in a state of shock.[59] The clinical signs and physical exam findings indicated that hypovolemic shock or cardiogenic shock was probable while other forms of shock could not be ruled out.[58,59] At presentation, only one of the criteria for SIRS or sepsis, hypothermia, was met although the white blood cell count or the presence of band neutrophils was not known.[60]

The primary goal of fluid resuscitation at the beginning of treatment was to stabilize the dog's vital signs and reverse signs of shock despite the underlying disease process. The plan for resuscitation was to aggressively administer crystalloid and colloid fluids IV in increments while monitoring vital signs every 15 minutes until stable vital signs were present. This pattern of resuscitation was consistent with small volume intravascular resuscitation and allowed hemodynamic stability to be reached by addressing the hypotension and hypovolemia while reducing the possibility of fluid overload, such as in cases of heart failure or anuric renal failure.[61,62] A bolus of an isotonic crystalloid replacement fluid was chosen initially due to the reported chronic vomiting and diarrhea over the last week, which may result in electrolyte abnormalities such as hypochloremia, hyponatremia and potential alkalosis due to loss of hydrogen ions in gastric fluids.[29] The initial dose of the isotonic crystalloid replacement fluid was 22.5 ml/kg IV over the initial 15 minutes of treatment, which approximates to one quarter of a 90 ml/kg shock dose of fluids based on canine blood volume.[2,4,62] A bolus of a low molecular weight tetrastarch, equivalent to one quarter of the recommended daily dose, was

also administered over 15 minutes. The purpose of administering this low molecular weight synthetic colloid was to increase intravascular volume through an increase in colloid oncotic pressure, improving microcirculation, and reducing the possibility of reperfusion injury while decreasing the amount of crystalloids that would need to be administered to accomplish the same effects on perfusion and blood pressure.[4,62]

A blood gas, electrolyte, and metabolite analysis, as opposed to a standard complete blood count and chemistry panel, was chosen as the initial blood panel for several reasons. First, the panel may be run on a small amount of whole blood, an important factor in patients with hypovolemia, hypotension or dehydration where venous access may be difficult or the intravascular volume is reduced. Secondly, the results of the panel are available within minutes, allowing rapid assessment of physiologic or metabolic abnormalities in a critically ill patient. Thirdly, the panel includes blood gas values and venous pH that enable the assessment of acid-base status, as well as electrolyte, glucose and hematocrit levels which are included on a complete blood count and chemistry panel. This information is valuable when choosing the correct fluid for resuscitation since a large amount of the fluid may be administered rapidly in the beginning of treatment, potentially exacerbating abnormalities if the incorrect fluid is used; it also provides a baseline to monitor acid-base status during treatment.

An acidemia was present on the initial panel.[26] The decreased HCO_3^- and TCO_2 levels were consistent with a metabolic acidosis.[26,27] The negative base excess in the extracellular fluid was also compatible with a metabolic acidosis.[74] It was determined that a respiratory acidosis was present as well by considering the carbonic acid-bicarbonate equation (Henderson-Hasselbach equation) and the calculation of the expected bicarbonate level in the venous blood in acute

conditions.[26] The expected HCO_3^- level on the initial panel equaled 23 mEq/L. This value was higher than the measured HCO_3^-, indicating that the measured pCO_2 level was higher than would be expected. Therefore, the decreased venous pH of the dog was secondary to a mixed metabolic and respiratory acidosis. The effect of the mixed metabolic and respiratory acidosis on blood pH was additive.[73]

Calculations of the plasma osmolality, measured and adjusted anion gap, and corrected chloride concentrations were reviewed during treatment to further classify the acidosis, refine the master problem list, and monitor recovery. Although the blood urea nitrogen was not known at the time of the initial blood panel, plasma osmolality was most likely low or normal due to the degree of hyponatremia (the value in the formula corresponding to sodium would equal 230) with negligible influence of glucose on osmolality (the value in the formula corresponding to glucose would equal 1.8).[30] In other words, blood urea nitrogen elevation would need to exceed 140 mg/dL to reach the normal osmolality range in dogs. The suspected low osmolality with decreases in impermeant solutes (sodium and glucose) suggested that water had moved from the extracellular space to the intracellular space, resulting in hypovolemia.[30]

The anion gap was normal and consistent with a normal anion gap acidosis. However, the normal anion gap insinuated that the chloride level was higher than measured because the HCO_3^- level was low.[26,77] The corrected serum chloride concentration on the initial panel was elevated at 119 mEq/L (107-113 mEq/L)**.**[76] The corrected hyperchloremia was associated with a hyperchloremic acidosis and was most likely secondary to either small bowel diarrhea, renal failure or renal tubular acidosis, or hypoadrenocorticism.[76] The corrected hyperchloremia also

indicated that the calculated anion gap may be inaccurate although the albumin concentration was not known. Lastly, the corrected hyperchloremia was compatible with decreased plasma free water and hypovolemia.[76] Therefore, hypovolemic shock secondary to hypoadrenocorticism seemed probable although other forms of shock, gastrointestinal disease, and renal failure could not be ruled out.

For the immediate treatment of the severe hyperkalemia, particularly the cardiotoxic effects of hyperkalemia, and hypoglycemia, several medications were used even though intravenous fluid therapy would help eliminate excess serum potassium through increased renal perfusion.[2] The dose of 10% calcium gluconate was administered to reestablish the normal gradient between the resting membrane potential and threshold potentials, allowing normal cardiac conduction.[2] Regular insulin was administered to promote simultaneous movement of glucose and potassium into cells and, therefore, out of circulation, via stimulation of sodium-potassium adenosine triphosphate pumps.[2,6] Following the injection of insulin, a diluted dose of 50% dextrose was given to treat the current hypoglycemia, counter the effects of administered insulin on serum glucose and stimulate the release of further insulin from the pancreas.[2,3]

It was not known if the hyponatremia was acute or chronic, or if the clinical signs at presentation were due to neurologic side effects of severe hyponatremia, such as brain edema secondary to decreased serum osmolality. Due to potential permanent neurologic abnormalities that may occur if the serum sodium level is corrected too quickly, leading to a sudden loss of water in the brain and secondary demyelination of nerve cells, gradual correction of the hyponatremia was needed. The maximum desired correction rate of severe hyponatremia was regarded to be 12 mEq/24 hours/day or 0.5 mEq/hr.[2,25,33] However, since

the current clinical signs were possibly caused by hyponatremia, initial correction at a 1-2 mEq/L rate was used to achieve an increased, but not fully corrected, sodium level, aiming for a serum sodium increase to approximately 120 mEq/L.[2,30]

The isotonic crystalloid replacement fluid, which contains 154 mEq/L of sodium, would result in a 2 mEq/L increase in serum sodium.[62,105] The initial 22.5 ml/kg bolus equaled 660 ml of fluid administered, or 1.3 mEq of expected sodium increase. The isotonic crystalloid replacement fluid permitted the relatively rapid but minor increase in the serum sodium level to treat potential neurologic signs associated with the hyponatremia. However, the more critical, long term concern associated with the hyponatremia was the correction rate over the first 24 hours of treatment and the potential for myelinolysis.[9,103]

Once the bolus of the isotonic crystalloid fluid was finished, a balanced electrolyte fluid, which contains 130 mEq/L of sodium, was given to reduce the rate of expected sodium change to avoid myelinolysis.[62] The change in serum sodium using this fluid was expected to be 0.8 mEq/L, a much slower and safer rate of correction.[105] A fluid rate of 4.2 ml/kg/hr was calculated based on daily fluid requirements, replacement of hypovolemia and dehydration, and countering potential ongoing fluid loss with vomiting or diarrhea through the use of crystalloids and colloids. The calculated metabolic fluid requirement would equal 955 mls day/24 hours/day or approximately 40 ml/hr.[62] Additionally, decreased plasma water and ongoing losses through continued vomiting or diarrhea, which were estimated to be a combined 10% deficit, were calculated to be a total of 2950 mls.[62] After subtracting the initial bolus of the isotonic crystalloid from the deficit, the total fluid deficit and potential ongoing fluid loss was considered to be 2286 mls to be corrected over 23 hours, or 99 ml/hr.

The tetrastarch colloid was continued as CRI for the continued treatment of hypoperfusion by minimizing the extravasation of the infused fluid into the extracellular space.[62] This rate of administration was determined based on a dose of 30 ml/kg/day for the particular colloid which was used and equaled 25 ml/hr. This dose was higher than the 20 ml/kg/day dose commonly listed in veterinary formularies but was lower than reported maximum safe dose reported in human case studies.[63,67] The type of colloid was chosen to provide continued intravascular volume expansion while minimizing the risk of kidney injury, coagulopathy, or increased tissue storage.[67] The calculated balanced electrolyte solution rate was decreased by 39 ml/hr, or approximately 28% of the calculated rate, to compensate for the added volume, oncotic pressure and increased intravascular volume provided by the colloid and to avoid potential fluid overload. At a rate of 100 ml/hr, a liter of the balanced electrolyte solution would be administered every 10 hours, thereby administering 0.08 mEq/hr of sodium for the slow correction of the hyponatremia. The tetrastarch colloid, which contains 154 mEq/L of sodium in a 500 ml bag at a rate of 25 ml/hr, would cause an expected 2 mEq/L, or 0.1 mEq/hr, increase in sodium.[105] When combined, the expected sodium increase from the balanced electrolyte solution and colloid would equal 0.18 mEq/hr, a rate well below the recommended 0.5 mEq/hr rate of sodium correction to avoid myelinolysis.[25,33]

Other medications that were used included antibiotics, antinausea, and antacid medications. Ampicillin-sulbactam was chosen as a prophylactic injectable antibiotic due to possible gastrointestinal disease and its effects against a variety of aerobic and anaerobic bacteria, particularly Clostridium perfringens.[100,101] Maropitant was administered for potential nausea due to its effective central and peripheral inhibition of Substance P, as the primary cause of

vomiting was not known.[99] Famotidine, a histamine H2-receptor antagonist, was the only injectable antacid available at presentation and was administered to reduce gastrointestinal acid production in the event of ulceration secondary to hypoperfusion.[2,7,96]

Sodium bicarbonate was not given for treatment of the acidemia even though the venous pH was less than 7.2. The bicarbonate level was only slightly below normal parameters while the bicarbonate deficit was calculated at a minimal 3 mEq/L. In addition, the administration of bicarbonate, which is converted to carbon dioxide as described by the Henderson-Hasselbach equation, may lead to increased respiratory acidosis in dogs with underlying pulmonary disease, respiratory depression or cardiac arrhythmias, all of which could not be ruled out as causes of the clinical and physiologic abnormalities.[73,95]

Within the first hour of presentation, the severe changes in the ECG were resolved and the vital signs were stabilized with appropriate treatment of the hyperkalemia and fluid therapy. The body temperature remained slightly below normal limits but was trending upward, likely due to increased perfusion. Mild tachycardia was present, which was attributed to increased perfusion, increased consciousness and possible mild anxiety.[137] The MAP was slightly elevated secondary to intravascular volume expansion or mild anxiety.[137,138]

Ultrasonography was the first imaging modality used because of its high sensitivity and specificity to detect trauma or disease in the thoracic and abdominal cavities in the critical patient that may not be detected on radiographs.[78] No signs of trauma or effusion were found. Ultrasonographic signs of hepatic neoplasia or parenchymal disease, such as focal or diffuse masses or nodules, changes in parenchymal echogenicity, irregular serosal contour, were not

evident.[79] The hepatic vasculature was non-dilated in appearance and was not suggestive of congestion secondary to right heart disease.[79] Changes to the gastrointestinal tract which may indicate inflammatory or infiltrative disease, such as alterations in normal gastric or intestinal wall layering and thickness, or disruption of normal wall delineation, were not present.[80,81] The lumen of the stomach and small intestines were empty with no signs of an obstructive pattern or fluid stasis which may indicate metabolic or mechanical ileus.[80,81] The appearance of the kidneys was not consistent with chronic renal disease while acute renal disease could not be ruled out.[85] The subnormal width and flattened contour of the adrenal glands was suggestive of destruction of the zona glomerulosa and zona fasciculata, resulting in inadequate production of glucocorticoid and mineralocorticoid hormones.[1,89,90]

The purpose of the echocardiogram was to evaluate the appearance and functionality of the heart while the thoracic ultrasound was used to assess the pleural space for effusion or signs of trauma.[78] In particular, the echocardiogram was used to assess the size of the left atrium and left ventricle for signs of chamber enlargement, overall size of the right atrium and ventricle, contractility of the left heart, and examine the heart for the presence of pericardial effusion. The size of the left atrium was normal for the dog's body weight with a left atrium to aorta ratio of approximately 1:1 despite aggressive fluid therapy, a suspected indication of previous or resolving decreased preload secondary to hypovolemia.[86,87] The fractional shortening was mildly decreased but was not consistent with systolic dysfunction or myocardial failure. The cardiac hypocontractility was most attributable to a decreased preload secondary to hypovolemia.[87]

The size and appearance of the right atrium and ventricle were not compatible with right heart

disease or elevated pressure, a finding which correlated with the normal hepatic veins and caudal vena cava width on the abdominal ultrasound.[79,86] Overall, the echocardiographic interpretation of chamber size and cardiac functionality, as well as the ultrasonographic evaluation of the thoracic space, was sufficient to determine that pericardial effusion or cardiac based neoplasia was not the primary cause of hypotension, hypoperfusion, and shock while primary cardiac disease was considered less likely.

Thoracic radiographs were taken to assess the internal lungs for signs of pulmonary disease or thoracic trauma while also correlating the radiographic cardiac size with the ultrasonographic interpretation of cardiac function. The subnormal vertebral heart score was consistent with the ultrasonographic interpretation of heart size and consistent with hypovolemia.[131] The normal appearance of the major lobar vessels was also suggestive that the presence of cardiac disease was less likely.[47] At the time of the radiographs, the cause of the unstructured interstitial pattern in the lungs was unknown and lower airway disease could not be ruled out. During the course of treatment, no signs of dyspnea, coughing, or abnormal lung sounds on thoracic auscultation were noted. While other causes could not be ruled out, the interstitial pattern was thought to be secondary to an artifact or mild uremic pneumonitis once the diagnosis of hypoadrenocorticism was made.[130] Additional thoracic radiographs were not taken as no clinical signs of lower airway disease were documented while mild inflammation secondary to uremia would likely resolve once the treatment for hypoadrenocorticism was successful.

After visualization of the small and flattened adrenal glands on ultrasound, in combination with the electrolyte and metabolite abnormalities, lack of significant or obvious pathology in other abdominal and thoracic organs, and response to treatment, hypoadrenocorticism was

considered the primary differential diagnosis. Dexamethasone sodium phosphate was given to provide glucocorticoid support.[2] The initial dose of dexamethasone was chosen as glucocorticoid therapy is generally instituted at two to ten times the physiologic prednisone requirements in dogs with an acute hypoadrenocortical crisis.[25] The physiologic dose of prednisone is generally regarded as 0.1-0.2 mg/kg/day.[2] The initial dose of dexamethasone provided the equivalent of at least 1.6 mg/kg of prednisone, or at least eight times the physiologic dose of prednisone for the dog. With a biological half-life of 48 hours, dexamethasone would provide adequate glucocorticoid activity in the dog for at least two days but would not provide long-lasting glucocorticoid effects if hypoadrenocorticism was not present.[93]

The complete blood count, chemistry panel, urinalysis and fecal analysis provided further information that hypoadrenocorticism was the primary differential diagnosis. The dog did not have a stress leukogram on the complete blood count. The lymphocyte numbers were perceived to be higher than normal in a state of illness or stress, while, in a healthy dog during stress, cortisol release will cause lymphocyte numbers to drop.[18] The lymphocyte count was 3.0 x 10^3/uL in the critically ill dog, a higher value than the reported 2.0 x 10^3 /uL in sick or stressed dogs which had a high specificity (85%) for the presence of hypoadrenocorticism.[18] The red cell distribution width percentage, which describes the size range percentage of red blood cells and may be increased in cases of anemia, was slightly elevated.[21] This elevated value was considered artifactual since the average red cell distribution width and mean corpuscular volume were within normal limits with no signs of anemia.[21] A degenerative left shift was not present and, combined with the previously mentioned criteria for the presence of a systemic

inflammatory response or sepsis, indicated that sepsis was not present.[60]

The diagnosis of prerenal azotemia, combined with the lack of acute or chronic renal abnormalities on ultrasound and normal urine production, was not indicative of anuric, acute or chronic renal failure as the primary cause of the electrolyte and metabolite abnormalities.[124] Gastrointestinal ulceration or bleeding was not considered likely due to the ultrasonographic appearance of the stomach and small intestine. When combined with the normal appearance of the liver on ultrasound, the unremarkable liver enzymes indicated that hepatic disease or insufficiency was unlikely. Peripheral edema, petechia, or cavitary effusion was not evident on physical or ultrasonographic examination, implying that vasculitis as a cause of hypoalbuminemia was not likely.[41] A trace amount of protein was present in the urine but significant proteinuria, which may indicate protein-losing nephropathy, was not found.[40] Protein-losing enteropathy could not be ruled out but was considered less likely due to the unremarkable ultrasonographic appearance of the small intestine.[82]

The estimated plasma osmolality on the chemistry panel was decreased at 283 mOsm/L. Now that the BUN level was known, the calculated plasma osmolality using the aforementioned formula was 290.5 mOsm/kg.[30] The calculated plasma osmolality value was consistent with a low normal plasma osmolality (290-310 mOsm/kg) but was higher than the estimated plasma osmolality provided by the chemistry panel.[30] This discrepancy indicated that plasma osmolality was initially low. The primary differential diagnosis for a hypovolemic, hypoosmolar hyponatremia is hypoadrenocorticism although gastrointestinal disease could not be ruled out.[30]

The hypoalbuminemia seemed the most likely cause of the decreased serum calcium level as the corrected calcium was within normal limits.[37] Other potential causes, such as primary or secondary parathyroid gland abnormalities, hypomagnesemia, or malabsorptive gastrointestinal disease, could not be ruled out but were considered less likely.[37] Using the initial panel and the previously mentioned formula for anion gap adjustment for albumin, the adjusted anion gap equaled 20.3.[77] The adjusted anion gap increased in value but remained within the accepted parameters. The primary differential diagnosis for the increased adjusted anion gap was uremia.[77] The hyperglycemia was most likely the result of the intravenous administration of 50% dextrose at presentation followed by the administration of the 5% dextrose solution via continuous rate infusion. Anorexia secondary to hypoadrenocorticism was the suspected cause of the hypocholesterolemia while a protein losing enteropathy was considered less likely.

The serum sodium level was still decreased but improved from the initial panel, while the serum chloride level was slightly decreased from the initial panel. The 3 mEq/L increase in sodium level, equal to a 2 mEq/hr rate of sodium administration, between the initial panel and the chemistry panel was higher than the desired 0.5 mEq/hr rate of sodium increase. This increase was considered to be acceptable for the initial treatment period when treatment of the level of hyponatremia was needed and considering the isotonic crystalloid fluid that was used. A slower, long term rate of sodium correction was expected with the change in fluids to the balanced electrolyte solution combined with the tetrastarch CRI.

The corrected serum chloride concentration was 112 mEq/L (107-113 mEq/L in dogs), a decrease in value from the initial corrected chloride of 119 and indicative of acidosis and

hypovolemia correction.[76] The serum potassium level was still elevated but much improved as the result of both fluid and medical therapy. Additional regular insulin administration was not elected as the ECG changes had resolved while continued dilution of serum potassium, elimination through increased renal perfusion, and correction of acidosis would continue to decrease the serum potassium level without medical treatment.[2,4,6] Fecal analysis was negative for whipworm ova which, in large numbers, may cause pseudohypoadrenocorticism.[3] Therefore, hypoadrenocorticism, marked but resolving hypovolemia, and acidosis were the most likely causes of the improving hyperkalemia.[2,25]

Due to the high suspicion of hypoadrenocorticism and the designation of other potential diseases as not present or unlikely, an ACTH stimulation test was performed to confirm the preliminary diagnosis of hypoadrenocorticism. Cosyntropin should stimulate the release of cortisol in healthy animals, whereas, in cases of hypoadrenocorticism, stimulation will not work and both samples of blood will contain low levels of cortisol.[44] Once the ACTH stimulation test was completed, treatment for hypoadrenocorticism with injectable DOCP and oral prednisone was elected without a definitive diagnosis of adrenal insufficiency.

The administration of desoxycorticosterone pivalate at this stage of treatment was controversial for several reasons. Some, if not most, clinicians advocate the use of a mineralocorticoid only when the patient has recovered and electrolytes have normalized.[2] This recommendation is based on two primary concepts: since DOCP may only be given SQ or IM, normal perfusion parameters are needed to ensure the injection is appropriately absorbed, and the administration of DOCP in cases of profound hyponatremia may contribute to an increased rate of sodium correction and, thus, myelinolysis and the associated neurologic abnormalities.[2]

Lastly, there have been no objective, evidence based studies that prove an advantage to using a mineralocorticoid during a hypoadrenocortical crisis.[2] In contrast, studies have shown that high doses of DOCP given to healthy dogs is not harmful, and there is no medical disadvantage to giving DOCP during a hypoadrenocortical crisis.[108.109] In this case, perfusion parameters were stabilized within one hour of treatment and remained stable through the initial 24 hours of treatment. Therefore, adequate absorption of the DOCP was probable. The most important factor in minimizing the degree of sodium correction is the choice and rate of administration of fluids in the initial 24 hours of treatment, as indicated in experimental studies in dogs and clinical experience in human beings.[9,103] Since DOCP is formulated as a microcrystalline depot, its absorption is slow which allows it to provide mineralocorticoid effects for approximately 25 days.[106] Therefore, the effect of DOCP on the sodium level is likely minimal in the initial 24 hours after administration. An oral, physiologic dose of prednisone was started since the dog was eating.[2,4,34]

The blood panels performed at six and 24 hours after presentation showed expected resolution of blood gas, electrolyte and metabolite abnormalities, primarily through fluid therapy, that occur secondary to hypoadrenocorticism. The calculated expected bicarbonate level on the six-hour panel equaled 22.4 mEq/L.[26] This value remained higher than the measured bicarbonate, indicating that the pCO_2 level was still elevated and respiratory acidosis was still present. However, the difference between the measured and expected bicarbonate from the initial panel and six-hour panel decreased, suggesting that the respiratory acidosis was resolving.

The calculated expected bicarbonate level on the 24-hour panel equaled 22.1 mEq/L.[26] This value was similar to the measured bicarbonate and fell within the +/- 2 mEq/L margin of error.

The normal venous pH and the normal expected bicarbonate change after 24 hours indicated that the mixed metabolic and respiratory acidosis had resolved.

Resolution of the acidosis was also supported through the calculation of corrected chloride levels. On the six-hour panel, the corrected serum chloride concentration was 112.5 mEq/L (107-113 mEq/L in dogs), a value similar to the corrected normal chloride value on the chemistry panel.[76] On the 24-hour panel, the corrected serum chloride concentration was 112.4 mEq/L (107-113 mEq/L in dogs), similar to previous calculations and compatible with resolving acidosis and hypovolemia.[76]

Persistent hyperglycemia was present but the degree of hyperglycemia decreased between the panels. This was attributed to decreased dextrose supplementation, intake of food, or stress. The decreased creatinine level, increased ionized calcium level, and resolving hyperkalemia were attributed to increased renal perfusion and correction of acidosis.[2,9] Since the acidosis resolved with fluid therapy and normal respiration, the metabolic component of the acidosis was attributed to hypoperfusion and secondary renal tubular or lactic acidosis, while the respiratory component of the acidosis was attributed to hypoventilation and increased carbon dioxide retention.[9,26]

The lactate levels were normal on the blood gas, electrolyte, and metabolite panels run in the hospital. This indicated that significant tissue hypoxia secondary to hypoperfusion had not occurred prior to presentation and during treatment.[70] However, the lactate level increased between the initial panel and the six-hour panel despite fluid therapy but decreased between the six and 24-hour panel. Although other causes of increased lactate production exist, the

initial increase in lactate suggested that emerging tissue hypoxia was possibly present in the initial stages of assessment and treatment and volume resuscitation helped resolve a developing hyperlactemia. Most importantly, the lactate trend indicated that tissue perfusion was adequate and implied that the prognosis was good.[70,72]

The rate of sodium correction was a principal concern on the monitoring panels. The serum sodium level increased 7 mEq/L in the initial six hours of fluid therapy, equal to a sodium change rate of 1.2 mEq/hr. Although this rate was higher than 0.5 mEq/hr, the rate of sodium change had decreased by 60% from the initial rate of 3 mEq/hr calculated from the chemistry panel. The serum sodium had risen to a level greater than 120 mEq/L and eliminated possible clinical signs secondary to hyponatremia.[30] However, the rate of sodium increase over the initial 24 hours of treatment was 0.8 mEq/hr, higher than both the accepted maximum sodium correction rate of 0.5 mEq/hr to avoid myelinolysis and the expected sodium increase of 0.18 mEq/hr based on the fluids used and rate of administration following the initial bolus. This was most likely due to increased renal perfusion, increased potassium excretion and increased sodium resorption via sodium-potassium adenosine triphosphate pumps in the renal tubules.[2,9] It is possible that the administration of DOCP prior to electrolyte normalization may have caused a minor increase in the expected rate of sodium correction.

The ACTH stimulation test demonstrated a lack of adrenal hormone reserve and was consistent with hypoadrenocorticism.[44] The type of hypoadrenocorticism was considered to be primary typical hypoadrenocorticism as both mineralocorticoid deficits, indicated by the hyperkalemia and hyponatremia, and glucocorticoid deficits, indicated by the abnormal ACTH response test, were present.[4,6] The lack of response to cosyntropin was consistent with the destruction of the

zona glomerulosa and zona fasciculata of the adrenal glands, resulting in the subnormal width and flattened contour of the glands noted on the ultrasound.[1,89]

Once the definitive diagnosis of hypoadrenocorticism was known, in conjunction with the correction of hypovolemia and dehydration, correction of most of the irregularities that were present on the initial blood panel, and the overall improved to normal physical appearance of the dog, the treatment plan focused on providing only the metabolic fluid requirement along with free choice water and food. The ability of the dog to maintain its current clinical state was observed. This was also done with the knowledge that sodium, chloride and creatinine, the remaining atypical analytes, would return to normal with continued but reduced intravenous fluid therapy and previously administered medications while the corrected irregularities would remain so. Ampicillin-sulbactam was discontinued as signs of gastrointestinal disease or bacterial translocation from the gastrointestinal tract had not been seen. Maropitant was discontinued as a normal appetite with no vomiting was present. Famotidine was discontinued in favor of oral omeprazole in order to more effectively increase gastric pH and treat potential gastric ulceration.[97,98] After 48 hours of treatment, the dog was clinically stable with a regular appetite and water intake. This complete recovery time from the hypoadrenocortical crisis was consistent with recovery times reported in the literature.[7,34,94] The decision to discharge the dog after 48 hours of treatment was based on the signs of a complete recovery and the apparent ability to maintain clinical stability without supportive care.

The monitoring protocol, which called for electrolyte rechecks at two, three, and four weeks after DOCP administration, allowed confirmation that electrolyte levels had returned to normal limits within two weeks, and likely much sooner, of DOCP administration. Recheck electrolytes

at three and four weeks after discharge showed adequate control of the hypoadrenocorticism. The potassium level appeared to be increasing while the sodium level appeared to be decreasing between days 21 and 28. This indicated that, although sodium and potassium levels were still within the reference range, a dosing interval of 25 days may be more appropriate.

DOCP was favored over fludrocortisone for the chronic treatment of the hypoadrenocorticism for several reasons. DOCP is given by injection every 21-30 days depending on response and electrolyte monitoring.[106] Although the initial dose of DOCP was 2.2 mg/kg IM, studies have shown that lower doses of DOCP may potentially be effective in controlling primary hypoadrenocorticism, thereby reducing cost for the owner.[107] Side effects with DOCP alone are rare as it only provides mineralocorticoid supplementation while the amount of supplemented glucocorticoid may be tapered to the lowest effective dose.[2] In contrast, fludrocortisone must be given orally every day which requires more owner compliance.[111] Other studies indicated that the dose of fludrocortisone increased over time, resulting in increased costs to the owner.[110] Since fludrocortisone has both glucocorticoid and mineralocorticoid properties, increasing the dose of fludrocortisone may cause adverse side effects commonly seen with iatrogenic hyperadrenocorticism.[2,110] If these signs are seen, lowering the dose of fludrocortisone may lead to poor mineralocorticoid control.[2] In some studies, dogs receiving fludrocortisone were switched to DOCP due to poor response, adverse effects, or cost.[2,7,110] Finally, plasma renin levels were significantly lower in dogs treated with DOCP than those treated with fludrocortisone, suggesting that DOCP may be a superior mineralocorticoid supplement compared to fludrocortisone.[2,57]

Owner education was critical once the dog recovered from the initial crisis. The owner

understood that lifelong therapy would be required and was advised of the potential costs associated with monitoring and treatment. The owner was informed of potential side effects, or signs associated with iatrogenic hyperadrenocorticism, which may occur with treatment. Most importantly, the owner understood that the dog could not respond to stress appropriately so they must anticipate the stress and increase glucocorticoids by two to ten times the dose in preparation.[2] The owner was taught to recognize subtle symptoms of inadequate control and signs of a hypoadrenocortical crisis so that they may seek veterinary care if these signs occurred.[2]

Several flaws or controversies in the management of this case are recognized. Electrolyte monitoring during hospitalization should have been done with greater frequency than six and 24 hours after the initial panel. Routine monitoring of electrolytes would have allowed better assessment of the clinical status of the dog and evaluation of the rate of sodium correction. The elevated rate of sodium correction may have been avoided through the manipulation of the fluid administration rate if the sodium concentrations were more closely analyzed. Additionally, closer monitoring of glucose levels should have been a priority following the administration of insulin and dextrose in the treatment of the hyperkalemia.

Traditionally, a right lateral and ventrodorsal or dorsoventral view of the thoracic cavity was considered to be adequate to assess the structures within the thoracic cavity. In recent times, three-view thoracic radiographs have arguably become the accepted standard of care, especially with digital radiography where the cost of additional views is minimal. In this case, the right lateral and ventrodorsal views permitted adequate visualization and interpretation of the lung parenchyma, cardiac size, pulmonary vasculature, and mediastinum. However, an

additional left lateral view, or even a dorsoventral view in combination with the ventrodorsal view, should have been taken to provide the most comprehensive study of the thoracic cavity.

The use of colloids in this case is controversial for several reasons. First, the continuous rate infusion of the colloid over 24 hours was not likely needed following the initial boluses of colloid during the initial resuscitation. Since the underlying disease process was not immediately known, the continuous rate infusion was initially chosen to reduce the amount of crystalloid that would need to be administered to achieve the same level of hemodynamic stability without potential fluid overload, such as in cases of heart failure or anuric renal failure. Once these diseases were eliminated and vital signs began to normalize, the continuous rate colloid infusion was not necessary. The dose of the colloid was higher than the dose listed in veterinary formularies. This dose was extrapolated from human studies and was chosen due to the lower molecular weight and shorter duration of action than higher molecular weight colloids.[67] Despite this information, the use of colloids at a higher dose increases the risk of potential adverse side effects such as coagulopathies or acute renal injury as reported in human literature.[62,64,65] Thirdly, even though the rate of colloid administration was low, the 154 mEq/L of sodium in the colloid solution yielded a higher rate of sodium correction than the balanced electrolyte solution. It is also feasible that the increased oncotic pressure and expanded intravascular volume provided by the colloid had some influence on a higher sodium-potassium exchange within the kidney. Both of these factors may have led to the elevated sodium exchange rate that was seen after 24 hours of treatment. Although other factors were possible, the continuous colloid administration may have contributed to the mildly elevated mean arterial blood pressure in the initial 24 hours of treatment. Notably, the mean arterial blood

pressure dropped once the colloid infusion was discontinued. The use of pressor medications may have been considered during the initial treatment of hypertension to avoid possible side effects associated with the use of colloids.

Summary

A dog presented in hypovolemic shock with cardiovascular compromise. Initial tests revealed severe electrolyte abnormalities, a mixed metabolic and respiratory acidosis, and hematological signs which were highly suggestive of an Addisonian crisis. A definitive diagnosis of primary hypoadrenocorticism was based on the low resting serum cortisol concentration combined with a subnormal or negligible response to exogenous ACTH administration. Through aggressive fluid therapy and medical treatment, the dog recovered in two days. Although the dog would require medical therapy and increased glucocorticoids in times of stress, the prognosis for a normal life expectancy was good with proper monitoring and owner compliance.

Endnotes

a. Cardell Veterinary Monitor 9500 HD, Midmark Animal Health, Versailles, OH

b. 18-gauge intravenous catheter, Covidien Animal Health, Mansfield, MA

c. 0.9% Sodium Chloride, Hospira Inc, Lake Forest, IL

d. Vetstarch, Abbott Laboratories, North Chicago, IL

e. Cardell Veterinary Monitor 9500 HD, Midmark Animal Health, Versailles, OH

f. Element POC Rapid Blood Analyzer, Heska Corp, Des Moines, IA

g. Calcium gluconate 10% injection, Vet One, Boise, ID

h. Mini-infuser 300XL syringe pump, Baxter Medical, Deerfield, IL

i. Novolin-R, Novo Nordisk, Bagsvaerd, Denmark

j. Dextrose 50% injection, Vet One, Boise, ID

k. Lactated Ringers Solution, Hospira Inc, Lake Forest, IL

l. Unasyn, West-Ward Pharmaceuticals, Eatontown, NJ

m. Cerenia 10 mg/ml, Zoetis Inc, Kalamazoo, MI

n. Famotidine 10 mg/ml, West-Ward Pharmaceuticals, Eatontown, NJ

o. General Electric Logiq e Vet, Sound Technologies, Carlsbad, CA

p. TruDR, Sound Technologies, Carlsbad, CA

q. Dexamethasone Sodium Phosphate, West-Ward Pharmaceuticals, Eatontown, NJ

r. HemaTrue Hematology Analyzer, Heska Corp, Des Moines, IA

s. Element DC Chemistry Analyzer, Heska Corp, Des Moines, IA

t. Multistix Urinalysis Reagent strips, Bayer Animal Health, Shawnee Mission, KS

u. Fecasol, Vetoquinol USA, Ft. Worth, TX

v. Fecal loop, Innovative Veterinary Products, New Buffalo, MI

w. Antech Diagnostics, Sandy Springs, GA

x. Cosyntropin 0.25 mg/ml, Amphastar Pharmaceuticals, Rancho Cucamonga, CA

y. Percorten-V 25 mg/ml, Novartis Animal Health, Greensboro, NC

z. Prednisone 10 mg, West-Ward Pharmaceuticals, Eatontown, NJ

aa. Science Diet i/d, Hills Pet Nutrition Inc, Topeka, KS

bb. Omeprazole 20 mg, Perrigo Co, Allegan, MI

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