RESUSCITATION FROM HYPOVOLEMIC SHOCK: EMERGENCY AND CRITICAL CARE
MOVING IN AND PREVENTING THE KILL
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Shock is a phenomenon manifesting as inadequate tissue perfusion resulting from loss of effective circulating volume. Significant loss of intravascular volume, or hypovolemia, results in decreased transport of oxygen and nutrients to the cells and impaired cellular waste removal. Profound hypovolemia can result from trauma, loss of plasma water during vomiting and diarrhea, extreme vasodilation from systemic inflammation, and significant hemorrhage. Hypovolemic shock occurs when the natural neuroendocrine compensatory responses fail to restore and maintain tissue perfusion. A positive outcome during hypovolemic shock resuscitation is optimized by diligent inspection and anticipation of the disease process, aggressive fluid resuscitation and hemostasis, followed by continuous monitoring and reassessment.

Cellular Homeostasis
Transmembrane ion pumps regulate intracellular water maintaining cellular and organelle function. Cellular function (i.e., organ function) is exclusively dependent on efficient pump function. Energy driving transmembrane ion exchange is supplied by cleavage of ATP. In contrast to 38 ATP molecules that are produced during aerobic metabolism with adequate oxygen supply, anaerobic metabolism (inadequate oxygen supply during hypovolemic shock) produces lactate and only two ATP molecules per glucose molecule.

Cardiovascular Contribution
The conduit for fluid transport is the vascular system. The heart serves as the conduit pump. Oxygen delivery is the product of arterial flow and arterial oxygen content. Hemoglobin concentration and its dissociation curve are the prime components of arterial oxygen content. Arterial flow is a product of cardiac output and systemic vascular resistance. Cardiac output is a product of myocardial contraction and heart rate. Reduced sinus node stretch caused by hypovolemia results in an increased heart rate and contractility, promoting volume ejection. Venous return (preload) increases the stretch of the heart chambers resulting in increased force of contraction. Factors influencing venous return to the heart include: mean circulatory filling pressures, right atrial pressures, and resistance of the arteries.

Blood flow is also influenced by pressure differences and compliance within the vascular circuit as well as viscosity of the fluid medium. Extrinsic and intrinsic regulation of the cardiovascular system will also affect blood flow to the tissues. Intrinsic metabolic autoregulation affects local organ blood flow, and is influenced by oxygen availability and removal of metabolic byproducts. Extrinsic control is produced by a combination of hormonal and catecholamine influences.

Since most tissues are unable to store oxygen, cellular oxygen uptake from the capillaries is considered equivalent to the metabolic consumption of oxygen. ATP production becomes heavily dependent on oxygen availability during high energy output states. Optimum ATP production, therefore, depends on both oxygen delivery (DO₂) to the cell and oxygen utilization (VO₂) by the cell. In addition to oxygen supplementation, reestablishing and maintaining intravascular fluid volume, hemoglobin, and cardiac output is necessary for maximum oxygen delivery.

Intravascular Fluid Maintenance
Fluids are in a constant state of flux across the capillary endothelial and cellular barrier, and travel through the interstitium between the intravascular and intracellular compartments. The amount of fluid that moves out of the capillary into the interstitial space depends on a number of factors including colloid osmotic pressure (COP), hydrostatic pressure, and capillary permeability. An alteration in any one of the factors can result in inadequate oxygen delivery to the cell, significantly reduced ATP production, and cessation of transmembrane transport of solutes. This produces an unregulated osmotic shift, loss of membrane integrity, and cellular rupture. Nuclear formation of proteins is suspended, contraction of cardiac muscle falters, and neuronal synapses fail. Hypovolemia is a factor that can exacerbate each of the shock states (cardiogenic, distributive, and hypovolemic), influencing oxygen transport to the cell.

Physiologic Response to Hypovolemia
Acute loss of effective circulating volume leading to poor oxygen delivery can occur with a number of disease processes, significant vasodilation (seen with anesthetic agents), decreased fluid intake and increased fluid loss, and
increased capillary permeability. With diseases causing a systemic inflammatory response syndrome (SIRS), increased capillary permeability results in translocation of significant quantities of fluid from the intravascular space.

**Compensatory Stage of Hypovolemic Shock**

An acute decrease in intravascular volume causes a decrease in venous return and cardiac output. Lack of stretch in the carotid body and aortic arch baroreceptors causes neurological impulse transmission to the brain stem initiating a decrease in peripheral vagal tone and an increased sympathetic stimulation. Vasoconstriction, increased heart rate, and increased cardiac contractility initiate a compensatory response to hypovolemia by mobilizing intravascular fluid.

Changes in transcapillary pressure gradient (increased intravascular COP, decreased intravascular hydrostatic pressure) result in increased water retention in the intravascular space. The renin-angiotensin-aldosterone system will increase water reabsorption by the kidneys. These mechanisms increase intravascular volume and venous return, which improves cardiac output and arterial flow. Energy is required to sustain this compensatory mechanism, and an adequate oxygen supply may be required to meet these energy needs. Glucose substrate required for cellular energy production is provided through the metabolic actions of the stress hormones (glucagon, growth hormone, cortisol, and ACTH).

These natural neuroendocrine responses can be adequate to compensate for mild to moderate acute decreases in intravascular volume, and result in the **compensatory stage** of hypovolemic shock. The cat does not typically display a compensatory shock response. Clinical signs in the dog include hyperemic mucous membranes, tachycardia, quick capillary refill time, and normal to increased arterial blood pressure, and should not be interpreted as normal. Maintaining arterial blood pressure is at the expense of an increased heart rate and mild vasoconstriction, which requires increased energy utilization. Rapid intravascular volume expansion therapy is necessary to stretch the baroreceptors, and remove the stimulus for this hypermetabolic state.

Should the natural neuroendocrine mechanisms be inadequate to restore baroreceptor stretch, should cardiac dysfunction exist, or should intravascular volume and systemic vascular resistance be inadequate, cardiovascular decompensation occurs.

**Early Decompensatory (Middle) Stage of Hypovolemic Shock**

Continued low cardiac output amplifies sympathetic stimulation, clinically manifesting as significant peripheral vasoconstriction and tachycardia. Selective vasoconstriction of the skin, mucous membranes, and splanchnic bed shunts arterial blood flow to preferred organs (i.e., heart and brain) to ensure basic life support. Cellular oxygen and energy demands increase as vasoconstriction intensifies. Oxygen consumption becomes dependent on oxygen delivery, and anaerobic glycolysis results in lactic acid production. Other vasoactive substances produced due to local tissue hypoxia at the capillary level cause local vasodilation and increased capillary permeability resulting in maldistribution of blood flow in the hypoxic tissue beds.

When chemical mediators (cytokines) produced locally in hypoxic tissues enter the systemic circulation they incite a SIRS. Significant vasodilation and damage at the endothelial lining resulting in increased capillary permeability further depletes intravascular volume. Redistribution of blood flow occurs, leading to further consequences.

This multilevel cellular dysfunction places the animal in the **early decompensatory (middle) stage** of hypovolemic shock. Clinical signs of this stage in the dog include tachycardia, pale mucous membrane color, prolonged capillary refill time, and hypotension. Cats with hypovolemic shock will present with a subnormal temperature, decreased heart rate, and a low arterial blood pressure. In the cat, the neuroendocrine response to hypovolemia appears to promote vasodilation, hypothermia, and bradycardia. Hypothermia can also lead to a poor response by the catecholamine receptors, augmenting vasodilation and bradycardia.

**Late Decompensatory (Final) Stage of Hypovolemic Shock**

When intravascular volume loss is massive, when earlier compensatory responses are ineffective or inadequately treated, when the insult is severe and overwhelming, or when central pathology blunts the typical compensatory response, **late decompensatory shock** ensues. The cells are unable to meet the demands for ATP, manifesting in
circulatory collapse and insufficient arterial flow to the brain and heart. The sympathetic center in the brain malfunctions, and the heart cannot sustain either a chronotropic or inotropic response.

Clinical signs of this terminal stage are a result of organ failure: bradycardia, hypotension, no capillary refill time, white or cyanotic mucous membrane color, and anuria. Cardiopulmonary arrest is imminent without extreme supportive measures of compromised organs and aggressive cardiovascular resuscitation. The key to survival is aggressive resuscitation early in the shock process.

**Resuscitation from Hypovolemic Shock**
The ultimate goal is to deliver sufficient oxygen and substrate to the tissues for the cells to produce energy. Needed are intravascular volume to fill the vessels, a functioning pump, hemoglobin, oxygen supply, vascular tone, and an intact vasculature. Oxygen is administered by nasal catheter (0.1–0.2 L/kg/minute) or using a mask, hood, or clear bag. Single or multiple intravenous catheters are placed, and analgesia administered a needed. Control of external hemorrhage is initially accomplished by direct compression or bandaging. Vascular access is established and fluid administration initiated. Life-threatening intrathoracic or intraabdominal hemorrhage may require emergency surgical intervention for hemostasis.

**The Fluid Therapy Plan**
The fluid therapy plan typically has a resuscitation, rehydration, and maintenance phase. Resuscitation implies an urgent need to restore tissue perfusion and oxygenation. Because hypovolemia can be a significant component of most types of shock (even cardiogenic shock), the intravascular volume status must always be established. The type, quantity, and rate of fluid administration required to reach the desired resuscitation end-points are determined and will depend on the type of shock and underlying conditions.

**Table 1: Crystalloid and Colloid Infusion Techniques**

<table>
<thead>
<tr>
<th>FLUID</th>
<th>LARGE VOLUME Dog</th>
<th>SMALL VOLUME Dog &amp; Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isotonic Replacement Crystalloid</td>
<td>20–30 ml/kg rapid infusion</td>
<td>10–15 ml/kg rapid infusion</td>
</tr>
<tr>
<td>Hydroxyethyl Starch</td>
<td>5–10 ml/kg rapid infusion</td>
<td>3–5 ml/kg rapid infusion</td>
</tr>
</tbody>
</table>

**Table 2: End-point Resuscitation Goals**

<table>
<thead>
<tr>
<th>NORMAL PARAMETERS</th>
<th>PERMISSIVE HYPOTENSION</th>
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<tbody>
<tr>
<td>MAP 80–100 mmHg</td>
<td>MAP 60 mmHg</td>
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<tr>
<td>HR normal</td>
<td>HR &lt;180 bpm</td>
</tr>
</tbody>
</table>

MAP: Mean arterial blood pressure  HR: Heart rate

**Table 3: Infusion Technique Based on Systems Affected**

<table>
<thead>
<tr>
<th>FLUID</th>
<th>LARGE VOLUME Dog</th>
<th>SMALL VOLUME Dog &amp; Cat</th>
<th>END VOLUME</th>
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</thead>
<tbody>
<tr>
<td>Hypovolemic shock</td>
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<tr>
<td>Hemorrhage</td>
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<td>Pulmonary disease</td>
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<td>Cardiac disease</td>
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<td>Neurological disease</td>
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<tr>
<td>Renal disease</td>
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<tr>
<td>20–30 ml/kg rapid infusion</td>
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<tr>
<td>10–15 ml/kg rapid infusion</td>
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<tr>
<td>60–90 ml/kg</td>
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<tr>
<td>ISOTONIC CRYSTALLOID</td>
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<tr>
<td>HYDROXYETHYL STARCH (HES)</td>
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<td>10–20 ml/kg rapid infusion</td>
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**Crystalloids**

A crystalloid is a water-based solution with small molecules that are osmotically active in the body fluids and permeable to the capillary membrane. The amount that remains in the vessel depends on Starling’s forces and the distribution of total body water (TBW; 66% is intracellular, 25% is interstitial, and 9% is intravascular). The sodium concentration provides the greatest contribution to crystalloid osmolality. Convention has defined an *isotonic* fluid as one that has an osmolality equal to that of erythrocytes and therefore does not affect the exchange of fluid across the erythrocyte membrane. A *hypertonic* fluid will decrease erythrocyte volume, and a *hypotonic* fluid will increase erythrocyte volume.

A hypotonic fluid has an osmolality less than intracellular fluid, such as 5% dextrose in water (D5W). The glucose is rapidly metabolized and the administered volume of water is distributed according to the osmotic gradients that determine the distribution of TBW (66% goes intracellularly). It is not used during the resuscitation or rehydration phase, but can be used for reestablishing intracellular water deficits after resuscitation and rehydration have occurred. It is also used as a carrier fluid for low volume constant rate infusion of medication.

Hypertonic fluids such as 7% and 23% saline have more osmotically active particles per unit volume than intracellular fluid. After administration, water moves via osmosis from the interstitial and intracellular compartments into the intravascular space. There is a rapid increase in intravascular volume until Starling’s forces bring the equilibrium back across the capillary membrane. It is necessary for the kidney to excrete the additional administered sodium.

Hypertonic saline has been reported to produce a mild inotropic effect, systemic and pulmonary vasodilation, and rapid intravascular volume expansion. It has been used in combination with crystalloids and colloids for rapid intravascular volume expansion in hypovolemic shock. Extreme caution is used if administered to patients that are dehydrated, hypernatremic, hyperchloremic, hyperosmolar, or have little tolerance for rapid intravascular volume increases (e.g., active hemorrhage, cardiac or neurologic dysfunction).

Isotonic replacement crystalloids (IRC) contain a sodium concentration similar to that of the extracellular space, making it the ideal crystalloid for the resuscitation and rehydration phase of the fluid therapy plan. Plasmalyte-A®, Normosol-R®, and lactated Ringer’s solution contain a buffer and are the preferred choice for restoring intravascular volume. The buffer lactate is converted to bicarbonate by the liver and does not affect plasma lactate unless severe liver dysfunction exists. Acetate and gluconate buffers are metabolized to bicarbonate by the liver as well as muscle tissue. The calcium in lactated Ringer’s solution prevents its administration through the same line as blood products due to potential precipitation with the citrate anticoagulant. Supplemental electrolytes can be added to isotonic fluids according to patient requirements. As a safeguard in preventing acute hyperkalemia, the rate of potassium administration added to resuscitation fluids should not exceed 0.5mEq/kg/hr unless carefully monitored.

Normal saline (0.9% sodium chloride) solution is an IRC with a comparable sodium concentration to plasma, but it does not contain additional electrolytes or buffer. This acidifying solution is specifically used for treating hypochloremic metabolic alkalosis.

Under normal conditions, the osmotic gradients across the extracellular membranes will cause approximately 80% of the crystalloids administered intravenously to filter into the interstitium within an hour. However, IRC can be an effective means for restoring perfusion parameters when the cause of hypovolemia can be rapidly corrected, and the interstitial compartment is capable of handling this additional fluid load. The detrimental effects of rapid, large volume, crystalloid administration increase when moderate to severe anemia is present, when increased capillary permeability exists, or when the interstitium cannot tolerate the additional fluid load (pulmonary, neurologic, or cardiac diseases). The addition of colloid fluids during resuscitation from hypovolemic shock in these situations becomes important.

**Colloids**

Colloid fluids are isotonic fluids containing a significant concentration of molecules larger in size than the capillary pore that contribute to COP. Whole blood, plasma, and concentrated albumin have natural colloids in the form of proteins. Hydroxyethyl starches (HES: hetastarch, tetrastarch) are synthetically derived colloids.

_Blood Products_
Blood products are administered when albumin, antithrombin, coagulation factors, platelets, or red blood cells are required. The blood product should be typed and cross-matched with the recipient when whole blood or packed red blood cell (pRBC) transfusions are needed. A DEA 1.1 negative transfusion is ideal to use if a cross-match is unavailable. A cross-match is always recommended in the cat, but may not be possible during life threatening blood loss. Plasma transfusion administration does not require blood typing or cross-match. An in-line 18-micron micropore filter is used during administration of plasma and a 170-micron blood administration set for red-cell containing products. Resuscitation from catastrophic hemorrhagic shock may require whole blood transfusion, with infusion rates compensating for on-going loss. Typically, blood products are administered at 5–15 ml/kg/hr. Care must be taken to definitively stop active hemorrhage and to prevent hydrostatic pressure from dislodging clots and exacerbating hemorrhage.

**Synthetic Colloids**

Synthetic colloid fluids contain large molecular weight particles that effectively increase COP beyond what can be obtained with blood product infusion alone. They maintain intravascular COP because their molecular size is too large to pass through the normal capillary pores.

Synthetic colloids are administered with IRC to reduce intravascular volume depletion. Synthetic colloids do not provide albumin, hemoglobin, antithrombin, platelets, or coagulation proteins, but can be administered simultaneously with blood products. Elimination of smaller molecular weight particles is through glomerular filtration. Larger particles are eliminated in bile, stored in tissue, or broken down into smaller particles by the monocyte-macrophage system.

Hydroxyethyl starch is the parent name of a synthetic polymer of glucose (98% amylopectin), made from a waxy species of either plant starch maize or sorghum. It is a highly branched polysaccharide closely resembling glycogen, formed by the reaction between ethylene oxide and amylopectin in the presence of an alkaline catalyst. The molecular weight and molar substitution can be adjusted by the degree of substitution of hydroxyl groups with oxyethyl groups at the C2, C3, and C6 positions on the glucose molecule. The greater the substitution on position C2 in relation to C6 (C2:C6 ratio), the slower the degradation of the molecule by amylase.

The number-averaged molecular weight ($M_n$) is the arithmetic mean of the molecular weights of the polymers in solution. Weight-averaged molecular weight ($M_w$) is the sum of the number of molecules at each number-averaged molecular weight divided by the total of all molecules. This weight is generally larger when larger polymers are present in solution.

The classification of different HES products includes the $M_w$/the proportion of substitution. There are several HES products clinically available in the United States at this time, including hetastarch and tetrastarch. Hetastarch can be purchased in 0.9% sodium chloride (Hespan™, Baxter; $M_w$ of 600 kD and 0.7 degree of substitution) or in LRS (Hextend™, BioTime, Inc; a $M_w$ of 670 kD and 0.75 degree of substitution). The electrolyte and buffer compositions of Hextend™ may reduce the incidence of hyperchloremic acidosis. Hextend™ also contains 0.45 mmol/L magnesium and 99 mg/dL (0.99%) dextrose. VetStarch™ (Abbott) has a $M_w$ of 130 kD and a 0.4 degree of substitution and Tetraspan™ 6% (Braun) has a $M_w$ of 130 kD and a 0.42 degree of substitution. HES 130/0.4 doses have been recommended up to 50 ml/kg in people.

HES can affect Von Willebrand’s factor, factor VIII function, and platelet function. Clinical evidence of bleeding has not been reported in animals receiving HES 600/0.7 at doses up to 20 ml/kg/day. A differential charge may exist between administered HES molecules and the capillary pore, blocking the passage of HES molecules into the interstitium. This property is independent of molecular size. HES may also down-regulate and decrease expression of endothelial surface adhesion molecules, which has been reported to decrease inflammation, endothelial injury, and leukocyte migration into the interstitium. HES have been shown to reverse changes in microvascular permeability caused by oxygen free radicals during reperfusion injury. This can explain why HES molecules remain in the vascular space in the septic patient when increased albumin does not.

Literature has reported evidence for an increased risk for acute kidney injury in critically ill people and people with severe sepsis when treated with HES. This complication has not been identified in dogs or cats.

**Additional Circulatory Support**
If fluid administration alone is unsuccessful at restoring perfusion end-points during decompensatory shock, causes of non-responsive shock are investigated for and administration of vasopressors or positive inotropes considered.

Table 4: Causes of Nonresponsive Shock

<table>
<thead>
<tr>
<th>Inadequate intravascular volume</th>
<th>Hypoglycemia</th>
<th>Excessive peripheral vasoconstriction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing fluid losses (blood or plasma)</td>
<td>Glucocorticoid deficiency</td>
<td>Decreased venous return</td>
</tr>
<tr>
<td>Myocardial depression or failure</td>
<td>Organ ischemia</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Inadequate oxygen carrying</td>
<td>Neurological failure</td>
</tr>
<tr>
<td>Cardiac tamponade</td>
<td>Ability</td>
<td>Severe pain</td>
</tr>
<tr>
<td>Electrolyte imbalances</td>
<td>Inadequate colloid osmotic pressure</td>
<td>Hyoxemia</td>
</tr>
</tbody>
</table>

Vasopressors

Underlying causes of nonresponsive shock must be investigated and treated. To verify that adequate volume replacement has been achieved, the central venous pressure (CVP) must be between 6–8 cm H2O before pharmacological intervention. Echocardiographic evaluation of cardiac contractility is ideal for making the decision to use positive inotropes versus vasomotor drugs.

Positive inotropic drugs such as dobutamine, dopamine, and epinephrine increase stroke volume and cardiac output. Dobutamine (dogs: 5-10 mcg/kg/min; cats: 1.5–5 mcg/kg/min) is primarily a myocardial beta1 stimulant, exhibiting less beta2 peripheral effects than dopamine. Dopamine is a norepinephrine precursor. At lower doses (3–5 mcg/kg/min), it stimulates beta and dopaminergic receptors providing positive inotropic activity, peripheral vasodilation, and renal afferent arteriolar dilation. Like dopamine, epinephrine also exerts cardiac inotropy at lower doses (0.005–1 mcg/kg/min) via beta1 action. However, epinephrine will increase myocardial oxygen demand more than dopamine predisposing the myocardium to arrhythmias and producing a lactic acidosis. Although dobutamine can cause down-regulation of receptors during prolonged infusions, it is the preferred positive inotrope for treating poor myocardial performance because it maintains its hemodynamic effect better than dopamine during continuous infusion. Dopamine depletes myocardial norepinephrine stores and may become ineffective with prolonged administration.

Vasopressors such as increased dose dopamine, phenylephrine, norepinephrine, and epinephrine may be used in catastrophic stages of hypovolemic shock. At increased doses, dopamine (5–15 mcg/kg/min) initiates alpha activity and peripheral vasoconstriction. Norepinephrine (1–10 mcg/kg/min) and phenylephrine (1–3 mcg/kg/min) are potent alpha agonists, increasing systemic vascular resistance and vascular tone with less beta stimulation than dopamine and epinephrine, with a potential bradycardic effect. When vasopressor support is indicated, dopamine should be used first. Should this fail to achieve the desired end-points, norepinephrine is administered in combination with very low dose dopamine (1–3 mcg/kg/min) to promote renal perfusion.

Continuous monitoring is essential with administration of positive inotropes and vasopressors, which have the potential of inducing ventricular arrhythmias and impair visceral organ blood flow. When circulatory drugs are required to maintain cardiac output and blood pressure, the prognosis decreases significantly.

Glucocorticosteroids

At this time, insufficient clinical evidence in companion animals exists to support the administration of high-dose glucocorticosteroids in hypovolemic shock. However, physiologic or low doses of glucocorticosteroids during resuscitation of the animal in an Addisonian crisis or hyperdynamic septic shock not responsive to resuscitation efforts can be beneficial.

Suggested Reading


