DEFINITION OF SHOCK

In 1872 the trauma surgeon Samuel D. Gross defined shock as “the rude unhinging of the machinery of life.” Shock represents progression of a cascade of events that begins when cells or tissues are deprived of an adequate energy source because of oxygen deprivation. Shock occurs as a result of inadequate tissue perfusion; the lack of an adequate energy supply leads to the buildup of waste products and failure of energy-dependent functions, release of cellular enzymes, and accumulation of calcium and reactive oxygen species (ROS) resulting in cellular injury and ultimately cellular death. Activation of the inflammatory, coagulation, and complement cascades results in further cellular injury and microvascular thrombosis. The amplification of these processes coupled with increased absorption of endotoxin and bacteria (as a result of liver and gastrointestinal dysfunction) leads to the systemic inflammatory response syndrome (SIRS) (see Chapter 2), multiple organ dysfunction (MOD), and if uncontrolled, ultimately death.

CLASSIFICATION OF SHOCK

Tissue perfusion is dependent on blood flow. The major factors affecting blood flow are the circulating volume, cardiac pump function, and the vasomotor tone or peripheral vascular resistance.

Cardiac output (CO) ultimately determines the blood flow to tissues and is regulated largely by the stroke volume (SV). SV is the result of ventricular preload (amount of blood returning from the body and entering the heart), the myocardial contractility (systolic cardiac function), and the ventricular afterload (the force the heart must overcome to push blood across the aortic and pulmonic valves into the peripheral or pulmonary vasculature). The interplay between these factors is seen in Figure 1-1.

Ventricular preload (referred to as “preload”), the third component of SV, is directly affected by vasomotor tone or peripheral vascular resistance. If vascular resistance or tone increases (hypertension), afterload also rises with a resultant fall in CO and tissue perfusion. The opposite extreme is a severe fall in vascular resistance, which results in pooling of blood in capacitance vessels and a drop in blood pressure and preload, and it ultimately results in inadequate perfusion and shock.

The fundamentals of treatment of shock revolve around restoration and maintenance of CO through manipulation of preload, afterload, myocardial contractility, and heart rate.

Shock most commonly occurs because of one of three primary disturbances and can be classified accordingly. Hypovolemic shock is the result of a volume deficit, either because of blood loss (e.g., resulting from severe hemorrhage), third-space sequestration (e.g., occurring with a large colon volvulus), or severe dehydration. Cardiogenic shock or pump failure occurs when the cardiac muscle cannot pump out adequate SV to maintain perfusion. Distributive shock or microcirculatory failure occurs when vasomotor tone is lost. Loss of vascular tone can result in a dramatic decrease in both blood pressure and venous return. Although the drop in blood pressure will initially decrease afterload (which will temporarily improve CO), the pooling of blood and loss of venous return results in a severe decrease in preload, and consequently, decreased CO and perfusion.
Common causes of distributive shock include neurogenic shock, septic shock, and anaphylactic shock. Because distributive shock is a consequence of a loss in effective circulating volume, fluid therapy is indicated to help restore perfusion. In contrast, cardiogenic shock is the result of pump failure, and aggressive fluid therapy may actually worsen clinical signs. Less commonly, shock can develop when increased metabolic demand results in relative perfusion deficits or when oxygen uptake is impaired because of mitochondrial failure, sometimes termed relative hypoxia or dyoxia.

It is important to recognize that although the inciting cause may differ, as shock progresses there is often failure of other organ systems as well. For example, untreated hypovolemic shock can result in microcirculatory failure (loss of vasomotor tone) as oxygen debt causes muscle dysfunction and relaxation. Alternatively, hypovolemic shock can result in myocardial failure as perfusion deficits affect energy supply to the myocardium (coronary artery blood flow), resulting in decreased myocardial contractility. Consequently, as shock progresses, treatment may require addressing all of these disturbances.

Obstructive shock represents an additional category, with its underlying mechanism the obstruction of ventilation or of CO. This process is most commonly caused by tension pneumothorax (resulting in decreased venous return); pericardial tamponade; diaphragmatic hernia or severe abdominal distension causing vena cava obstruction, leading to inadequate ventricular filling; decreased preload; and consequently, decreased SV and CO. Over time as aortic blood pressure falls, coronary artery blood flow is reduced, and myocardial ischemia and finally myocardial failure may develop. Because obstructive shock is ultimately a combination of the other three categories, it will not be discussed further.

**PATHOPHYSIOLOGY OF SHOCK**

A blood loss or hypovolemic model of shock will be used to describe the pathophysiology of shock.

Shock is usually defined by the stage or its severity. **Compensated shock** represents an early or mild shock, during which the body's response mechanisms are able to restore homeostasis. As blood volume is depleted, pressure within the vessels falls. Baroreceptors and stretch receptors located in the carotid sinus, right atrium, and aortic arch sense this fall in pressure. These receptor responses act to decrease inhibition of sympathetic tone while increasing inhibition of vagal activity and decreasing the release of atrial natriuretic peptide (ANP) by cardiac myocytes. The increase in sympathetic tone and fall in ANP results in vasoconstriction, which increases total peripheral resistance and thereby increases blood pressure. Increased sympathetic activity at the heart increases heart rate and systolic cardiac function, hence increasing SV and CO. This interplay between the parasympathetic and sympathetic nervous systems is referred to as **autonomic traffic** (see Figure 1-1). In addition, peripheral chemoreceptors stimulated by local hypoxemia respond by enhancing this vasoconstrictive response. In mild to moderate hypovolemia these responses are sufficient to restore perfusion. Because these compensatory responses result in tachycardia, increased SV (increased pulse pressure), and shortened capillary refill time (CRT), the term **hyperdynamic** is often used to describe this stage of shock.

The vasoconstrictive response will vary between organ systems, with the greatest response occurring in the viscera, integument, and kidney. Cerebral and cardiac flow is preferentially maintained in mild to moderate hypovolemia. Although this response improves central blood pressure and flow, it also decreases perfusion to individual microvascular beds, worsening local tissue hypoxemia. Consequently, as volume depletion worsens, certain tissues and organs will become ischemic more rapidly than others.

A decrease in renal perfusion results in secretion of renin from juxtaglomerular cells located in the wall of the afferent arteriole. Renin stimulates production of angiotensin I, which, after conversion to angiotensin II, increases sympathetic tone on peripheral vasculature and promotes aldosterone release from the adrenal cortex. Aldosterone restores circulating volume by increasing renal tubular sodium and water reabsorption. Arginine vasopressin (AVP, previously known as antidiuretic hormone, ADH), released from the posterior pituitary gland in response to decreased plasma volume and increased plasma osmolality, is a potent vasoconstrictor and stimulates increased water reabsorption in the renal collecting ducts. Finally, an increase in thirst and a craving for salt is mediated by both the renin-angiotensin-aldosterone system (RAAS) and a fall in ANP (Figure 1-2).

With more severe blood loss, compensatory mechanisms become insufficient to maintain arterial blood pressure and perfusion of vital organs (**decompensated shock**). Ischemia to more vital organs including the brain and myocardium begins to develop. Blood pressure may be maintained, but clinical signs including resting tachycardia, tachypnea, poor peripheral pulses, and cool extremities are present. Mild anxiety may be apparent as well as sweating from increased sympathetic activity. Urine output and central venous filling pressure will drop. As blood loss progresses, compensatory mechanisms are no longer capable of maintaining arterial blood pressure and perfusion to tissues. Severe vasoconstriction further worsens the ischemia such that energy supplies are inadequate and cellular functions (including the vasoconstriction responses) begin to fail. In addition, accumulations of waste products of metabolism (lactate and carbon dioxide) cause progressive acidosis and further cellular dysfunction.

At the cellular level, the combination of decreased oxygen delivery and increased accumulation of waste products results in loss of critical energy-dependent functions, including enzymatic...
As the situation deteriorates, compensatory mechanisms designed to continue to perfuse more vital organs like the heart and brain will continue to limit flow to other organs. This response results in the sparing of one organ with irreversible damage to another. Consequently, an individual may recover with aggressive intervention only to succumb later because of failure of these “less vital” organs. If blood flow is restored, reperfusion injury results from the activated cellular and immunochemical products washed into the venous circulation and leads to SIRS, MOD, and death (see Chapter 2). Intervention can no longer stop the cascade of events because cellular, tissue, and organ damage is too severe for survival.

**CLINICAL SIGNS OF SHOCK**

Clinical signs of shock depend on the severity and persistence of blood volume loss or redistribution. The American College of Surgeons advanced trauma life support guidelines divide shock into four classes depending on volume of blood loss. With mild blood loss of less than 15% total blood volume (class I), the body is capable of restoring volume deficits via compensatory responses and there may be little to no change in the physical findings other than a drop in urine output. Blood pressure is maintained. Clinical signs typically become apparent when blood loss exceeds 15%. Class II blood loss (15%–30%) is defined as the onset of hyperdynamic shock. Clinical signs include tachycardia, tachypnea, and a bounding pulse (increased CO and peripheral vascular resistance). Mental agitation or anxiety is present, and increased sympathetic output results in pupillary dilation and sweating. Although these compensatory mechanisms can normalize blood pressure, perfusion deficits will persist and can be detected by blood gas analysis (increased lactate and a high anion gap metabolic acidosis). If blood loss continues, or if hypovolemia persists, compensatory mechanisms can become
insufficient to restore circulating volume and hypodynamic/decompensatory shock begins (class III or moderate hypovolemic shock). At this time profound tachycardia and tachypnea, anxiety, and agitation are present. Urine output may cease, jugular filling and CRT are prolonged, pulse pressure is weak, and extremity temperatures are decreased. If blood gases are collected, a lactic acidosis will be present (Table 1-1). Blood pressure will drop despite increases in heart rate, cardiac contractility, and total peripheral resistance. Without intervention, continued cellular hypoxia and acidosis result in failure of compensatory mechanisms, causing peripheral vasodilation and decreased myocardial contractility. A vicious cycle ensues with decreased coronary artery perfusion causing decreased cardiac function, resulting in decreased CO and a further drop in perfusion (see Figure 1-4).
**CHAPTER 1  SHOCK**

**Shock** therapy is the vital first step to restoring oxygen delivery. Extensive research efforts have addressed the ideal type and volume of fluid for treating hypovolemic shock. The ideal resuscitation fluid should produce a predictable and lasting increase in intravascular volume, with an electrolyte composition as close as possible to that of extracellular fluid, being metabolized and excreted without any accumulation in the tissues, without producing adverse metabolic or systemic effects, and remain cost effective, especially for administration in larger equine patients. Currently, the ideal resuscitation fluid does not exist.

In the past, recommendations have been to rapidly infuse large volumes of isotonic crystalloids to replace circulating volume ("aggressive fluid therapy"). Because of their accessibility and low viscosity, crystalloids can be administered fast and quickly restore the circulating volume. However, approximately 80% of the volume will rapidly diffuse out of the vascular space into the interstitial and intercellular space. Consequently, when using crystalloids, replacement volumes must be four to five times greater than the volume lost. In acute blood loss or hypovolemic states, this approach will result in excess total body water and extreme excesses of sodium and chloride. This movement of fluid out of the vascular space is further exacerbated if the underlying disease process causes increased microvascular permeability (as a result of lost endothelial glycocalyx and impaired endothelial cell function). In addition, if the electrolyte constituents of isotonic crystalloids differ from those in the intracellular space, cellular swelling will ensue. Cellular swelling affects the activity of various protein kinases; increases intracellular calcium concentrations; alters ion pump activity, membrane potential, and cytoskeletal structure; and activates phospholipase A2. Consequently, high volumes of crystalloids can trigger or potentiate an inflammatory response and have a negative impact in the face of ischemia and reperfusion. Furthermore, large-volume infusions can result in significant complications including abdominal compartment syndrome, acute respiratory distress syndrome, and others.

**TREATMENT**

**Fluid Administration**

Regardless of the underlying etiology of shock (cardiac failure, blood loss, or sepsis), the greatest need is to restore perfusion and oxygen delivery to the tissues. Delivery of oxygen (DO$_2$) is defined by the content of oxygen in the arterial blood (CaO$_2$) as well as the amount of blood perfusing the tissue (CO).

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$

The content of oxygen per volume of blood is determined by the amount of hemoglobin (Hb) or red cell mass and the saturation of that Hb (SaO$_2$). It is important to assess Hb concentration and SaO$_2$ because these variables will affect oxygen delivery. Decreased oxygen delivery is most commonly the result of decreased perfusion, not decreased oxygen content, but it is critical to evaluate all contributing factors when planning a treatment protocol for an individual in shock. Because hypovolemia is the most common cause of shock in adult horses, fluid therapy is the vital first step to restoring oxygen delivery. Extensive research efforts have addressed the ideal type and volume of fluid for treating hypovolemic shock. The ideal resuscitation fluid should produce a predictable and lasting increase in intravascular volume, with an electrolyte composition as close as possible to that of extracellular fluid, being metabolized and excreted without any accumulation in the tissues, without producing adverse metabolic or systemic effects, and remain cost effective, especially for administration in larger equine patients. Currently, the ideal resuscitation fluid does not exist.

If uncontrolled, clinical signs will progress from tachycardia and anxiety to bradycardia, obtundation, anuria, profound hypotension, circulatory collapse, and death (class IV, *uncompensated* life-threatening hemorrhagic shock).

A paper published in 2012 described moderate to severe elevations in cardiac troponin I (cTnI) and the development of potentially life-threatening ventricular arrhythmias in horses suffering from severe hemorrhage, with the magnitude of cTnI elevation and the presence of arrhythmia being association with poor outcomes.

Monitoring (via ECG, echocardiography, and serial cTnI measurements) is indicated in critical patients with arrhythmias or unexplained tachycardia. Antiarrhythmic therapy is indicated if the arrhythmia becomes hemodynamically relevant.

**TREATMENT**

**Fluid Administration**

Regardless of the underlying etiology of shock (cardiac failure, blood loss, or sepsis), the greatest need is to restore perfusion and oxygen delivery to the tissues. Delivery of oxygen (DO$_2$) is defined by the content of oxygen in the arterial blood (CaO$_2$) as well as the amount of blood perfusing the tissue (CO).

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$

The content of oxygen per volume of blood is determined by the amount of hemoglobin (Hb) or red cell mass and the saturation of that Hb (SaO$_2$). It is important to assess Hb concentration and SaO$_2$ because these variables will affect oxygen delivery. Decreased oxygen delivery is most commonly the result of decreased perfusion, not decreased oxygen content, but it is critical to evaluate all contributing factors when planning a treatment protocol for an individual in shock. Because hypovolemia is the most common cause of shock in adult horses, fluid therapy is the vital first step to restoring oxygen delivery. Extensive research efforts have addressed the ideal type and volume of fluid for treating hypovolemic shock. The ideal resuscitation fluid should produce a predictable and lasting increase in intravascular volume, with an electrolyte composition as close as possible to that of extracellular fluid, being metabolized and excreted without any accumulation in the tissues, without producing adverse metabolic or systemic effects, and remain cost effective, especially for administration in larger equine patients. Currently, the ideal resuscitation fluid does not exist.

In the past, recommendations have been to rapidly infuse large volumes of isotonic crystalloids to replace circulating volume ("aggressive fluid therapy"). Because of their accessibility and low viscosity, crystalloids can be administered fast and quickly restore the circulating volume. However, approximately 80% of the volume will rapidly diffuse out of the vascular space into the interstitial and intercellular space. Consequently, when using crystalloids, replacement volumes must be four to five times greater than the volume lost. In acute blood loss or hypovolemic states, this approach will result in excess total body water and extreme excesses of sodium and chloride. This movement of fluid out of the vascular space is further exacerbated if the underlying disease process causes increased microvascular permeability (as a result of lost endothelial glycocalyx and impaired endothelial cell function). In addition, if the electrolyte constituents of isotonic crystalloids differ from those in the intracellular space, cellular swelling will ensue. Cellular swelling affects the activity of various protein kinases; increases intracellular calcium concentrations; alters ion pump activity, membrane potential, and cytoskeletal structure; and activates phospholipase A$_2$. Consequently, high volumes of crystalloids can trigger or potentiate an inflammatory response and have a negative impact in the face of ischemia and reperfusion. Furthermore, large-volume infusions can result in significant complications including abdominal compartment syndrome, acute respiratory distress syndrome, and others.

**TREATMENT**

**Fluid Administration**

Regardless of the underlying etiology of shock (cardiac failure, blood loss, or sepsis), the greatest need is to restore perfusion and oxygen delivery to the tissues. Delivery of oxygen (DO$_2$) is defined by the content of oxygen in the arterial blood (CaO$_2$) as well as the amount of blood perfusing the tissue (CO).

$$\text{DO}_2 = \text{CO} \times \text{CaO}_2$$

The content of oxygen per volume of blood is determined by the amount of hemoglobin (Hb) or red cell mass and the saturation of that Hb (SaO$_2$). It is important to assess Hb concentration and SaO$_2$ because these variables will affect oxygen delivery. Decreased oxygen delivery is most commonly the result of decreased perfusion, not decreased oxygen content, but it is critical to evaluate all contributing factors when planning a treatment protocol for an individual in shock. Because hypovolemia is the most common cause of shock in adult horses, fluid therapy is the vital first step to restoring oxygen delivery. Extensive research efforts have addressed the ideal type and volume of fluid for treating hypovolemic shock. The ideal resuscitation fluid should produce a predictable and lasting increase in intravascular volume, with an electrolyte composition as close as possible to that of extracellular fluid, being metabolized and excreted without any accumulation in the tissues, without producing adverse metabolic or systemic effects, and remain cost effective, especially for administration in larger equine patients. Currently, the ideal resuscitation fluid does not exist.

In the past, recommendations have been to rapidly infuse large volumes of isotonic crystalloids to replace circulating volume ("aggressive fluid therapy"). Because of their accessibility and low viscosity, crystalloids can be administered fast and quickly restore the circulating volume. However, approximately 80% of the volume will rapidly diffuse out of the vascular space into the interstitial and intercellular space. Consequently, when using crystalloids, replacement volumes must be four to five times greater than the volume lost. In acute blood loss or hypovolemic states, this approach will result in excess total body water and extreme excesses of sodium and chloride. This movement of fluid out of the vascular space is further exacerbated if the underlying disease process causes increased microvascular permeability (as a result of lost endothelial glycocalyx and impaired endothelial cell function). In addition, if the electrolyte constituents of isotonic crystalloids differ from those in the intracellular space, cellular swelling will ensue. Cellular swelling affects the activity of various protein kinases; increases intracellular calcium concentrations; alters ion pump activity, membrane potential, and cytoskeletal structure; and activates phospholipase A$_2$. Consequently, high volumes of crystalloids can trigger or potentiate an inflammatory response and have a negative impact in the face of ischemia and reperfusion. Furthermore, large-volume infusions can result in significant complications including abdominal compartment syndrome, acute respiratory distress syndrome, and others.
syndrome, congestive heart failure, gastrointestinal motility disturbances, and dilutional coagulopathy.11,12

Multiple human clinical trials have questioned the need for complete and rapid restoration of volume to maximize survival. In several hemorrhagic shock models, aggressive fluid therapy before hemorrhage was controlled was associated with more severe blood loss, poorer oxygen delivery, and a higher mortality rate compared to more controlled, limited fluid therapy.13,14 Both the Advanced Trauma Life Support and the current Surviving Sepsis Campaign guidelines recommend the use of lower-volume bolus crystalloid therapy (30 mL/kg within the first 3 hours after presentation) combined with frequent assessment of the hemodynamic status to improve survival of human patients presenting with signs of hemorrhagic or septic shock.5,15

Clearly there are pros and cons to immediate, large-volume fluid resuscitation in the treatment of hypovolemic shock. Perfusion deficits need to be addressed, but the goal of therapy may need to be considered in light of the potential negative effects of rapidly infusing a large volume of fluids. Large-volume fluid therapy has also been associated with cardiac and pulmonary complications in both healthy human patients undergoing elective surgery and patients with risk factors for cardiopulmonary disease.16,17 Large-volume fluid therapy in patients with underlying SIRS or patients that have a low colloid oncotic pressure can result in significant edema, which can negatively affect intestinal motility and barrier function, and can also affect the function of other organ systems.18

Despite this discrepancy in the literature, the reality is that shock is a manifestation of perfusion deficits, and the goal of therapy should be to restore perfusion and improve oxygen delivery. Prompt, goal-directed fluid therapy is indicated in the emergency situation to increase the circulating blood volume, maintain CO and blood pressure, and ultimately provide adequate perfusion to the tissues. The amount and type of fluids should be determined by the individual needs of each patient. Careful, frequent monitoring to assess responses and prevent fluid overload is essential.

A “balanced fluid therapy approach” of administering isotonic crystalloids for hypovolemic shock is currently recommended in equine practice.12 Initially a rapid 20 mL/kg (10 L for a 500-kg horse) bolus is administered over the first 30 to 60 minutes with assessment of the cardiovascular system at regular intervals to monitor the response (for more details, see “Current Recommendations,” below).

Types of Fluids

Isotonic Crystalloids

Commercially available isotonic crystalloids (balanced electrolyte solutions [BES]) for large animal medicine are designed to be replacement fluids, not maintenance fluids, meaning that the electrolyte composition is designed to closely approximate the electrolyte composition of the extracellular fluid and not the daily replacement needs. The common BES available for horses include lactated Ringer solution, Plasma-Lyte, and Normosol-R and are principally composed of sodium and chloride with varying amounts of calcium, potassium, and magnesium. Physiologic saline solution (0.9% NaCl) differs in that it contains only sodium and chloride but no other electrolytes (see Chapter 3).

In cases of moderate to severe blood loss, infusion of large volumes of crystalloids alone can cause dilutional anemia and hypoproteinemia, although the oxygen-carrying capacity (red blood cell mass) will remain unchanged or become improved following fluid therapy. Therefore, intravenous crystalloid fluid therapy should never be withheld, even when the packed cell volume (PCV) and total solids (TS) are reduced. In the treatment of severe blood loss, dilutional coagulopathy resulting from thrombocytopenia and dilution of clotting factors can occur, leading to further bleeding and deterioration. These patients may require subsequent plasma or whole blood transfusions to improve coagulation, oncotic pressure, and oxygen content of blood. Patients with endotoxemia or SIRS often have underlying coagulopathies as part of their disease process, leaving them at particular risk for further problems with aggressive high-volume crystalloid therapy.19,20

Hypertonic Crystalloids

Hypertonic saline solution (HSS) is available in several concentrations, with 7.2% being the most commonly used formulation. At this concentration, HSS has approximately eight times the tonicity of plasma. An intravenous infusion of HSS will expand the intravascular space by approximately twice the amount infused, pulling fluid from the intracellular and interstitial spaces. This expansion is short lived and, similar to the effects of isotonic crystalloids, the majority of fluid (and electrolytes) will ultimately diffuse into the interstitial space. Because of the variation in reflection coefficients for sodium, HSS principally pulls volume from the intracellular space, not the interstitial space. This is particularly beneficial in the shock state, where endothelial cell volume rises with loss of membrane pump function. The decrease in endothelial cell volume increases capillary diameter and improves perfusion. In addition, HSS appears to blunt neutrophil activation and may alter the balance between inflammatory and antiinflammatory cytokine responses to hemorrhage and ischemia.21 The recommended dose of HSS is 2 to 4 mL/kg or 1 to 2 L for a 500-kg horse. Hypertonic saline is invaluable in equine surgical emergencies when rapid increases in blood volume and perfusion are needed to stabilize a patient before general anesthesia. The use of these fluids enables the clinician to quickly improve CO and perfusion to allow immediate surgical intervention. Additional blood volume expansion will be needed and can be provided during and after surgery to further restore homeostasis.

Colloids

Colloids are solutions containing large molecules that, because of their size and charge, are principally retained within the vascular space. Because colloid concentrations are higher in the intravascular space, they exert an oncotic pressure that opposes the hydrostatic pressure and helps retain water in or draw it into the intravascular space. Normal equine plasma has a colloid oncotic pressure (COP) of about 20 mm Hg. Colloids with a high COP can actually draw additional fluid into the intravascular space. Consequently, infusion of certain synthetic colloids such as hydroxyethyl starch (HES) (COP ~30 mm Hg) will increase intravascular volume by an amount that is greater than the infused volume. Although this effect is similar to HSS, the benefits of colloids are prolonged.

Both synthetic and natural colloids are available. Natural colloids include plasma, whole blood, and bovine albumin. The advantage of natural colloids is that they provide protein such as albumin, antibodies, critical clotting factors, antithrombin 3, and other plasma constituents. Because fresh frozen plasma must be thawed before infusion, it is often not useful in an emergency situation where immediate fluid therapy may be indicated. In
addition, hypersensitivity reactions occur in up to 10% of horses receiving plasma. The most common synthetic colloids are HES (i.e., hetastarch and tetrastarch) and dextrans. Multiple formulations of HES exist; containing amylopectin molecules of sizes ranging from 30 to 2300 kDa (average 480 kDa).

The elimination of HES occurs via two major mechanisms: renal excretion and extravasation. Larger molecules are degraded over time by \( \alpha \)-amylase. The different HES products are differentiated by the molecular weight (high, medium, low) and molar substitution ratio (number of hydroxyethyl groups per glucose molecule) of the starch molecules. Recently, a low molecular weight and molar substitution HES solution (6% HES, 130 kDa/0.4: tetrastarch) has replaced the previous higher molecular weight and molar substitution HES (6% HES, 600 kDa/0.75: hetastarch) because of concerns identified in human medicine over higher mortality, increased risk of renal replacement therapy, and coagulopathies with the higher molecular weight and molar substitution products. The current recommendations from the FDA and Surviving Sepsis Campaign are to avoid the use of hydroxyethyl starches for intravascular volume expansion in human patients with sepsis and septic shock.

Currently, there are no published reports of increased risk of renal complications or increased mortality following administration of HES products in horses, although work in this area is ongoing. Given the findings in human medicine, HES products should be used cautiously especially in patients with preexisting renal disease.

In horses, a dose of 10 mL/kg will significantly increase oncotic pressure in some patients for longer than 120 hours. Though evidence of spontaneous bleeding in healthy horses has not been documented, an increase in the cutaneous bleeding time was seen with larger doses (20–40 mL/kg) and has been associated with a decrease in von Willebrand factor antigen (vWF:Ag). Consequently, the judicious use of large volumes of HES should be considered in light of the induction of bleeding tendencies in patients. Measurement of COP must be used to assess the response to HES, because its infusion results in an expanded intravascular compartment and consequently a dilution of TS or total protein (TP), making estimates of the COP after HES infusion inaccurate.

**Whole Blood**

Whole blood is the ideal replacement fluid in patients with hypovolemic shock as a result of severe blood loss. The use of blood or plasma provides clotting factors and prevents dilutional coagulopathy. By providing red blood cells (RBCs) and protein, it helps to retain fluid within the intravascular space and improves the oxygen carrying capacity of the blood. However, there are several disadvantages. It is unusual for equine referral hospitals to store whole blood and it must be collected each time it is needed. In addition, its viscosity makes it difficult to rapidly infuse large volumes in an emergency situation. Despite these drawbacks, the use of blood or blood components can be a valuable adjunct in preventing some of the potential side effects of large-volume resuscitation, namely dilutional coagulopathy, dilutional hypoproteinemia, and anemia. The use of whole blood is generally unnecessary in patients with mild to moderate hypovolemia because restoration of perfusion often results in adequate oxygen delivery. In more severe cases of hypovolemia or in cases with ongoing bleeding, whole blood may be indicated to provide oxygen-carrying capacity, colloid oncotic support, platelets, and coagulation factors.

**Current Recommendations**

The debate regarding the use of crystalloids versus colloids is extensive. Despite this intense focus, clear benefits of colloids or hypertonic solutions over isotonic crystalloids have not been demonstrated. Rather than always using one or the other, the choice should depend on the situation. In a case of severe blood loss, hypovolemia, and impending circulatory collapse, the rapid expansion of blood volume using hypertonic and isotonic crystalloids may be imperative. The addition of colloids, whether synthetic or natural, and whole blood should depend on the severity of shock and the underlying disease process as well as the response to initial treatment.

When presented with an adult horse in hypovolemic shock it is critical to use a large 10- or 12-gauge catheter and large-bore extension set to maximize flow rate in the initial resuscitation phase. Because crystalloids have the lowest viscosity, they can be infused more rapidly than colloids or blood. If necessary, a fluid pump can be used to increase the rate of infusion. The guidelines to determine the fluid deficit (% body weight) present, based on the physical examination and clinical laboratory findings, are found in Table 3-6 in Chapter 3. In an adult horse, the circulating blood volume is estimated to be 7% to 9% of the total body weight or 35 to 45 L for a 500-kg horse. Clinical signs of blood loss will occur after the loss of 15% of circulating blood volume or approximately 6 L, during an acute hemorrhage.

As mentioned earlier, the fluid deficit should be replaced initially with a 20 mL/kg (10 L for a 500-kg horse) crystalloid intravenous bolus given over 30 to 60 minutes followed by reassessment of the hemodynamic situation. If required, an additional 10 to 20 mL/kg bolus can be given rapidly with the remainder of the estimated deficit, including any ongoing losses, and the maintenance requirement can be replaced (2–4 mL/kg/h) over the next 12 to 24 hours. If the patient fails to respond with improved hemodynamic indices following the two fluid boluses (within 3 hours of commencing therapy), additional diagnostic and therapeutic interventions are necessary.

Given the pros and cons of large-volume resuscitation fluid, goals should be estimates and not absolutes. Signs of improved intravascular volume include a decreased heart rate, improved CRT and jugular filling, skin temperature, and mentation. If possible, the measurement of urine output is extremely useful in assessing perfusion, although urine specific gravity is less accurate because it will be affected by the infusion of large quantities of crystalloids and will no longer accurately reflect hydration status. However, high urine specific gravity in the face of fluid therapy likely indicates that a fluid deficit still exists. The assessment of blood pressure can be useful in monitoring trends (i.e., an improvement of pressure toward normal). In situations where bleeding is uncontrolled, normalization of blood pressure should not be the goal because this may promote continued bleeding (permissive hypotension, i.e., mean arterial blood pressure [MAP] >65 mm Hg, rather than MAP >90 mm Hg).

**Vasopressors**

Vasopressors are rarely used in standing adult horses in hypovolemic shock. Restoration of circulating volume is the primary treatment goal. However, if the administration of appropriate fluid volumes and types is insufficient to stabilize the patient, vasopressors may be indicated, particularly as shock progresses and vasomotor tone and cardiac ischemia cause a further fall in...
perfusion. The most commonly used drug in awake, adult horses is dobutamine. Dobutamine is a strong β₁-adrenoreceptor agonist with relatively weaker β₂- and α-adrenoreceptor affinity. Its primary use is to improve oxygen delivery to the tissues via its positive inotropic action. Dobutamine has been shown to improve splanchnic perfusion in multiple species, although clinical data are lacking in the horse. Recommended dosages are 1 to 5 μg/kg/min. Higher doses have been reported to cause hypertension, tachycardia, and arrhythmias in the adult horse.

Norepinephrine has been reported to be useful in restoring adequate organ perfusion in vasodilatory shock in neonatal foals. Norepinephrine has strong β₁- and α-adrenoreceptor affinity, resulting in vasoconstriction and increased cardiac contractility. It has been successfully used in combination with dobutamine to improve arterial pressure and urine output in persistently hypotensive foals. The use of norepinephrine in standing sedated healthy adult horses has been evaluated recently, with norepinephrine counteracting the vasodilatory and hypotensive effects of acepromazine with no arrhythmias or excessive hypertension detected.

Vasopressin is released from the pituitary gland following periods of hypotension and is a powerful vasoconstrictor in addition to its effects in the kidney. It is administered exogenously as a vasopressor when treating vasodilatory shock in humans and occasionally in horses under general anesthesia, if hypotension does not respond to other vaspressors.

Plasma concentrations of AVP have been shown to increase in horses with colic, presumably as a compensatory mechanism for hypotension, but the use of exogenous AVP in standing horses to treat systemic hypotension has not yet been investigated. In hypotensive anesthetized neonatal foals, the use of AVP resulted in less splanchnic circulation than norepinephrine or dobutamine.

At this time, there is little published information on the use of vasopressors to treat hypovolemic shock in awake adult horses. Consequently, it is difficult to make further recommendations for their use. Close monitoring of urine output and blood pressure is recommended when using vasopressor therapy.

Monitoring

The body’s compensatory responses are designed to restore many of the variables used to assess hypovolemia or perfusion deficits. Consequently, in the early stages of shock, there is no perfect measure to assess progression. Despite this, there are several physical and laboratory variables that can be useful in monitoring the patient’s progression and response to treatment.

Repetitive physical exams focusing on assessment of CO and perfusion may be the most sensitive method to assess a patient, especially during early compensated shock when subtle changes may indicate impending decompensation. Heart rate, CRT, jugular venous fill, extremity temperature, pulse pressure, urine output, and mentation are all useful when repeatedly evaluated. Steady improvement and stabilization of these variables in response to treatment would suggest a positive response. Continued tachycardia and poor pulse pressure, CRT, jugular fill, and deteriorating mentation despite treatment suggest that additional blood loss or decompensation is occurring.

Capillary Refill Time

CRT is usually prolonged in hypovolemic shock. However, CRT can also be affected by changes in vascular permeability such as seen with endotoxemia or sepsis. In these situations, CRT may actually decrease because of vascular congestion and pooling of blood in the periphery. Though CRT at any one time point can be misleading, if repeatedly assessed over time, it is useful in evaluating the progression of shock.

Central Venous Pressure

Central venous pressure (CVP) assesses cardiac function, blood volume, and vascular resistance or tone. Jugular fill is a relatively crude assessment of venous return or CVP. Holding off the jugular vein should result in visible filling within 5 seconds in a normally hydrated horse that is standing with an elevated head. If filling is delayed, venous return or CVP is decreased. A more accurate estimate of CVP can be obtained with a water manometer, attached to a large-bore jugular catheter and placed at the level of the heart base or point of the shoulder. Normal CVP in standing horses ranges from 7 to 12 mm Hg, with pressure measured by inserting a catheter into the cranial vena cava/right atrium. Measurement of pressure in the jugular vein using a standard IV catheter will result in falsely elevated CVP; however, this measurement can still be a useful estimation to monitor changes over time in response to therapy. During an experimental blood loss model, intrathoracic CVP (measured somewhere within the cranial vena cava/right atrium) fell to zero or below with a loss of 15% to 26% of circulating volume. In an experimental hypohydration model, intrathoracic CVP also fell below zero following loss of 4% to 6% body weight. Because CVP is a measure of venous return, it can be used to assess the adequacy of fluid resuscitation and prevent fluid overload, especially in patients at risk for edema (i.e., those with concurrent renal disease). If clinical signs are deteriorating despite a normal CVP, hypovolemia alone is not the cause. Low CVP can occur with hypovolemia or a drop in effective circulating volume, as occurs with distributive shock. Cardiogenic shock, fluid overload, or pericardial effusion can result in an elevated CVP, because forward failure of the cardiac pump results in backup of blood within the venous side of the system. In this case, jugular veins may appear distended even with the head held high. Cardiogenic shock is a relatively rare cause of shock in adult horses but should be considered in patients with unexplained tachycardia and other signs of cardiac disease.

Urine Output

Urine output is a sensitive indicator of hypovolemia with normal urine production being approximately 1 mL/kg/h or more, depending on how much water an individual is drinking. Production of less than 0.5 mL/kg/h suggests significant volume depletion, and fluid therapy is indicated to prevent renal ischemia. Urine output is rarely measured in adult horses, though it is relatively simple to perform and commonly done in neonatal medicine. A sterile urinary catheter (Foley catheter or similar) is placed and attached to a closed collection system (e.g., empty resterilized 5-L fluid bag connected to an administration set and Christmas tree adapter) that is subsequently affixed to the ventral aspect of the horse (e.g., using a postoperative colic abdominal support bandage). Care should be taken to remove the catheter as soon as adequate urine production is established to reduce the risk of nosocomial infection. Increased urine production coupled with improvement in physical exam abnormalities suggests a positive response to treatment. Though urine specific
gravity can be used to assess renal concentrating efforts and consequently the water balance of the animal, it will be affected by intravenous fluid therapy and is not an accurate reflection of dehydration or volume status once bolus intravenous fluids have begun.

**Arterial Blood Pressure**

Arterial blood pressure is a reflection of CO and total vascular resistance. Consequently, the measurement of a normal blood pressure does not directly correlate with adequate perfusion and oxygen delivery to peripheral tissue beds. Because of the compensatory increase in peripheral resistance, blood pressure does not consistently fall below normal until the blood volume is profoundly decreased (30% or more). Though a normal blood pressure does not rule out hypovolemic shock, a low blood pressure is often an indicator of significant blood loss. Treatment goals should be to maintain the MAP above 65 mm Hg to ensure adequate perfusion of the brain. Blood pressure can be measured directly via arterial catheterization of the transverse facial artery in the adult horse or the transverse facial, metatarsal, radial, and auricular arteries in neonates. Indirect measurement of the blood pressure can be achieved using the coccygeal artery in adult horses and the metatarsal artery in foals.35 In healthy individuals, there is good agreement between direct and indirect measurements.35–38 Direct, invasive blood pressure monitoring is more accurate during states of low flow and significant hypovolemia.45–47 However, the same is not true in horses with arrhythmias.

**Lactate**

L-lactate is the end product of the anaerobic metabolism of glucose. Aerobic metabolism of glucose results in the production of 36 moles of adenosine triphosphate (ATP) per molecule of glucose. In the absence of adequate oxygen to meet energy demands, anaerobic metabolism of glucose to lactate results in production of only 2 moles of ATP. Consequently, inadequate oxygen delivery to the tissues increases blood lactate concentrations (type A hyperlactatemia). Less commonly, hyperlactatemia can develop despite appropriate tissue oxygenation (type B hyperlactatemia) as a result of hepatic dysfunction (impaired clearance), pyruvate dehydrogenase inhibition, catecholamine surges, and sepsis or SIRS.48–50

However, the increase in lactate concentrations in type 2 cases is generally less than what is seen in horses with hypovolemia. Because the lactate concentration generally correlates with oxygen delivery and uptake by the tissues, it is a useful marker for determining perfusion deficits and response to treatment. Delayed lactate clearance is shown to be associated with a poorer prognosis in many human and veterinary studies.48,49 A decrease in lactate following therapy indicates improved oxygen delivery and use, suggesting improved perfusion. Conversely, an increased or persistently elevated lactate level indicates continued tissue oxygen deficits. In some cases of severely reduced tissue perfusion, resuscitation attempts resulting in improved tissue perfusion can result in increased plasma lactate concentrations as the lactate is flushed out of the tissues, temporarily exceeding the metabolism and clearance capacity. For this reason, trends should be observed over 12 to 24 hours, while caution should be used when interpreting short-term (1–2 hours) changes in lactate.

**Oxygen Extraction**

The normal response to a decrease in perfusion or CO is to increase the oxygen extraction ratio (O2ER) of the blood as it moves through the capillaries. By increasing the oxygen extraction, the body is able to maintain oxygen delivery to the tissue despite a fall in blood flow. Oxygen extraction is determined by the difference between the oxygen saturation of arterial blood (SaO2) and oxygen saturation of venous blood (SvO2):

\[
O_2\text{ER} = (SaO_2 - SvO_2) / SaO_2
\]

It can be determined by measuring central venous saturation and arterial oxygen saturation. Alternatively, O2ER can be estimated by measuring jugular venous saturation and by using a pulse oximeter to assess arterial oxygen saturation. In the normovolemic, healthy individual, DO2 far exceeds oxygen need or uptake (VO2), and the O2ER ranges from 20% to 30% (one of the four O2 molecules from each Hb is removed). The O2ER can increase with decreased perfusion to a maximum of 50% to 60% (two of the four O2 molecules are removed) at which point oxygen delivery becomes supply or flow dependent and a further drop in perfusion will result in a decrease in oxygen delivery. Because of this relationship, the O2ER can be used to estimate the severity of global perfusion deficits and is a useful measurement in evaluating the response to resuscitative strategies.

**Mixed Venous Partial Pressure of Oxygen**

Mixed venous partial pressure of oxygen (PvO2) is a useful measure to assess oxygen delivery for the same reasons that O2ER is. In low-perfusion states, more oxygen is extracted per volume of blood and, consequently, PvO2 will fall. Mixed venous blood is ideally measured by catheterizing the pulmonary artery, because a sample from the jugular vein or cranial vena cava only assesses venous blood returning from the head. Jugular venous pressure of oxygen (PjvO2) is usually greater than PvO2 in the shock state, but it still is useful in estimating global tissue hypoxemia.47,48 Normal PjvO2 ranges from 40 to 50 mm Hg and SjvO2 from 65% to 75%.47,49 Increased venous partial pressure of oxygen in the presence of significant perfusion or supply deficits (DO2) can signify impaired oxygen consumption caused by mitochondrial or cellular dysfunction. This syndrome has been recognized in septic shock or after cardiopulmonary resuscitation.

**Cardiac Output**

CO monitoring evaluates both volume return to the heart and cardiac function. With prolonged or specific types of shock (septic), cardiac function may deteriorate and increasing fluid resuscitation will not resolve the clinical signs of end organ perfusion deficits. The gold standard for CO monitoring is the pulmonary thermodilution method, which requires catheterization of the pulmonary artery. This technique is rarely performed in the equine clinical setting. An alternative technique, lithium dilution, is relatively easy to use once experienced, and it has
been validated in the equine clinical setting. Injection of lithium dye into the venous system results in generation of a lithium concentration–time curve, which is used to calculate CO. Lithium dilution has been shown to monitor CO in adult horses and critically ill foals.60–62 Note that repetitive sampling can result in toxic accumulation of lithium.24

Transcutaneous 2D echocardiography is becoming a more commonly utilized tool for noninvasive assessment and monitoring of the cardiovascular status in critical patients. Volumetric methods (“four chamber area length,” “Simpson,” and “bullet”) for measuring CO have been shown to have better agreement with lithium dilution CO than Doppler-based methods.51,55–57 Because Doppler measurements require the ultrasound beam to be parallel with flow, which is difficult to achieve in an adult horse, there is large variability in the accuracy of this technique.31,56,58 An ultrasound velocity dilution method has been described in foals.59 This technique uses a bolus injection of saline and an arteriovenous loop connected to ultrasound velocity sensors. Pulse contour analysis or pulse pressure changes that are useful for measuring responses to therapy in humans have not been evaluated in horses but deserve further investigation as noninvasive measures of CO.15

CO measurement has its greatest benefit in cases that fail to respond as expected to initial resuscitation efforts, cases with complex disease involving multiple organ systems, or those with cardiac disease. Assessment of CO and blood pressure is essential when monitoring the response to vasopressor treatment. Because CO does not assess local tissue perfusion, its accuracy in evaluating tissue oxygenation is poor. Many of the standard monitoring techniques are limited because they principally assess global function (e.g., CO) and global oxygen debt (e.g., mixed venous lactate), not regional tissue deficiencies. These global measures, while being helpful, do not assess the perfusion to high-risk organs such as the gastrointestinal tract, and may provide a false sense of security when used to monitor treatment response. With the exception of urine output, none of the above-described measurements evaluate perfusion to regional vascular beds. Because of the large variation in perfusion to specific tissues, such as the gastrointestinal tract and the brain, these global measures have poor sensitivity in determining oxygen delivery and uptake to “less important tissues.”

Regional Perfusion
Several techniques have been developed in an effort to more specifically assess these differences in regional perfusion. Noninvasive measures of regional tissue perfusion in human patients include sublingual capnometry, near-infrared spectroscopy to monitor muscle tissue oxygen saturation, transcutaneous tissue oxygenation, orthogonal polarization spectral imaging, and capnometry.60–62 Slightly more invasive techniques include gastric tonometry, which evaluates CO₂ production in the stomach wall; infrared spectroscopic assessment of splanchic perfusion; and measurement of bladder mucosal pH.53,54 These alternative techniques are based on the idea that the body preferentially shunts blood away from the skin and gastrointestinal tract to spare more vital organs. As such, these methods will detect abnormalities in perfusion before many of the more established techniques. Although not yet fully evaluated in the veterinary field, these techniques have been shown to be sensitive markers of regional perfusion deficits in early shock in humans.

Hypotensive Resuscitation and Delayed Resuscitation
As previously discussed, aggressive large-volume fluid therapy to restore blood pressure to normal values has potentially negative consequences. In situations of uncontrolled bleeding, this treatment will result in increased blood loss. Dilution of blood components (platelets and clotting factors) may additionally worsen bleeding. Increasing systolic blood pressure to normal values may dislodge or “blow out” a tenuous clot, leading to further bleeding. Hypotensive resuscitation has been advocated to prevent or minimize further blood loss until surgical control or formation of a stable clot has occurred. In these situations, resuscitation to a lesser end point is recommended. The ideal end point or goal in hypotensive resuscitation is unclear. Strategies include achieving a MAP of 60 to 65 mm Hg, using a predetermined, lower fluid infusion rate, or in some situations, completely delaying fluid resuscitation until bleeding is surgically controlled.65 In multiple animal models, controlled resuscitation (goal of MAP 40–60 mm Hg, or systolic blood pressure of 80–90 mm Hg) resulted in decreased blood loss; better splanchic perfusion and tissue oxygenation; less acidemia, hemodilution, thrombocytopenia, and coagulopathy; decreased apoptotic cell death and tissue injury; and increased survival.13,66–73 In cases of severe or ongoing bleeding, resuscitation with blood components is recommended to minimize the risk of coagulopathy, although data with respect to outcome compared to resuscitation with crystalloids in horses are currently lacking. This strategy of hypotensive resuscitation (with whole blood as part of the fluid plan) is indicated in situations such as bleeding of the uterine artery in a pregnant mare, where ligation of the vessel is unlikely and of great risk to the mare and fetus. There are currently no specific recommendations for end points of treatment in large animal species. If using blood pressure as the end point, direct measurement is currently recommended to ensure Accuracy.

Predicting Outcome
In a critical review, high-risk surgical patients were used as a model for shock because time relationships could be precisely documented.74 Nonsurvivors had reduced CO and DO₂ in the intraoperative and immediate postoperative period. Survivors had lower O₂ER; higher hematocrits, VO₂, and blood volume; and normal blood gases. In human trials, time is a strong predictor of survival, with survivors showing fast improvement or normalization of CO, perfusion, oxygen uptake, and clinical variables.75 To this end, rapid control of hemorrhage, restoration of perfusion, normalization of blood gas values, and prevention of dilutional coagulopathy are predictors of survival. In patients with ongoing blood loss, controlled hypotension has been shown to decrease in-hospital complications and possibly increase survival rates. Lactate values, particularly lactate clearance, have been shown to be strongly associated with survival in both clinical and experimental studies of shock.60–62 Though the data are not as robust, single lactate measurements and delayed lactate clearance have been shown to be associated with higher mortality rates in both adult horses and foals.14,67–71 A poor or absent response to resuscitative attempts with continued evidence of perfusion deficits or the development of clinical evidence of organ dysfunction, or both, are associated with a poorer outcome.
On the Horizon

Treatment

Although further research is required, there is strong evidence that a “balanced resuscitation” plan with goal-directed therapy in patients with hypovolemic shock provides improved outcomes of survival when compared to the previous “aggressive resuscitation” strategies aimed to replace volume deficits in a short period of time. The perfect fluid protocol for treatment remains elusive, and the debate between crystalloids versus colloids continues. Liposome-encapsulated Hb may offer more benefits than other fluids because of its oxygen-carrying capacity. The presence of Hb reduces the need for blood products, thereby lowering the associated risks to the patient. In contrast to other synthetic oxygen carriers, liposome-encapsulated Hb vesicles do not appear to cause peripheral vasoconstriction and in a rat model of hemorrhage appear to be as effective in restoring hemodynamic and blood gas variables.

Monitoring

The ideal method to assess shock and treatment response would enable measurement of oxygen delivery at the tissue level as well as oxygen uptake and use. The ability to measure end organ perfusion in veterinary patients, particularly in “less important” organs like the epidermis, has potential implications in assessing the severity of the shock state, developing treatment goals, and predicting outcomes. The implementation and evaluation of these techniques in equine critical care medicine is warranted.

Physiologic Response to Trauma

The metabolic response to trauma or injury has classically been divided into two phases—the ebb phase, which occurs during the first several hours after injury, and the flow phase, which occurs in the ensuing days to weeks. The ebb phase is characterized by hypovolemia and low flow or perfusion to the injured site. Once perfusion is restored, the flow phase begins. The flow phase is divided into a catabolic period and an anabolic period. The catabolic period is triggered by many of the same mediators discussed in the earlier section on the pathophysiology of shock, and many of the clinical signs will mimic those seen in shock. The anabolic period is characterized by the return to homeostasis. Cortisol levels fall during this final period and normalization of physiology occurs. The physiologic response to trauma is complex, and the duration and progression will vary depending on the injury site, severity, and underlying condition of the patient. For more specific information regarding trauma of specific organs or body cavities, the reader is referred to chapters dealing with those specific systems. This section is designed to provide an overview of the complex pathophysiology of trauma.

Mediators of the Stress Response: Ebb Phase

The stress response to trauma is initiated by pain, tissue injury, hypovolemia, acidosis, shock, hypothermia, and psychological responses. Direct tissue injury, ischemia, and inflammation activate afferent nerve endings, which exert local and systemic effects via the central nervous system. Hypovolemia, acidosis, and shock exert their effects via baroreceptors and chemoreceptors located in the heart and great vessels. Fear and pain have conscious effects in the cortex, and they stimulate cortisol secretion via the hypothalamic-pituitary-adrenal axis (HPA), which increases sympathetic output. Because of this effect, modulation of pain has been shown to be important in controlling the stress response to trauma, and pain control should be strongly considered in the trauma patient.

The sympathoadrenal axis is stimulated through direct input from injured nerves and by hypovolemia, acidosis, shock, and psychologic responses (fear, pain, anxiety). Catecholamines have widespread effects on cardiovascular function (see “Pathophysiology of Shock,” earlier in this chapter) and metabolism (see “Metabolic Response to Injury” in Chapter 6), and they stimulate release of other mediators, including cortisol and opioids. The catecholamine response is beneficial; however, prolonged sympathoadrenal stimulation can be detrimental because of its effects on general body condition. Catecholamines increase peripheral vascular resistance, so ongoing stimulation leads to long periods of tissue ischemia.

Other triggers of cortisol secretion in trauma and shock include AVP, angiotensin II, norepinephrine, and endotoxin. The degree of hypercortisolemia correlates with the severity of injury and persists until the anabolic phase of healing begins. Cortisol secretion results in sodium and water retention (edema), insulin resistance, gluconeogenesis, lipolysis, and protein catabolism. Cortisol also affects leukocytes and inflammatory mediator production and, although cortisol is critical for recovery from acute injury, prolonged cortisol secretion can result in pathologic suppression of the immune response.

AVP and the RAAS are important mediators of the stress response. The reader is referred to the section on pathophysiology of shock for further review of these mediators.

Endogenous opioids released from the pituitary gland as well as from the adrenal glands in response to sympathetic stimulation are important mediators in the modulation of pain, catecholamine release, and insulin secretion. Endogenous opioids modulate lymphocyte and neutrophil function and may act to counter cortisol’s effect on immune function.

Local mediators released in response to injury trigger a multitude of cascades. Tissue factor exposure activates the coagulation and complement cascades and ultimately stimulates the inflammatory response. Cell membrane injury results in release and activation of the arachidonic acid cascade and production of various cytokines, including prostaglandins, prostaeryclines, thromboxanes, and leukotrienes. These mediators have a multitude of functions including further activating coagulation and platelets; altering blood flow via vasoconstriction and vasodilation; and increasing chemotactic activity mediating the influx and activation of inflammatory cells, with subsequent release of lysosomal enzymes and reactive oxygen species (ROS). Microvascular thrombosis at the site of endothelial injury causes further pathologic changes in perfusion. If perfusion is restored, elevated local concentrations of ROS, coupled with influx of oxygen, can induce further oxidative stress and production of highly toxic ROS that result in more tissue damage. Amplification of this response coupled with reperfusion can lead to the development of SIRS and MOD.

Response to Trauma: Catabolic Period

Psychological response to trauma and shock is manifested in changes in behavior, withdrawal, immobilization or reluctance to move, fear, anxiety, aggression, and malaise. These psychological responses can persist for long periods depending on the severity
of the injury and pain. In people, the psychological effect may persist long after the injury has resolved. Whether the same happens in horses has yet to be determined.

Many of the changes in vital signs will mimic those seen with hypovolemic shock. Cardiovascular changes including tachycardia, tachypnea, and other clinical signs of the hyperdynamic response may be seen. Fever during the early period after injury is typically a response to injury and inflammation itself, particularly in patients with head trauma. Infectious causes of fever should be suspected if fever persists or is recurrent days after the injury. Other clinical signs will depend on the severity of blood loss and the organ injured. Cardiovascular changes including hypotension, decreased perfusion, decreased urine output, and reduced cardiac contractility are likely to occur with significant blood loss or thoracic contusion. Endotoxemia and bacteremia are likely with gastrointestinal injury, such as strangulating injury to the intestine.

Edema at the site of injury is caused by vascular injury from the trauma and the inflammatory response, which results in loss of capillary integrity and extravasation of protein and fluid. In severe injury, edema may become generalized. This generalized edema results from systemic inflammatory, hormonal, and autonomic responses that increase capillary pressure and salt and water retention. The presence of hypoproteinemia can exacerbate clinical edema as colloid oncotic pressure is decreased.

The metabolic response to trauma is complex and results in changes in the metabolic rate as well as the mobilization and utilization of energy stores. Decreased appetite and malaise are also seen in response to pain, cytokines, and hormones. The reader is referred to Chapter 6 for a more detailed description of the metabolic changes occurring with injury.

Coagulation is activated by endothelial injury and the expression of tissue factor. Tissue factor also activates complement and inflammation. These changes combined with release of arachidonic acid from damaged cell membranes stimulate production of multiple inflammatory mediators, platelet activation and adhesion, and fibrinolysis. Blood loss coupled with crystalloid replacement can further dilute platelets and coagulation factors, which, in combination with factor consumption to control bleeding at the site of injury, can result in development of a hypocoagulable state. Coagulation dysfunction is recognized in many types of injury including large colon volvulus, severe traumatic injury, SIRS, and septic shock.

Circulating leukocytes increase in the initial response to injury with subsequent accumulation in injured microvascular beds. This accumulation may be exacerbated by vasoconstriction in response to hypovolemia and catecholamine surges, and may play a role in reperfusion injury because activated neutrophils are a major source of reactive oxygen metabolites. In addition to changes in circulating leukocytes, the immune response can be altered significantly with severe trauma. Decreases in antibody production, neutrophil chemotaxis, and serum opsonic activity; increases in serum immunosuppressive factors; and activation of T-cell suppressors mediated by neurohumoral stress response are just some of the changes that may occur.

**Response to Trauma: Anabolic Period**

The final stage in recovery is the anabolic phase of flow. During this period, many of the responses return to normal. Appetite returns, body protein is synthesized, and weight is restored, resulting in improved organ function and energy stores. Metabolic demands diminish, water balance is restored, and as hormonal levels decrease, a generalized feeling of well-being develops. The length of this period will depend on the severity of the injury, the number and type of complications, the patient’s condition before injury, and the length of the catabolic period of recovery. Healthy individuals that do not develop complications will likely recover more rapidly than debilitated patients that suffer complications, such as infection, and have a prolonged catabolic phase of recovery.

**REFERENCES**

CHAPTER 1 SHOCK


