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Disturbances of Diagnostic Parameters in Critically Ill Patients

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As veterinary critical care becomes increasingly distinguished from emergency medicine, many veterinary centers are building intensive care units (ICUs) and employing staff to specifically care for patients deemed critically ill rather than emergent. These staff members must be familiar with various tests used in an ICU. Diagnostic parameters—such as blood glucose, magnesium, and lactate levels; central venous oxygen saturation ($Scvo_2$); and colloid osmotic pressure (COP)—are used to identify global disturbances in critically ill patients. Changes can be dramatic in a critically ill patient's blood glucose level, so monitoring it can be crucial to knowing when to correct a disturbance. The blood lactate level is an excellent perfusion parameter that helps assess fluid and volume deficits. The blood magnesium level is seldom mentioned in routine electrolyte discussions, although it plays an important role in homeostasis. $Scvo_2$ is an advanced and rarely used perfusion parameter that is gaining recognition and may be more accurate than traditional physiologic parameters such as heart rate and blood pressure. COP is useful in guiding colloidal therapy and diagnosing edematous states. As testing of these parameters becomes more common in critical care, ICU veterinary technicians should be familiar with interpreting these tests and with the pathophysiology of disturbances of these parameters.

Glucose Disturbance

This section focuses on hyperglycemia in critically ill patients. While hypoglycemia can be easily recognized and treated, supranormal glucose levels (i.e., 200 to 400 mg/dL) are often overlooked as "stress" related. However, maintaining normoglycemia can decrease the hospital stay and the morbidity and mortality of critically ill patients.[1]

Pathophysiology

Glucose is absorbed from ingested carbohydrates in the small intestine. Glucose is then taken up by tissues and stored as glycogen in the liver. Glucose can also be created from fat and amino acids in the liver through a process called *gluconeogenesis*. Glucose is transported into cells via uptake by proteins that become present on cytoplasm as a result of insulin stimulation.[1] Inside cells, glucose is converted to glycogen or pyruvate, which produces cellular energy in the form of ATP. This process is called *glycolysis*. Glucose either traverses the mitochondria, producing ample ATP for cellular use, or remains in the cytoplasm (in a hypoxic state), where only a few ATP molecules are produced. When oxygen is not present, lactate is formed as a by-product.

Mr. Liss discloses that he serves on the advisory board of VPI Pet Insurance.

Testing Methods and Normal Glucose Limits

Glucose levels of 130 to 150 mg/dL constitute mild hyperglycemia; at glucose levels >180 mg/dL, hyperglycemia is considered severe.[1] Glucose can be tested using chemistry analyzers, glucometers, and blood gas analyzers.

Causes

Glucosuria develops as the renal threshold for glucose is exceeded. The renal threshold of glucose is 180 to 220 mg/dL in dogs and 260 to 310 mg/dL in cats.[1] Glucosuria creates osmotic diuresis, contributing to volume depletion. In critically ill patients, hyperglycemia can result from insulin resistance and increased release of glucocorticoids and catecholamines. In patients with hypovolemia or pain, cortisol is released. Cortisol decreases activity of a protein called *GLUT 4*, which transports glucose into cells.[1] When GLUT 4 activity is decreased, cells cannot take in as much glucose that is absorbed during digestion or produced by the liver for cellular use. As a result, insulin has reduced efficacy because cellular proteins cannot effectively shift glucose from the extracellular space to the intracellular space. Causes of hyperglycemia in critically ill patients include surgery or administration of total parenteral nutrition (TPN), steroids, vasopressors, or anesthetics.[1] Hyperglycemia was reported in 30% of patients receiving TPN.[1] Analgesics such as ketamine, medetomidine, and opioids have been implicated in hyperglycemia.[1] In patients with early sepsis, a catabolic state or a need for glycogen can signal hyperglycemia.[1]

Hyperglycemia induces inflammation but limits the body's ability to fight infection (e.g., diabetic patients have a reduced ability to fight infection).[1] Inflammation increases because of an increase in cytokine (e.g., interleukin-1 and -6, tumor necrosis factor α) production, but immune function and response decrease because hyperglycemia reduces the ability of phagocytic cells to

Box 1. How to Set Up an Insulin Constant-Rate Infusion

1. Calculate the patient's daily dose of insulin: 1–2 U/kg/d of regular insulin.[1]
2. Add the prescribed amount of insulin to a 250-mL bag of normal saline (0.9%).
3. Flush the line with at least 50 mL of the insulin/fluid preparation to prevent insulin from binding to the plastic.
4. Administer the fluids at 10 mL/h and carefully monitor the blood glucose level.
5. Monitor the blood glucose level every 1 to 3 hours and adjust the CRI as follows:

Blood Glucose Level (mg/dL)	Dextrose in Fluids (%/L)	Insulin CRI Rate (mL/h)
>250	0	10
>200–250	0	7
>150–200	2.5	5
100–150	5	3
<100	5	0; stop the CRI

fight infection and glucose inactivates immunoglobulins.[1] Therefore, during infection, hyperglycemic patients produce an inflammatory chemical response but cannot phagocytose pathogens or develop immunity.

Hyperglycemia can adversely affect the coagulation system. Glucose activates the tissue factor pathway, increases the levels of circulating coagulation factors, and inhibits natural anticoagulants such as protein C.[1] Glucose also stimulates platelet activation and inhibits the fibrinolytic system.[1] Therefore, hyperglycemia can lead to hypercoagulation, putting affected patients at risk for thromboembolic events and complications.

Hyperglycemia has detrimental cardiovascular effects. A high extracellular glucose level increases lipolysis and, subsequently, the concentration of free fatty acids, which are toxic to the myocardium.[1] This may result in cardiovascular effects such as arrhythmias or myocardial dysfunction.

Hyperglycemia can be detrimental in patients with traumatic brain injuries. The brain needs a constant supply of glucose because it cannot store glycogen.[1] If a patient has a traumatic brain injury and develops hyperglycemia, the additional fuel provided by glucose, in a hypoxic state, produces lactate as a by-product, which is toxic to brain cells. An increased lactate level increases production of free radicals and stimulates excitatory neurotransmitters (i.e., glutamate), potentiating seizure activity, cerebral edema, or vasoconstriction and resulting in ischemia–reperfusion injury, brain herniation, or cell death, respectively.[1]

Treatment and Therapy

In critically ill humans, there is evidence that normoglycemia decreases mortality as well as the incidence of ventilation, transfusion, infection, and acute renal failure.[1] Therefore, maintaining a normal blood glucose level appears to be beneficial. Corresponding veterinary studies are lacking, but more information may be available soon. Tight glycemic control is used routinely in critically ill humans. Based on the evidence in humans, tight glycemic control is used for managing critically ill veterinary patients. Insulin is used to lower the blood glucose level, prevent the detrimental effects of a high glucose level, decrease inflammation, and decrease the concentration of tumor necrosis factor α.[1] To lower the blood glucose level, the inciting drug or therapy (e.g., TPN) may only need to be discontinued, but insulin administration often helps. Insulin can be administered by intermittent injections or constant-rate infusion (CRI; **BOX 1**). Although CRI of insulin is not standard in veterinary medicine, many clinicians use it or intermittent boluses to maintain normoglycemia. Some patients require one or two doses of insulin to resolve hyperglycemia. Other patients may require insulin by CRI for a prolonged period of time. The adverse effects of insulin therapy are hypoglycemia, hypokalemia, hypophosphatemia, and hypomagnesemia.[1] Insulin therapy has not been associated with increased morbidity or mortality in veterinary patients, but a recent study found that 63% of cats with hyperglycemia had a decreased length of hospitalization after becoming normoglycemic.[2]

Magnesium Disturbances

Pathophysiology

Magnesium is an intracellular cation that, like calcium, exists in several forms, including ionized, protein bound, and complexed with other anions.[3] Magnesium is absorbed in the small intestine and excreted by the kidneys.[3] A cofactor in ATP production, magnesium assists with many biologic processes, including intracellular pumping of ions across the cell membrane.[3] Magnesium is also important in skeletal and cardiac muscle function. Measurement of ionized magnesium (i.e., the biologically active form) is rare, so clinicians often rely on total magnesium measurements. Although the total magnesium level is a crude measure of the ionized magnesium level, it may be useful as a screening test for patients suspected of having hypomagnesemia.[3]

Testing Methods and Normal Limits

A blood chemistry panel is usually used for testing magnesium disturbances. Many in-house testing devices measure magnesium, but they typically only measure total magnesium. Ideally, ionized magnesium, which is available for biologic processes, should be tested. However, machines that measure ionized magnesium are usually not available. The normal limits for the total magnesium level are 1.6 to 2.5 mg/dL in dogs and 1.7 to 3.0 mg/dL in cats.[3]

Causes

Hypomagnesemia can have gastrointestinal causes (e.g., diarrhea, decreased intake, malnutrition, malabsorption) and renal causes (e.g., diabetes mellitus, administration of diuretics, polyuria, acute renal failure).[3,4] Hypokalemia, hypercalcemia, and hypophosphatemia can develop with hypomagnesemia.[3,4] Critically ill patients are predisposed to magnesium disturbances because of

transfusions, dialysis, fluid therapy, and administration of diuretics and insulin.[3,4]

Hypomagnesemia can increase muscle and nerve activity; therefore, the clinical signs include tremors, tetany, and ataxia.[3] Patients with hypokalemia and concurrent, undiagnosed hypomagnesemia may develop a refractory hypokalemia despite potassium supplementation. Magnesium is a cofactor involved in assisting the cellular electrolyte pumps. Without magnesium, the pumps fail and potassium is not properly equilibrated across the cell membrane and the intravascular space; therefore, hypokalemia does not resolve when hypomagnesemia is present.[3] In one study, 31% of patients with hypokalemia also had hypomagnesemia.[3,5] Affected patients require potassium and magnesium supplementation. Cardiac effects of hypomagnesemia manifest as arrhythmias such as ventricular tachycardia, atrial fibrillation, and torsades de pointes.[3]

Hypermagnesemia is rare in veterinary patients. However, in one study, six of 48 dogs in an ICU had hypermagnesemia.[3,5] Hypermagnesemia is a clinical concern because it can occur with acute renal failure, which is common in critically ill patients. The major clinical sign associated with hypermagnesemia is hypotension.[3] Affected patients may also have electrocardiographic abnormalities, including P-R interval elongation.[3] Treatment includes cessation of magnesium supplementation, administration of a loop diuretic (e.g., furosemide), and parenteral calcium supplementation, which antagonizes magnesium at the neuromuscular junction.[3] Calcium gluconate should be administered slowly at a dose of 50 to 150 mg/kg (diluted in half with normal saline) IV.[3]

Treatment and Therapy

Magnesium can be supplemented parenterally or enterally. Milk of magnesia can be used for oral supplementation. IV supplementation can be achieved with magnesium sulfate, magnesium chloride, or balanced crystalloid solutions (Normosol-R [Hospira], Plasma-Lyte [Baxter]), which also contain 3 mEq/L of potassium.[3] However, parenteral administration of magnesium by CRI is often needed to correct the imbalance; the dose is typically 0.75 to 1 mEq/kg/d.[3]

Lactate Disturbances

Pathophysiology

Lactate production results from anaerobic cellular metabolism. Lactate is a by-product of pyruvate metabolism, which produces ATP for cellular energy.[6] Glycolysis produces pyruvate in the cytoplasm of cells. Under aerobic conditions, pyruvate enters the mitochondria and produces many ATP molecules via the Krebs cycle.[7] In red blood cells, which do not have mitochondria, lactate dehydrogenase converts pyruvate to lactate to produce ATP. The excess lactate diffuses from the cells and back to the liver to help produce glucose via gluconeogenesis. This is called the *Cori cycle*.[7]

When cellular hypoxia is present, pyruvate cannot enter the mitochondria. Therefore, lactate dehydrogenase converts pyruvate to lactate, producing a small amount of ATP.[7] As lactate accumulates, it crosses the intravascular space and becomes present in the extracellular fluid. Hyperlactatemia develops when the liver can no longer clear lactate.[7] Lactate is dissociated from a hydrogen ion at physiologic pH. Excess hydrogen lowers blood pH and creates acidemia.[7] Lactate is metabolized by the liver and excreted by the kidneys.[7]

Testing Methods and Normal Limits

The lactate level can be measured with various instruments, such as blood gas analyzers (e.g., Nova Critical Care Xpress [Nova Biomedical], i-STAT [Abbott Point of Care], RapidLab [Bayer]). In-house veterinary chemistry analyzers (e.g., Catalyst [Idexx]) and lactate analyzers can also measure the lactate level.

A normal lactate level is <2 mmol/L, hyperlactatemia is defined as a lactate level >2 mmol/L, and lactic acidosis is defined as a lactate level >5 mmol/L.[6]

Causes

There are two types of lactic acidosis:

- In **type A**, tissue hypoxia is present with normal mitochondrial function.
- In **type B**, oxygen delivery is adequate, but carbohydrate metabolism and mitochondrial dysfunction are present.[7]

Type A lactic acidosis indicates a decrease in oxygen delivery to tissues through a decrease in cardiac output, hypovolemia, a decrease in oxygen in the blood (as in anemia), or a decrease in the ability to extract oxygen (e.g., edematous states).[7] Oxygen-starved cells produce (1) lactate as a by-product of anaerobic metabolism and (2) only a small amount of ATP, risking cell death if perfusion is not restored.

Type B lactic acidosis is a rare form of hyperlactatemia and has three subtypes:

- **Type B1** is due to decreased clearance of lactate,[7] which may occur with liver failure, diabetes (due to abnormal carbohydrate metabolism), renal failure, or neoplasia.
- **Type B2** is due to drugs or toxins (e.g., ethylene glycol, carbon monoxide, salicylates, acetaminophen) that affect a portion of glycolysis called *oxidative phosphorylation*.[7]
- **Type B3** is due to mitochondrial diseases.[7]

Treatment and Therapy

Because the primary cause of hyperlactatemia is hypoperfusion, IV fluids and/or blood products can help restore cellular equilibrium, depending on the nature of the disturbance. Treatment of type B hyperlactatemia depends on its cause. Patients that have ingested ethylene glycol require specific therapy, as do patients with liver failure. Recognizing the underlying pathophysiology of an elevated lactate level in these patients is a crucial diagnostic step.

There is some evidence that lactate can serve as a prognostic indicator. Lactate measurement may help determine the severity of a disease. A study involving patients with gastric dilatation–volvulus revealed that 74% of patients with a lactate level >6.0 mmol/L had gastric necrosis.[7] The incidence of gastric necrosis

increased to 80%, 92%, and 100% of patients at lactate levels of 7, 8, and 10 mmol/L, respectively.[7] While this information may be useful in predicting the degree of gastric damage, patients often have elevated lactate levels and normal-appearing anatomy on surgical examination. Thus, this information should be carefully considered when making prognostic evaluations.

Evaluation of lactate in abdominal fluid may reveal septic effusion. Lactate in abdominal fluid should always be evaluated with glucose measurements. A blood:fluid glucose difference of >20 mg/dL is 100% sensitive and specific for septic peritonitis.[7] A blood:fluid lactate difference of >2 mmol/L is highly suggestive of septic effusion.[7] While glucose measurements represent the major diagnostic criteria for a septic abdomen, lactate measurement can aid the diagnosis.

Disturbances in Central Venous Oxygen Saturation

Pathophysiology

Central venous oxygen saturation ($Scvo_2$) represents the hemoglobin saturation in the cranial vena cava (or right atrium).[8] $Scvo_2$ is used as a perfusion parameter because it represents the relationship between oxygen delivery and oxygen uptake by tissue (Vo_2).[8]

Testing Methods and Normal Limits

An anticoagulated blood sample needs to be measured with a machine capable of measuring—not calculating—saturation; this process is called *cooximetry*. Most analyzers can only calculate saturation, but Nova Critical Care Xpress and RapidLab are capable of cooximetry.

Causes

$Scvo_2$ is influenced by oxygen saturation (Sao_2), Vo_2, the carbon dioxide level, and the hemoglobin level.[8] If a patient is not anemic, measurement of $Scvo_2$ can help determine how much oxygen is needed by tissues. In hyperdynamic or hypoxemic states, Vo_2 is increased, indicating that the tissues are starving for oxygen.[8] Thus, the Sao_2 of blood returning to the heart to be oxygenated is decreased. Normal $Scvo_2$ is >65%.[8] In early hypoxic states, oxygen extraction increases, removing more oxygen from the blood. Therefore, an $Scvo_2$ of <65% may indicate global or regional tissue hypoxia.[8] A human study revealed that 39% of patients who lost blood during trauma had a low $Scvo_2$ despite normal vital signs.[8] Thus, patients that appear cardiovascularly stable and perfused may have subtle signs of tissue hypoperfusion, which requires correction. $Scvo_2$ measurement can help identify this. Sepsis may produce inconsistent $Scvo_2$ measurements that may be normal or increased; therefore, in septic patients, $Scvo_2$ is not as useful for determining volume requirements or perfusion status.[8]

Treatment and Therapy

$Scvo_2$ measurement can be used as an adjunctive perfusion parameter. If a patient has a central venous catheter and the hospital has an instrument for measuring hemoglobin saturation of a blood sample, $Scvo_2$ measurement may be used to rule out or identify perfusion derangements or tissue oxygen deficit. $Scvo_2$ is probably most appropriate to measure in patients with normal macroperfusion parameters (e.g., heart rate, blood pressure, urine output, mucous membranes, capillary refill time).

Disturbances in Colloid Osmotic Pressure

Pathophysiology

Colloid osmotic pressure (COP), which is also called *colloid oncotic pressure*, is the pressure exerted by large molecules (plasma proteins) in the vasculature.[9] COP keeps water inside the vasculature as a result of Starling's forces. Starling's equation represents fluid dynamics between the intravascular and interstitial spaces:

$$\mathbf{Flow = K[(P_c - P_t) - d(\pi_c - \pi_t)]}$$

This says that flow is equal to the hydrostatic capillary and interstitial pressures, minus the oncotic capillary and interstitial pressures. COP determines fluid flow from the vasculature.

Testing Method and Normal Limits

Normal COP values are 23 to 25 mm Hg.[9] For whole blood, the normal values are approximately 25 mm Hg in cats and 20 mm Hg in dogs.[9] For whole blood samples, only lyophilized heparin should be used as the anticoagulant.[9]

COP is measured with an osmometer. Portable, bedside osmometers are available from several laboratory equipment manufacturers. Osmometers work in complex ways involving diffusion of fluids and subsequent pressure generation. Basically, an osmometer pushes a patient's plasma across a membrane. After being zeroed with saline, which has a COP of 0 mm Hg, the osmometer's transducer reads the patient's plasma. The plasma molecules, which are suspended in saline solution, exert pressure in the sample chamber. This pressure is sensed by the transducer, converted to electrical energy, and displayed as a reading in mm Hg.

Causes

Edema, a common sign associated with COP derangements, has many causes, including increased hydrostatic pressure (fluid overload, heart disease), increased capillary permeability (sepsis, neoplasia, vasculitis, systemic inflammatory response syndrome), hypoproteinemia, and lymphatic obstruction (which cannot be evaluated by measurement of COP).[9] Measurement of COP is beneficial for identifying a hypooncotic state, which typically signals loss of plasma proteins, which are responsible for holding water within the vasculature. Measurement of COP is useful when a patient has a hypooncotic edema, but it is not necessarily of great diagnostic value if a patient has edema due to lymphatic obstruction or increased hydrostatic pressure. A low COP is obtained when a patient lacks sufficient plasma proteins to maintain vascular shape and form. Because the main plasma protein is albumin, alterations in the albumin level are often the focus in critically ill patients. Hypoalbuminemia may develop in critically ill patients for many reasons. Albumin may be lost through the gastrointestinal tract, the kidneys, or malnutrition.[9,10] Albumin may also be lost through skin lesions, such as burns, or third spacing. In addition, massive fluid therapy for treating shock (after

blood loss) may contribute to a dilutional effect, or albumin may not be produced because of severe liver disease.[10]

Treatment and Therapy

Treatment of hypooncotic states usually includes supplementation of albumin, plasma, or synthetic colloids to increase COP. The numerous positive and negative biologic effects associated with each type of treatment are beyond the scope of this article. Organ edema leading to organ dysfunction may appear long before peripheral edema.[9] Affected patients have low COP. Thus, monitoring COP might help detect organ edema and potential dysfunction earlier than waiting for peripheral edema to develop. Studies regarding the associated morbidity and mortality rates have had conflicting results, but it appears that raising COP may reduce mortality in critically ill patients.[9]

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1. **Which hormone decreases glucose transport into cells?**
   - **a.** insulin
   - **b.** cortisol
   - **c.** thyroxine
   - **d.** amylase

2. **A patient with hypokalemia is receiving potassium supplementation (80 mEq/L). However, in a period of 12 hours, the patient's potassium level has not changed. Which electrolyte may need to be given as a supplement?**
   - **a.** cortisol
   - **b.** insulin
   - **c.** magnesium
   - **d.** lipase

3. **How is insulin administered?**
   - **a.** CRI or oral administration
   - **b.** intermittent injections or oral administration
   - **c.** intermittent injections or CRI
   - **d.** none of the above

4. **Which type of magnesium is most often measured?**
   - **a.** complexed
   - **b.** ionized
   - **c.** total
   - **d.** protein bound

5. **How can magnesium be supplemented?**
   - **a.** intramuscularly, subcutaneously, or orally
   - **b.** orally or intravenously
   - **c.** orally or intramuscularly
   - **d.** all of the above

6. **What does a lactate disturbance typically indicate?**
   - **a.** the tissues need oxygen
   - **b.** mitochondrial storage disease
   - **c.** ongoing drug therapy
   - **d.** liver failure

7. **Which organs and/or systems are affected by hyperglycemia?**
   - **a.** the brain, heart, and pancreas
   - **b.** the brain, heart, and kidneys as well as coagulation
   - **c.** the heart and brain, the immune system, and coagulation
   - **d.** none of the above

8. **What can $Scvo_2$ help identify?**
   - **a.** low perfusion
   - **b.** pancreatitis
   - **c.** respiratory disease
   - **d.** cardiac disease

9. **Which is/are a cause of edema?**
   - **a.** increased hydrostatic pressure
   - **b.** low oncotic pressure
   - **c.** lymphatic obstruction
   - **d.** all of the above

10. **Which might be present *before* peripheral edema develops?**
    - **a.** sepsis
    - **b.** organ edema
    - **c.** paralysis
    - **d.** blood work abnormalities