SHOCK HAS TWO FACES: RBCs and Anemia

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Shock has two faces. Shock is defined as an inadequate production of cellular energy, very commonly brought on through forms of circulatory failure. Hypovolemic (inadequate circulating blood volume), cardiogenic (inability for heart to create forward flow), distributive (loss of systemic vascular resistance), and obstructive (obstruction of large vessels, sometimes not considered its own category) shock describe one aspect of inadequate delivery of oxygen (DO_2) leading to inadequate production of cellular energy. Shock despite proper circulatory function arises from metabolic dysfunction due to inadequate substrate supply or dysfunctional metabolic mechanisms. Oxygen is a very important component in carrying out aerobic metabolism, a vastly more efficient and sustainable method of energy production than anaerobic metabolism which takes place with the absence of oxygen. Lack of oxygen being delivered to tissues from inadequate oxygen content in arterial blood lead to what is known as hypoxemic shock, and may occur from varying reasons.

Oxygen in Energy Production

The importance of maintaining adequate DO_2 lies in the difference of the amount of adenosine triphosphate (ATP) produced in the presence and absence of oxygen. ATP is considered the "currency of cellular energy", providing energy for cellular processes required to maintain life as phosphate groups are cleaved off resulting energy release and formation of adenosine diphosphate (ADP) or adenosine monophosphate (AMP). ATP is involved in cellular signaling, DNA and RNA synthesis, muscle contraction, cytoskeletal maintenance, active transporting, and many other cellular functions. There is a finite amount of ATP available within a body, and a constant recycling of ADP and AMP into ATP is required to keep up with energy demands. In the presence of oxygen, 38 ATP molecules are generated from metabolism of a single glucose molecule undergoing oxidative phosphorylation occurring in the mitochondria. In contrast, a single glucose molecule yields two ATP molecules through anaerobic metabolism. The presence of oxygen is imperative in efficient energy generation.

Provided there is adequate intravascular volume and tissue perfusion, DO_2 is dependent on the oxygen level contained in the blood (arterial oxygen content, CaO_2) and how quickly the body can circulate the blood to the tissues (cardiac output, CO). The resulting mathematical expression of DO_2 is: $DO_2 = CaO_2 \times CO$. Oxygen contained within blood exists in two forms; dissolved in the plasma and bound to hemoglobin. The amount of oxygen dissolved in plasma depends on the partial pressure of oxygen (PaO_2), with 1 mmHg creating enough tension to result in 0.0031mL of dissolved O2 per dL of plasma. Each gram of hemoglobin is able to theoretically carry 1.39mL of O_2 when fully bound with oxygen, making up a significant portion of oxygen content of blood. In reality, there are portions of dysfunctional hemoglobin lowering this to approximately 1.34mL. In addition not every hemoglobin molecule will be fully bound to oxygen in every situation (SaO_2, or arterial oxyhemoglobin saturation) adding some variability. With all of these considerations in mind, the resultant formula to quantify DO_2 is the following, expressing the impact lowered hemoglobin concentration and saturation of the hemoglobin will have on overall delivery of oxygen: $DO_2 = [(1.34 \times Hgb \times SaO_2) + (0.0031 \times PaO_2)] \times CO$.

In animals without disease, DO_2 is significantly above oxygen consumption (VO_2), supplying a very comfortable buffer of available oxygen for energy production. This buffer allows for sudden changes in oxygen demand through changes in cellular metabolic rate or reduction in CaO_2. When DO_2 is significantly compromised (termed critical oxygen delivery), tissue hypoxia results and increased lactate levels and lowered pH are seen. The oxygen extraction ratio can also be used to express the level of oxygen consumed in relation to DO_2 ($O_2ER = VO_2/DO_2$). Higher oxygen consumption or lower DO2 leads to a higher ratio. The normal O_2ER value is approximately 0.2, though different organ systems have varying O_2ER (normal O_2ER of the heart is 0.6, making it more sensitive to hypoxemia). A normal DO_2, VO_2, and O_2ER in dogs were observed to be 790ml/min/m^2, 164ml/min/m^2, and 0.205, respectively in one study. Another couple of studies cite a normal DO_2 of 20-25ml/kg/min and observed critical oxygen delivery levels of 8-11ml/kg/min regardless of the cause (anemia, hypoxemia, and cardiac tamponade). A patient is said to be in hypoxemic shock when Hgb, SaO_2, or PaO_2 levels are low enough for DO_2 to reach this critical oxygen delivery level. In clinical settings, measurement of specific values such as CO and VO_2 (though can be estimated) are rather difficult, and we utilize this concept in determining when a patient is suspected to be in hypoxemic shock rather than making direct comparisons.

Oxygen Carrying Capacity

Though reduction of CaO_2 can result from any conditions leading to reduced levels of functional hemoglobin or respiratory dysfunction, oxygen carrying capacity is affected by the number of functional hemoglobin present in the blood stream. Oxygen carrying capacity is affected by a reduction in number through anemia, or conversion of hemoglobin into a dysfunctional form.

RBC Loss: One of the most common causes of reduced hemoglobin is due to an increased rate of RBC loss. Blood can be lost through internal or external hemorrhaging. Internal hemorrhage involves blood loss into the internal spaces such as peritoneal, retroperitoneal, pleural, pericardial, and gastrointestinal spaces. Trauma, surgical accidents, and ruptured neoplasms can cause physical damage to vessels resulting in acute or gradual hemorrhaging. Coagulation factor deficiencies, thrombocytopenia, and thrombocytopathia may render a patient unable to prevent bleeding from normal damage to the vasculature. Parasitism can lead to external hemorrhage (fleas, ticks, lice) or internal hemorrhage (Ancylostoma, Uncinaria). Gastrointestinal ulcers and hemorrhagic gastroenteritis are GI specific sources of hemorrhage.

RBC Destruction: Various types of defects in RBCs can cause an increased rate of destruction leading to a reduced hemoglobin level. Anemia due to hemolysis result in lowered red cell mass and subsequent reduction in oxygen carrying capacity without significant changes in plasma volume. Hemolysis can be intravascular (destruction of RBC within the blood stream), extravascular (phagocytosis by macrophages in the spleen, liver, bone marrow, and lymph nodes), or both. Intravascular hemolysis will result in the presence of free hemoglobin in the plasma, leading to hemoglobinemia and hemoglobinuria (when renal threshold is exceeded). Hemoglobinuria leads to tubular necrosis resulting in acute kidney injury in humans, and while not documented in veterinary medicine, poses similar concerns in veterinary medicine. Extravascular hemolysis can lead to splenic enlargement and jaundice, though other intravascular signs of hemoglobinemia, hemoglobinuria are not seen. Jaundice may be seen in patients with RBC destruction rate exceeding the liver's ability to process bilirubin. In addition, the presence of red blood cell fragments along with the presence of inflammatory processes may trigger disseminated intravascular coagulopathy.

Hemolysis is most commonly caused by acquired RBC defects, resulting in direct membrane injury or osmotic lysis. Exposure to chemicals and drugs that cause Heinz body formation will lead these red cells to be taken out of circulation through the phagocytic system or cause direct lysis. Causes include toxins contained in food (onion, garlic, propylene glycol), drugs (acetaminophen, vitamin K1 and K3, benzocaine), and chemicals (copper, naphthalene, skunk musk, zinc). Cats are more prone to Heinz body formation, but are also more forgiving towards red cells containing Heinz bodies, allowing for a longer survival time. Because of this, feline patients may show RBCs with Heinz bodies without anemia. Cats can develop Heinz bodies when exposed to propylene glycol, and are more prone if inflicted with diabetes mellitus, lymphoma, or hyperthyroidism. Cats with diabetes mellitus or hepatic lipidosis may develop hypophosphatemia which also can cause hemolysis; phosphate supplementation is recommended if a phosphate level below 0.5mmol/L is seen.

Hemolysis may be caused by antibody or complement response to the surface antigens of red blood cells by the patient's own immune system, termed immune-mediated hemolytic anemia (IMHA). Extravascular hemolysis can result from an immunoglobulin G (IgG) mediated type II hypersensitivity (cytotoxic) reaction. Phagocytic loss of RBC membranes reduces the surface area of the RBC, leading to formation of spherocytes (RBCs that have lost the biconcave structure). Gross agglutination of red cells may also be seen. If the immune response is initiated by factors such as cancer, drug administration, or infection, the hemolytic anemia is considered to be secondary IMHA. Passive acquirement of anti-red cell antibodies through blood transfusions and colostrum can cause an IMHA as well. The latter results in a phenomenon called neonatal isoerythrolysis, where anti-red cell antibody is passively acquired by a nursing neonate, resulting in the destruction of red cells. When no causative agents can be identified, the hemolytic anemia is considered to be primary IMHA, or auto-immune hemolytic anemia (AIHA).

Changes in rheology and passage of RBCs through narrow vessels can cause mechanical and shearing damage to the membranes. Hemoglobinemia and hemoglobinuria result as this is a form of intravascular hemolysis. Fragmented schistocytes and keratocytes are seen on blood smears as an indication of mechanical damage. Patients with cardiac disease, severe heartworm infection, hemangiosarcoma, patent ductus arteriosus, and any other causes of altered blood flow and microangiopathy may show signs of fragmentation of RBCs. DIC can be a cause of fragmentation, and at the same time precipitate DIC.

Reduced RBC Production: Decreased hemoglobin level can result from a reduced production of red cells as well. One cause for reduced red cell production is through a decreased level of erythropoietin (EPO), leading to reduced erythropoiesis. Patients with chronic renal disease often become anemic as EPO production by the kidneys are diminished. Other factors such as uremic toxins leading to a lowered red cell half-life, hemorrhagic loss due to GI ulcers, increased bleeding tendencies due to platelet dysfunction, inhibition of iron store release, suppression of erythropoiesis by the parathyroid, and reduced nutrient intake may also contribute.

Suppression of response to EPO is another cause for reduced production. In the presence of chronic inflammatory disease such as chronic infections, chronic immune conditions, malignant cancers, or in acute inflammatory diseases, red cell production is reduced. This is attributed to an increased production of hepcidin by hepatocytes during inflammatory disease, which inhibit the iron exporting action of ferroportin in macrophages and enterocytes. This reduces the iron available for erythropoiesis. In addition, inflammatory mediators (tumor necrosis factor-α and interleukin-1) released from leukocytes reduce surface EPO receptors on erythroid stem cells, leading to a reduced response to EPO.

Dysfunction of the bone marrow may be another cause for reduced RBC production. Irradiation, toxicities, viral or bacterial infections, and administration of certain drugs can result in marrow aplasia, leading to a lack of marrow stem cells. Myelopthisis, or marrow suppression secondary to marrow infiltration by tumors can displace or inhibit production of hematopoietic cells. Both of these situations result in a pancytopenia. In FeLV infections in cats or immune-mediated erythroid stem cell destruction in dogs, erythrocyte precursor cells are specifically reduced in number, leading to red cell aplasia.

When nutrients required for producing the signaling system for erythropoiesis and functional erythrocytes are deficient, anemia will occur. Folic acid, vitamin B12, cobalt and intrinsic factor (a glycoprotein aiding in absorption of vitamin B12) deficiency can result in a dysfunction of DNA and RNA synthesis, leading to production of erythrocytes of abnormal shape and size. These abnormal cells are destroyed in the bone marrow, thus never making it into circulation. Administration of drugs that antagonize folate (methotrexate for malignant tumors), inhibit folate metabolism (sulfonamides), and deplete folate concentrations (phenobarbital) are potential causes. A genetic disorder in Giant Schnauzers, Beagles, and Border Collies involving selective malabsorption of vitamin B12 has been reported and lead to a non-regenerative anemia. A deficiency in iron results in production of erythrocytes with a reduced concentration of Hgb, or lead to delay in red cell production leading to anemia.

Methemoglobinemia: When ferrous iron (Fe^{2+}) in the heme groups of hemoglobin undergoes oxidation to ferric iron (Fe^{3+}), it is called methemoglobin (metHb). MetHb is unable to bind oxygen and is considered a "dyshemoglobin", not contributing to oxygen carrying capacity. In addition, the oxidation of iron in one heme group increases the oxygen affinity of the rest of the heme groups on the hemoglobin, reducing oxygen unloading. The proportion of total hemoglobin existing as metHb due to natural oxidation is kept at approximately 1% at any given time, as normal oxidation is reduced by cytochrome-b_5-reductase (Cb_5R, also known as methemoglobin reductase). Methemoglobinemia occurs when the animal is exposed to high levels of oxidative compounds (acetaminophen ingestion, phenazopyridine therapy, skunk musk exposure, vitamin K_3 administration, benzocaine administration) or has reduced levels of Cb_5R (inherited conditions), such that the reduction mechanism is overwhelmed. Significant methemoglobinemia manifests in chocolate-brown colored blood and can be measured via co-oximetry. Treatment lies in eliminating the oxidative factor through diuresis and administration of medication enhancing elimination (N-acetylcysteine for acetaminophen).

Carboxyhemoglobin: Smoke inhalation, exposure to car exhaust, heating systems, gasoline-powered generators, and other forms of smoke and fume inhalation can lead to carbon monoxide toxicity. Carbon monoxide binds to hemoglobin at over 200 times higher affinity than oxygen, leading to formation of carboxyhemoglobin (COHb). Carbon monoxide binds to two of the four heme groups resulting in a 50% reduction of oxygen carrying capacity, and reduces the functional heme groups' ability to unload oxygen. The presence of significant amount of COHb manifests in cherry red colored mucous membranes, and is treated with high concentration oxygen therapy to compete and decreasing the half-life of carbon monoxide through displacement.

Sulfhemoglobin: A toxic ingestion of sulfur containing chemicals can lead to sulfhemoglobinemia through sulfide bonding with hemoglobin, inducing inability of carrying oxygen. The condition is rare and is most commonly associated with toxic ingestions of sulfur compounds (sulphonamides, sulfasalazine). Treatment is supportive.

Therapy

Regardless of the cause of decreased hemoglobin levels or modification of hemoglobin, the primary treatment is to address the underlying cause. In the meantime, the patient may reach a point where oxygen delivery is not sufficient due to inadequate arterial oxygen content from reduced oxygen carrying capacity. A red cell transfusion or administration of hemoglobin based oxygen carrier (HBOC) solution will help supplement the oxygen carrying capacity as the underlying cause is addressed.

Because both of these options are not without risk, the need for oxygen carrying capacity should be carefully considered. The first of this step is to make certain any reduction in CO is being properly addressed. In the case of acute hemorrhage causing hypovolemia, crystalloid bolus administration for intravascular volume expansion will, in most situations, restore perfusion necessary to circulate the reduced red cell mass for adequate oxygen delivery. Patients with more gradual or chronic anemia will most likely have normal or increased plasma volume and adequate perfusion due to compensatory mechanisms. Perfusion status for patients with dysfunctional hemoglobin will likely be normal; though this will depend on the inciting cause (e.g. a fire victim with smoke inhalation may have a negative fluid balance).

RBC Transfusions: When oxygen carrying capacity is suspected to be the cause of reduced DO_2 and hypoxemic shock, a RBC transfusion or HBOC solution administration is warranted. The hemoglobin contained within the erythrocytes directly supply oxygen carrying capacity. RBCs can be provided through whole blood or packed RBC transfusions. Precautions for transfusion related complications should always be taken when RBC transfusions are decided on. Complications include non-immunologic complications (circulatory overload, citrate toxicity, hypothermia) and immunologic complications (hemolytic transfusion reactions, febrile non-hemolytic transfusion reactions, allergic/ anaphylactic reactions, serum sickness). Proper risk assessment and compatibility testing is required before transfusions.

Hemoglobin-based Oxygen Carrier Solutions: Hemoglobin glutamer-200 (Oxyglobin®, OPK Biotech) is an acellular, bovine origin, polymerized hemoglobin solution intended for use in providing oxygen carrying capacity. The solution is stable at room temperature for 3 years. The hemoglobin is stored in a deoxygenated form, and should be discarded within 24 hours after the seal is compromised to avoid bacterial contamination and development of metHb.

HBOC solutions have an advantage over RBC products in its acellular nature, eliminating the need for RBC antigen based compatibility testing. In comparison to native hemoglobin, hemoglobin contained in Oxyglobin has a "right shifted" oxygen-hemoglobin dissociation curve, indicating a lower affinity to oxygen and better oxygen unloading ability at the tissue level. In addition, bovine hemoglobin is more significantly affected by Bohr and Haldane effects, allowing for better uptake of oxygen at the blood-gas barrier (lungs) and oxygen release at the tissues, being an overall superior oxygen carrier. Free plasma hemoglobin is normally rapidly cleared by the kidneys, but Oxyglobin's polymerized hemoglobin allows for longer persistence (half-life of 15-50 hours) in the plasma.

The solution does provide a higher colloid osmotic pressure than RBC solutions and synthetic colloids, requiring careful risk assessment in terms of circulatory overload. Increased arterial blood pressures have been observed in patients receiving Oxyglobin, with some association to increased mortality. In one study, 29 out of 44 cats receiving Oxyglobin exhibited pulmonary edema or pleural effusion. In another study, Oxyglobin administration to dogs showed increased systemic vascular resistance and resultant reduction of cardiac output, though overall beneficial effects in systemic and regional aerobic metabolism were observed.

HBOCs are most useful in its use as a temporary "oxygen bridge". The hemoglobin will have shorter half-life when compared to native RBCs, and supplying of compatible RBCs or addressing of anemia during the duration of action will be most beneficial to the patient. HBOCs can be used as a life-saving measure in those awaiting acquiring of, or compatibility testing of RBCs. Because of its acellular nature, the use of HBOCs in place of RBCs may be beneficial when providing oxygen carrying capacity to patients with immune mediated hemolytic anemia or patients with high degree of alloimmunization due to previous transfusions. One study observed benefits in HBOC transfusions equal to that of pRBC in dogs with babesiosis.

Recommended dosage for dogs is 15-30ml/kg with a rate of up to 10ml/kg/hr. The dosage and administration rate should be adjusted depending on the volume status of the patient. Lower rates of less than 5ml/kg/hr for dogs are recommended in patients with euvolemia or expanded plasma volume due to chronic anemic conditions. Cats exhibit a higher likelihood of circulatory overload and an administration rate of 0.5-3ml/kg/hr is recommended. CRI dosing may be considered in cases where longer term oxygen carrying capacity supplementation is required. Bolus dosing in hypovolemic dogs may be considered to take advantage of its hyperoncotic nature, providing a better hemodynamic state. Circulatory overload is much more common in cats, and bolus dosing is not recommended. Bolus dosing will result in a significant decrease in PCV due to hemodilution, though will not reflect an accurate oxygen carrying capacity based off of the PCV alone. A hemoglobinometer will allow for a more accurate assessment of oxygen carrying capacity, taking into account plasma hemoglobin concentration provided by the HBOC.

Monitoring during HBOC infusion includes physical perfusion parameters (HR, pulse quality, MM color, CRT, extremity temperature, mentation), respiratory character, and blood pressure. Signs of clinical anemia should continue to be monitored for improvement with infusion. Blood work such as pH and lactate values will also give insight into adequate oxygen carrying capacity. Repeated use of HBOCs may lead to sensitization to foreign hemoglobin and lead to immunologic responses, though experimental administration did not lead to anaphylaxis, allergic reaction, or serum sickness.

With the combination of HBOCs and RBC products available as therapeutic options (Oxyglobin is not available in the US at time of writing), our ability to provide adequate oxygen carrying capacity provides life-saving measures. Use of these options is not without risk, however, and careful consideration of the effect of each patient's oxygen carrying capacity on DO_2 is necessary for the best possible outcome.

References:

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Suggested Readings:

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