SHOCK HAS TWO FACES: THE KEYS TO PERFUSION

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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 functional hemoglobin levels and normal respiratory function, DO_2 is dependent on the ability to circulate the oxygen containing blood to tissues requiring oxygen, called perfusion. The 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.

Tissue Perfusion

The maintenance of normal blood pressure and tissue perfusion depends on adequate CO, and systemic vascular resistance (SVR). The most common form of reduced DO_2 and shock occurs secondary to reduction in CO or SVR. CO is can be reduced through a loss of intravascular volume, leading to hypovolemic shock. Hypovolemic shock can be caused by many situations leading to hypovolemia, such as internal or external hemorrhaging, fluid loss through vomiting, diarrhea, polyuria, exposed subcutaneous surfaces (burns, bit wounds) and/or reduced water intake. A loss in

circulating blood volume leads to a diminished venous return and preload to the heart, reducing the stroke volume (SV). A significant degree of reduced CO due to decreased SV is compensated for through an increase in heart rate (CO = SV x HR). SV itself is improved through increased contractility, or a more forceful contraction of the heart to eject a larger volume of blood. Reduced blood flow to the kidneys stimulates the renin-angiotensin-aldosterone system, increasing production of aldosterone leading to sodium retention, increasing plasma osmolarity and encouraging shifting of fluid to the intravascular compartment. Increased antidiuretic hormone (vasopressin) also promotes water retention, reducing urinary fluid loss. While vasoconstriction does not directly add to intravascular volume, its occurrence increases systemic vascular resistance, improving blood pressure and circulation of the reduce blood volume.

Patients faced with hypovolemia initially show signs of compensatory shock, involving tachycardia, normal prolonged capillary refill time (CRT), normal to pale mucous membranes, tachypnea, and cool extremities. Pulse quality and blood pressure may be mostly normal, and subtle depression in mentation may be seen. As intravascular volume continues to be lost, compensatory mechanisms will be unable to adequately maintain proper perfusion, and later signs of shock such as pale mucous membrane, prolonged CRT, poor pulse quality, depressed mentation, and hypotension will be seen. Uncorrected poor perfusion will lead to organ ischemia, leading to organ failure and death.

CO can be significantly affected by cardiac dysfunction as well. Congestive heart failure from cardiomyopathy can reduce contractility of the heart or reduce end-diastolic volume, decreasing SV and subsequently, CO. Cardiac arrhythmias may lead to improper filling, ejection, and effectiveness of the heart to create CO. Cardiac tamponade, occurring when effusion fills the pericardial space creating external pressure on the myocardium significant SV. Certain drugs may have cardiovascular depressant effects or cause myocardial conduction defects, leading to reduced CO. Any cardiogenic cause leading to reduced CO and resultant shock is called *cardiogenic shock*.

Distributive shock is another form of shock characterized by an inappropriate distribution of blood flow and volume. One example can be considered vasodilatory shock, resulting in profound vasodilation causing "relative hypovolemia" and a reduction in SVR, leading to reduced BP and poor perfusion. Systemic inflammatory response syndrome (SIRS) and septic shock (SIRS due to an infectious cause) involves vasodilation caused by cytokine and other inflammatory mediator secretion leading to a hyperdynamic phase involving hyperemic mucous membranes, bounding pulses, fever, and tachycardia. As the hypoperfused state is allowed to persist, myocardial damage leads to reduced cardiac output, and clinical changes to the patient to more classic signs of shock. Tachycardia, pale mucous membranes, prolonged CRT, cold extremities, poor pulse quality, and depressed mentation will be signs of significantly impaired perfusion.

Patients suffering from gastric dilatation-volvulus (GDV) will have a distended stomach compressing the intra-abdominal vessels (caudal vena cava, portal veins, and splanchnic vessels), impeding venous return to the heart leading to a reduced CO. This is considered *obstructive shock* by many (while many others consider it a form of distributive shock), where major blood vessels are occluded or carry reduced blood flow contributing to poor CO. The cause of shock in GDV is actually muti-faceted, since the occlusion of major vessels leads to portal hypertension and splanchnic pooling, leading to effusion of intravascular fluid into the abdominal cavity and interstitium, contributing to hypovolemia. Additional fluid loss may also occur due to vascular injury to gastric vessels as it is stretched, and repeated vomiting. Many disease processes involve different causes of shock occurring in varying in degrees, leading to the cumulative effect of reduced CO and DO_2.

Monitoring

The effectiveness of therapy can be determined through physical parameters as well as laboratory values. Physical perfusion parameters consist of mentation, heart rate, pulse quality, mucous membrane color, CRT, core to extremity temperature gradient. A patient in shock will have dulled mentation, increased heart rate (bradycardic in decompensated shock), poor pulse quality, pale mucous membrane (hyperemic if early vasodilatory shock), prolonged CRT, and a significant difference in core vs extremity temperature. These physical parameters should be monitored as shock is treated to ensure signs of poor perfusion are alleviated as therapy is continued. Except during compensatory shock, hypotension would be present and thus blood pressure should be monitored for changes. If hypotensive, initiation of therapy should be aimed to increase to a normal ranges (MAP 70-120mmHg). Blood pressure may be measured indirectly via Doppler, oscillometric monitors, or directly through an arterial catheter and pressure transducer setup.

Hypoperfusion of tissues and inadequate oxygen delivery results in anaerobic respiration. Anaerobic respiration is performed in hypoxic situations, leading to hyperlactatemia, and resultant metabolic acidosis. Normal lactate level dogs and cats is 0.5-2.0 mmol/L. Elevated lactate measurement indicates significant lactate production overwhelming the liver's metabolic clearance rate. Serial lactate measurements as fluid resuscitation is performed will allow monitoring of changes in the lactate level. A swift decrease in lactate level during fluid resuscitation serves as a positive prognostic indicator in patients with shock.

Other assessment tools such as central venous pressure may help guide fluid therapy and monitor fluid balance in a patient as fluid therapy is continued. Mixed venous oxygen saturation (SvO_2), or oxygen saturation of hemoglobin

at the pulmonary artery (after maximal oxygen extraction), will be decreased when DO_2 is decreased. Since pulmonary arterial catheters are not commonly placed in veterinary medicine, central venous oxygen saturation ($ScvO_2$) can be used as an indicator for SvO_2, as the values parallel each other closely, and a reduced $ScvO_2$ typically correlates to a reduced SvO_2. Urine output serves as an indicator for adequate renal perfusion, and will be greater than 1ml/kg/hr when blood flow is adequate. Urinary catheters are placed in critical care patients for the purpose of urine output monitoring. In the absence of renal disease, urine specific gravity may give clues as to adequate fluid infusion rate as well. Cardiac output itself can be monitored through advanced modalities such as thermodilution or lithium measurement, though not readily available in veterinary medicine.

Therapy

Treatment for shock will vary depending on the underlying cause. Hemorrhaging may require surgical intervention, or treatment of coagulopathies. Treatment of sepsis is a very intensive process including early antimicrobial administration. Cardiomyopathies may require various anti-arrhythmics, anti-hypertensives, or inotropics. These are only a few examples. Regardless of the underlying cause, there is a general strategy that can be applied to treating patients in shock which is aimed at reversing the restoration of tissue perfusion and preventing progression of shock while the underlying causes are treated.

Obtaining vascular access is one of the first steps in restoring cardiovascular stability in states of shock. A larger diameter, shorter catheter will cause the least amount of resistance for fluid boluses to be administered and recommended. Many of these patients, however, will have a compromised cardiovascular system often making placement of intravenous catheters difficult. Placement of a jugular venous catheter or intraosseous catheters may be more readily possible compared to placement of peripheral venous catheters and should be considered very early in attempting vascular access.

The first line of therapy is isotonic crystalloid therapy in all forms of shock aside from shock arising from cardiomyopathies (adding intravascular volume in congestive heart failure will exacerbate the congestion). A IV crystalloid bolus dose of 20ml/kg may be given, and the patient re-evaluated for further need. Crystalloids are thought to remain in the intravascular space only for a short amount of time (25% remaining approximately 30 minutes after infusion), and may require re-dosing at this point. In the case of hemorrhaging, hypotensive resuscitation, keeping the MAP approximately 60mmHg, may be beneficial in preventing exacerbation of bleeding. Infusion of crystalloids is aimed at replacing lost intravascular volume, or adding intravascular volume to combat relative hypovolemia caused by vasodilation.

Synthetic colloids such as hetastarch and tetrastarch provide higher osmolarity than crystalloids, allowing better retention and even causing shifting of fluid into the intravascular space, increasing intravascular volume and better tissue perfusion. In human medicine, there was recently a warning issued regarding the use of hetastarch and it being linked to renal injury. While human kidneys and canine/feline kidneys seem different in terms of sensitivity to insult, hetastarch is now recommended to be used with caution. Natural colloids are available in the form of albumin contained in plasma or albumin concentrate. Plasma may be used to supplement albumin levels in hypoalbuminemia. Hypoalbuminemia may result due to protein losing enteropathy or nephropathy, septic peritonitis, trauma, burns, and any other pathologies causing protein loss. However, the dose required for this particular use is 20-25mL/kg to achieve an increase of 0.5g/dL in plasma albumin. For example, a 25kg patient with an albumin level of 1.0g/dL will require 1000-1250mL of plasma to regain a low normal plasma albumin level of 2.0g/dL. In addition, this is not taking into account ongoing loss from the patient's pathology. Use of plasma in this manner will pose a higher transfusion related complication risk, be an inefficient use of plasma, and will be at a significant cost to the owners. Serum albumin concentrate is a better source of albumin.

Human serum albumin (HSA) has been used in canine patients with hypoalbuminemia. However, these infusions have a significant chance of an immunologic reaction as human albumin differs from canine albumin by 20% of its amino acid sequence. Previous sensitization to human albumin and subsequent acute hypersensitivity reactions are especially a concern when repeat doses are necessary. A study found presence of anti-albumin antibodies in dogs without prior exposure to human serum albumin, which was hypothesized to be from prior vaccinations involving production in bovine albumin cultures. Canine specific albumin has recently been produced as a commercial product, observed to increase serum albumin levels in the recipients with a low chance of immunologic complications. The most recent published study indicated albumin administration in dogs with septic peritonitis to have improved albumin level, Doppler blood pressure values, and colloid osmotic pressure measurements, as well as a comment on the association between albumin transfusion and survival. A connection between an improvement in serum albumin level and ultimate survival continues to be a topic under investigation,

Hypertonic saline (7% compared to 0.9% in normal saline) possesses higher osmolarity than crystalloids, which provides a hyperosmolar shifting of fluids into the intravascular space upon injection. The effect of hypertonic saline has a fast onset though the effect is also short lived. There may be additional beneficial effects such as reduced endothelial swelling, modulation of inflammation, and increased cardiac contractility. A mixture of hypertonic saline

and synthetic colloids given simultaneously has been seen to improve hemodynamic status better than each given individually. Blood products such as pRBC and plasma may need to be administered in cases of severe hemorrhaging or coagulopathy. Blood products are not recommended to be used solely as volume replacement due to potential immunologic and non-immunologic complications. RBCs are warranted for existing or anticipation of clinically significant anemia due to the rate of hemorrhaging seen. Plasma is useful in replacing coagulation factors. Hemoglobin based oxygen carrying solutions such as Oxyglobin, if available, will allow replacement of oxygen carrying capacity as well as providing colloidal effects without risk of immunologic complications.

When efforts in providing better intravascular volume are not sufficient in restoring adequate perfusion, vasopressor and inotropic therapy is required. Vasopressors function to provide vasoconstriction improving perfusion by increasing SVR. Vasopressors such as dopamine, norepinephrine, phenylephrine, epinephrine, and vasopressin may commonly be used. Inotropes such as dobutamine improve cardiac output through increasing myocardial contractility.

As with many conditions, successful treatment of shock depends on early recognition, assessment, and swift response and treatment of shock. Quick determination of the cause of impaired perfusion will allow for the appropriate fluid resuscitation strategy and medical management. Technicians play a large role in providing the monitoring of the patient as therapy is performed, through frequent monitoring of physical perfusion parameters and working in conjunction with the veterinarian to provide additional measures.

Suggested Readings & References:

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