Pathophysiology of Shock

An understanding of the pathophysiology of shock allows the veterinary practitioner and support team to promptly identify and categorize shock, facilitating rapid and effective resuscitation tailored to the individual patient and underlying disease process. Learn from Technician Emily Chryst, CVT about treatment considerations for patients experiencing shock.

Shock is commonly seen in both the emergency room and the primary care clinic. It is a potentially reversible condition that significantly contributes to the death of patients from a variety of illnesses. An understanding of the pathophysiology of shock allows the veterinary practitioner and support team to promptly identify and categorize shock, facilitating rapid and effective resuscitation tailored to the individual patient and underlying disease process. This review focuses on the pathophysiology and clinical signs of shock, with treatment discussed in the context of physiology but not covered in detail.

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The Definition of Shock

Shock is defined as a state of cellular and tissue hypoxia, where oxygen delivery is decreased relative to oxygen consumption. Fundamentally, this can be represented as:

Oxygen delivery ≠ Oxygen consumption ($DO_2 \neq VO_2$)

Oxygen delivery to tissues is a function of cardiac output and the oxygen content of arterial blood, as represented by the following formula:

$$DO_2 = CO \times CaO_2$$

Where CO is cardiac output, defined as:

$$CO = \text{Heart rate} \times \text{Stroke volume}$$

And CaO_2 is the oxygen content of arterial blood, defined as:

$$CaO_2 = (SpO_2 \times 1.34 \times [Hb]) + (0.003 \times PaO_2)$$

Thus, a state of shock can develop when any component of these formulas is altered secondarily to a number of underlying disease processes. Shock most commonly occurs from inadequate tissue perfusion due to low or unevenly distributed blood flow, though metabolic disturbances and hypoxemia can also lead to a state of VO_2/DO_2 mismatch. The resulting tissue hypoxia disrupts normal aerobic cellular metabolism, necessitating anaerobic metabolism for energy production.

The Classification of Shock

Shock can generally be classified into the six categories as shown in Table 1 below. This review will primarily focus on the four types of circulatory shock: hypovolemic, obstructive, distributive and cardiogenic. It is important to note that patients rarely fit into one category neatly, and many patients can also experience multiple types of shock simultaneously.

Category	Examples	Definition	Pathophysiology
Hypovolemic	Hemorrhage, severe dehydration	Decrease in circulating blood volume	Decreased circulating blood volume → decreased preload → decreased stroke volume → decreased cardiac output → decreased DO_2
Obstructive	GDV, cardiac tamponade	Physical impediment of blood flow in large vessels	Physical blockage → blood trapped distal to obstruction → decreased preload → decreased stroke volume → decreased cardiac output → decreased DO_2
Distributive	Septic shock, anaphylactic shock, heat stroke	Inappropriate changes in vascular resistance	Vasodilation → maldistribution of blood volume → decreased preload → decreased stroke volume→ decreased cardiac output → decreased DO_2 Multifactorial, distributive shock may also cause: Increased vascular permeability → fluid leaks from vasculature → hypovolemia Release of cytokine mediators → decreased contractility → decreased cardiac output → decreased DO_2 Activation of the coagulation system → clot formation → vessel occlusion → decreased preload → decreased cardiac output → decreased DO_2
Cardiogenic	DCM, arrhythmias	Decrease in forward flow from the heart	Lack of contractility → decreased cardiac output → decreased DO_2 May be complicated by: Increased afterload → decreased cardiac output → decreased DO_2
Hypoxemic	Anemia, severe pulmonary disease, carbon monoxide toxicity, methemoglobinemia	Decrease in oxygen content in arterial blood	Decreased O_2 in arterial blood → decreased DO_2
Metabolic	Hypoglycemia, cyanide toxicity, cytopathic hypoxia of sepsis, mitochondrial dysfunction	Deranged cellular metabolism	Increased VO_2 → normal DO_2 inadequate to maintain cellular function Or Impaired cellular ability to utilize O_2 → Inadequate ATP production

In the case of hypovolemic and obstructive shock, cardiac output is decreased. Stroke volume, determined by preload, afterload and contractility, is affected first because of either an absolute (in hypovolemic shock) or relative (in obstructive shock) decrease in circulating blood volume. When venous return to the heart is decreased, ventricular filling is also decreased, thereby reducing preload and stroke volume. The mainstay of therapy in these types of shock is to increase preload with intravenous crystalloid fluid resuscitation and to correct the underlying cause of shock (i.e. gastric decompression and de-rotation in the case of GDV). Cardiac output is also decreased in cardiogenic shock, however most of these patients have a normal to high preload depending on the primary disease process, and thus fluid resuscitation is contraindicated. The focus of therapy in cardiogenic shock is correcting the reason for

decreased cardiac output with positive inotropes, anti-arrhythmic medications, or diuretics. If the cardiogenic shock patient requires fluid therapy, low-volume colloid administration is generally recommended over crystalloid fluids.

The cause of the reduction of DO_2 in distributive shock is multifactorial and can vary depending on the underlying disease. In all cases, changes in systemic vascular resistance initially occur, resulting in an ineffective distribution of circulating blood volume. Most cases of distributive shock are caused by a decrease in systemic vascular resistance. Inappropriate vasodilation of peripheral vessels leads to maldistribution of blood to the periphery, ultimately causing a reduction in preload. In heatstroke, this is caused by the body's attempt to thermoregulate through peripheral vasodilation. In septic shock, vasodilation occurs by gram-negative endotoxemia. Endotoxins on the outer membrane of circulating gram-negative bacteria activate the inflammatory and coagulation cascades through the release of cytokines. Cytokine activation also alters myocardial function, contributing to reduced contractility. Additionally, damage to the endothelium through activation of the inflammatory cascade can cause vascular permeability, allowing fluid shifts from the intravascular space into the interstitial space, further reducing preload. Similar inflammatory processes can occur in anaphylactic shock, though by different inciting mechanisms. Distributive shock requires aggressive volume resuscitation and concurrent vasopressor support is often necessary to restore hemostasis. Positive inotropic therapy may also be required to increase cardiac contractility.In the case of hypovolemic and obstructive shock, cardiac output is decreased. Stroke volume, determined by preload, afterload and contractility, is affected first because of either an absolute (in hypovolemic shock) or relative (in obstructive shock) decrease in circulating blood volume. When venous return to the heart is decreased, ventricular filling is also decreased, thereby reducing preload and stroke volume. The mainstay of therapy in these types of shock is to increase preload with intravenous crystalloid fluid resuscitation and to correct the underlying cause of shock (i.e., gastric decompression and derotation in the case of GDV). Cardiac output is also decreased in cardiogenic shock, however, most of these patients have a normal to high preload depending on the primary disease process, and thus fluid resuscitation is contraindicated. The focus of therapy in cardiogenic shock is correcting the reason for decreased cardiac output with positive inotropes, anti-arrhythmic medications or diuretics. If the cardiogenic shock patient requires fluid therapy, low-volume colloid administration is generally recommended over crystalloid fluids.

In hypoxemic shock, organ perfusion and cardiac output is often normal. Oxygen delivery is decreased due to a reduction in arterial oxygen content by impaired pulmonary function, reduced fraction of inspired oxygen, or

decreased oxygen carrying capacity of blood. Treatment for hypoxemic shock is focused on correction of CaO_2. This is accomplished through transfusions, conversion of nonfunctional hemoglobin to functional hemoglobin, oxygen supplementation, or a combination of these therapies.

In metabolic shock, there is normal perfusion and normal CaO_2, though cellular ability to utilize the delivered oxygen to make energy is deranged. The most common metabolic shock emergency seen in veterinary medicine is hypoglycemia, though there are a number of other etiologies. The treatment for metabolic shock is determined by the underlying condition.

Compensatory mechanisms

In response to tissue hypoxia, neural and hormonally mediated compensatory mechanisms are initiated to increase cardiac output and vasomotor tone in an attempt to restore tissue perfusion. An immediate increase in sympathetic tone by the release of catecholamines causes vasoconstriction to shunt blood from the less important periphery to the heart in order to increase stroke volume. Sympathetic tone also increases cardiac contractility and heart rate to return cardiac output towards normal. Transcapillary shifts occur, in which fluid shifts from the interstitial space to the vasculature at the capillary level in order to increase circulating blood volume. Proteins are also shifted into the vasculature, thereby increasing oncotic pressure in the blood to assist with additional fluid shifts into the intravascular compartment.

The kidneys additionally provide assistance in increasing venous return through the renin-angiotensin-aldosterone system. When baroreceptors near the glomerulus sense decreased blood flow, the kidneys secrete renin. Renin converts angiotensinogen to angiotensin I, which is in turn converted to angiotensin II in the lungs. Angiotensin II binds to receptors on blood vessels and causes them to vasoconstrict. This vasoconstriction shunts blood from the peripheral tissues to the heart to increase preload and assists in maintaining tissue perfusion. Angiotensin II promotes water reabsorption in the kidneys to increase intravascular volume and also stimulates the secretion of aldosterone from the adrenal gland cortex. Aldosterone increases sodium retention in the kidneys, promoting fluid shifts to the intravascular compartment. The release of vasopressin/antidiuretic hormone from the pituitary gland in response to decreased blood volume also causes vasoconstriction and free water retention.

The Stages of Shock

Because these compensatory mechanisms can be very effective at the onset of shock, clinical signs are sometimes subtle initially. This is termed the compensatory phase of shock. Blood pressure can be maintained within normal range during this stage, as can mucous membrane color, capillary refill time, rectal temperature and pulse quality. Increased sympathetic tone will cause tachycardia, and tachypnea is seen due to pain, stress or perceived oxygen debt.

In ongoing shock, compensatory mechanisms become exhausted or are overwhelmed by increasing shock severity. This marks the transition of the patient to the decompensatory phase of shock. In this stage, perfusion is severely reduced. This results in myocardial ischemia, decreasing the ability of the heart to contract and thus causing bradycardia. Cerebral hypoxia worsens mentation, and respiratory fatigue results from respiratory muscle hypoxia. Mucous membrane color becomes pale due to vasoconstriction and shunting of blood from the periphery, and color progresses to muddy as waste products of cellular metabolism diffuse into capillaries. Blood vessels ultimately lose vascular tone and this, coupled with significantly reduced cardiac output, causes severe hypotension and eventually circulatory collapse.

Parameter	Compensated shock	Decompensated shock
Heart rate	Increased	Increased to decreased
Respiratory rate	Increased	Increased to decreased to agonal
Mucous membrane color, capillary refill time	Normal to pale pink, normal CRT	Pale to muddy to white, prolonged to absent CRT
Pulse quality	Normal	Weak to absent
Peripheral limb temperature	Cool	Cold
Mentation	Mild depression	Depressed to obtunded
Blood pressure	Normal to decreased	Decreased to unreadable
Rectal temperature	Normal to decreased	Decreased
Urine output	Normal to decreased	Oliguria to anuria

Distributive shock is classified as hyperdynamic or hypodynamic. They hyperdynamic phase of distributive shock can also be referred to as vasodilatory shock and is due to cytokine mediated peripheral vasodilation and vasoplegia. Clinical signs of hyperdynamic shock are tachycardia, fever, bounding pulses, and hyperemic mucous membranes with a rapid capillary refill time. Blood pressure may be normal to decreased.

If left untreated, cardiac output worsens due to cytokine mediated myocardial depression and myocardial ischemia. Signs of hypoperfusion

dominate; this is the decompensated state of distributive shock and is referred to as hypodynamic shock. Hypodynamic shock is characterized by tachycardia, pale mucous membranes, prolonged capillary refill time, hypothermia, poor peripheral pulses and depressed mentation. Without aggressive intervention, this stage of shock rapidly leads to multiple organ dysfunction and death.

Often times, feline patients in shock present differently than canine patients. Cats rarely display signs of hyperdynamic or compensated shock. They most commonly present with a dull mentation, tachypnea or dyspnea, weakness, hypothermia, bradycardia, pale mucous membranes and weak pulses. The reason for this difference is not completely understood. The sinoatrial node in cats is temperature sensitive, which may be a contributing factor to their bradycardia. In addition, the “shock organ” in cats is the lungs; this is the organ that receives markedly decreased perfusion during vasoconstrictive conditions. This may be the reason cats in shock often present in respiratory distress.

Sequelae

In addition to the underlying cause of shock and the direct effects of hypoperfusion on the shocked patient, there are a number of sequelae resulting from prolonged tissue hypoxia that cause further damage and complicate treatment. Hyperlactatemia and lactic acidosis, inflammatory cascade activation, ischemic-reperfusion injury, and acute coagulopathy of trauma and shock will be discussed in the following sections. All of these disorders are contributors to the progression from shock to multiple organ dysfunction syndrome, systemic inflammatory response syndrome, disseminated intravascular coagulopathy, and acute respiratory distress syndrome. While these syndromes are beyond the scope of this article, it should be noted that patients who progress to these conditions have a high mortality rate and an additional goal of therapy in critically ill patients should be directed toward prevention of their development.

Hyperlactatemia and lactic acidosis

As point-of-care lactate testing has become more widespread in the veterinary world, lactate measurement has become a gold standard in veterinary medicine and is becoming increasingly available to the primary care veterinarian. More veterinary-specific research is needed to fully understand species variations in our animal patients, but much of the human research translates well to the understanding of the pathophysiology of hyperlactatemia and lactic acidosis in critically ill animals.

Hyperlactatemia is defined as an abnormally elevated lactate concentration in the blood and lactic acidosis is the presence of hyperlactatemia with a decreased systemic blood pH. Causes of hyperlactatemia can be divided into type A or type B hyperlactatemia. Type A hyperlactatemia occurs by increased lactate production due to tissue hypoxia and is most relevant to this discussion.

Glycolysis is the first step in glucose metabolism. It is an anaerobic process that results in the production of pyruvate and ATP. Under normal aerobic conditions, the pyruvate produced by glycolysis is utilized by the Krebs cycle to produce additional ATP. The healthy individual creates a small amount of lactate daily, which can be used to produce energy by some tissues or is excreted from circulation by the liver and kidneys. However, in anaerobic conditions, glycolysis is the only means of energy production for hypoxic cells. Sustained periods of anaerobic metabolism result in the excess accumulation of pyruvate, converted to lactate by the enzyme lactate dehydrogenase, causing a hyperlactatemia. Hypoxia also causes hydrogen ions that would normally be phosphorylated in the Krebs cycle to accrue, creating a systemic acidosis. Acidosis has a direct effect on cardiac output by reducing myocardial function, and it can contribute to organ hypoperfusion, leading to increased levels of hypoxia. Tissue hypoprofusion should be considered in cases of hyperlactatemia with or without clinical signs of hypoperfusion, as clinical signs may be difficult to detect during the compensatory phase of shock.

Type B hyperlactatemia is caused by mitochondrial dysfunction, inadequate lactate clearance or some toxicities. It is significantly less common and is not directly caused by states of hypoperfusion. Clinically, type A and type B lactic acidosis can be differentiated by measuring lactate in response to treatment. Because type B lactic acidosis is not a result of hypoxia, it will not resolve by increases in DO_2 when poor perfusion is adequately corrected.

Hyperlactatemia alone is not a specific enough marker to prompt particular therapies, but it does imply the potential for severe or systemic disease. The development of lactic acidosis signals the presence of abnormal metabolic regulation due to marked ischemia and warrants aggressive treatment to reestablish tissue perfusion. As treatment is initiated, resolution of VO_2/DO_2 mismatch will cause a subsequent reduction in lactate as aerobic metabolism is restored and excess lactate is cleared by the liver and kidneys. Thus, serial measurement of lactate can help to determine the effectiveness of the medical team’s interventions and guide therapies for critically ill patients. Human studies have shown that a decrease in lactate levels within 120 minutes of initiation of treatment is a favorable prognostic indicator. Additionally, the degree of hyperlactatemia and severity of acidosis are directly related to the severity of tissue

hypoxia. In humans, it has been demonstrated that patients with lactic acidosis have a higher mortality rate than patients without lactic acidosis and are more at risk of developing multiple organ dysfunction syndrome and acute respiratory distress syndrome.

Inflammatory cascade

Inflammatory signaling pathways are rapidly activated after the initiation of tissue hypoxia. In response to hypoxia, vascular endothelial cells trigger leukocytes to release reactive oxygen species that directly damage the endothelium. The resulting endothelial hyperpermeability causes protein and plasma fluid loss from the intravascular space and into surrounding tissues. Inflammatory mediators, most predominantly cytokines, leukotrienes and tumor necrosis factor, are also released by activated white blood cells. These inflammatory mediators in turn bind to cell surface receptors, eventually leading to the upregulation of additional cytokines and nitric oxide. Nitric oxide possesses potent vasodilatory properties, and excess nitric oxide is converted to peroxynitrite, a free radical that damages mitochondria, thereby decreasing ATP production and further promoting inflammation and cell death. In the case of septic shock, gram-negative endotoxemia is an additional contributor to this pro-inflammatory state.

Prolonged systemic inflammation culminates in systemic inflammatory response syndrome and can lead to multiple organ dysfunctions. The loss of vascular tone, primarily from excessive nitric oxide production, results in circulatory collapse. These rapidly progress to hypodynamic distributive shock and require aggressive fluid therapy, vasopressor support, positive inotropes or a combination of these treatments to maintain restore perfusion.

Ischemic-reperfusion injury

The pro-inflammatory state caused by prolonged tissue ischemia causes tissues to be vulnerable to further injury upon reperfusion, termed ischemic-reperfusion (I-R) injury. Reactive oxygen species (ROS) are created when oxygen is reintroduced to hypoxic tissues during reperfusion. This predominantly occurs through the xanthine dehydrogenase/xanthine oxidase (XD/XO) pathway. In short, ischemic states cause intracellular calcium ion redistribution into the cytoplasm, resulting in activation of the enzyme calpain and a subsequent buildup of XO and hypoxanthine, a derivative of ATP. When the tissues are reperfused, the reintroduction of oxygen allows xanthine oxidase to convert hypoxanthine to xanthine, a process that also forms toxic ROS. ROS are potent oxidizing agents that directly damage cellular membranes. The interaction of these ROS with

intracellular unsaturated fatty acids results in end products that further damage cells, leading to metabolic dysfunction and cell death. Additionally, ROS stimulate leukocyte activation as in the inflammatory cascade, with the same deleterious results.

Clinical signs of I-R injury are dependent on the organ system affected. The most relevant veterinary disorders that carry a high risk of I-R injury include traumatic brain injury and GDV, however it may occur in any condition that causes prolonged tissue ischemia. In the case of traumatic brain injury, I-R injury is a large contributor to the secondary injury cascade and can be associated with intracranial hypertension, worsening mentation and seizures. I-R injury to both the bowel and myocardium can occur from GDV. These patients may experience ventricular arrhythmias, such as ventricular tachycardia or fibrillation. Ischemia of the gastrointestinal tract results in impaired mobility and absorption. In addition, intestinal permeability is increased, causing bacterial translocation into the portal and systemic circulation. Intestinal bacterial translocation is one of the contributing factors to the development of systemic inflammatory response syndrome and multiple organ dysfunction syndrome.

Acute coagulopathy of trauma and shock

Acute coagulopathy of trauma and shock (also seen as the acronym ACoTS), sometimes referred to as acute traumatic coagulopathy, can also develop within minutes of hypoxic injury, tissue trauma and systemic inflammation. Although there is no consensus definition for ACoTS, it is well documented in people with a handful of reports in veterinary literature. The development of ACoTS is likely due to protein C activation, shedding of the endothelial glycolax (a layer of the endothelium with anticoagulant properties) and increased levels of thrombomodulin from damaged endothelium. Together, these factors result in profound systemic hypocoagulation and hyperfibrinolysis. It is important to note that ACoTS is not associated with disseminated intravascular coagulation and develops only when tissue trauma is combined with hypoperfusion. The ability to detect ACoTS in most veterinary practices is limited, as PT and aPTT testing do not evaluate the fibrinolytic system, and the viscoelastic hemostatic assays required to diagnose a hyperfibrinolytic state are not widely available outside the university setting. Despite this, ACoTS may be an important consideration in critically ill trauma patients with continued hemorrhage and no definitive source of bleeding.

Summary of Shock

Shock is a complex condition that is often challenging to evaluate and treat. It can take multiple members of a highly qualified team to be

successful. Effective resuscitation requires rapid assessment and decision-making, often in the absence of a complete medical history. When understanding the pathophysiology behind shock, medical teams will be better prepared to quickly assess and treat critically ill patients.

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