HYPOVOLEMIC SHOCK AND RESUSCITATION

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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 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. The neuroendocrine responses to hypovolemia become ineffective once 40% of the intravascular volume is lost and irreversible organ failure begins. 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 integrity. Cellular function is exclusively dependent on efficient pump function. Energy required to drive transmembrane ion exchange is supplied by cleavage of ATP. In contrast to 38 ATP molecules that are produced during aerobic metabolism, anaerobic metabolism produces lactate and only 2 ATP molecules per glucose molecule. Oxygen and glucose are transported from the intravascular space to the cell through a fluid medium. Carried by hemoglobin to the capillaries, oxygen normally diffuses with great ease through the capillary membrane to the cells when the interstitial compartment is normal.

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. Sinus node stretch results in an increased heart rate, 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, 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 intravascular 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. Vasconstriction, 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) results in movement of water from the interstitial space into 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 a supranormal oxygen supply may be required to meet these energy needs. Substrates required for cellular energy production are 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 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 splanchic bed shuts 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 sub normal temperature, decreased heart rate and a low arterial blood pressure. It is suspected that the hypothermia leads to a poor response by the catecholamine receptors, preventing the compensatory tachycardia and vasoconstriction.

**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**
Oxygen is administered by nasal catheter (0.5 L/kg/minute) or flow by methods (5-15 L/minute) using a mask, hood, bag or by simply holding the oxygen delivery tubing up to the nose. 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 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.

**Vascular access**
Easily accessible peripheral veins for rapid catheterization include the cephalic, lateral saphenous, and median veins, which may require cutdown approach with severe hypovolemia. Central venous (jugular and femoral) access is not used during resuscitation unless technical experience is excellent, or a cut down procedure is used. Central access permits measurement of central venous pressure, when the end of the catheter rests in the intrathoracic cavity close to the right atrium.

Intraosseous catheter placement may be faster and easier to place in young and small animals. The proximal femur, humerus, cranial tibia or wing of the ilium can be used. Most isotonic crystalloids and colloids can be infused through an intraosseous catheter, but greater force may be required for infusion.

If the animal is in the decompensatory stage of hypovolemic shock, and weighs over 25kg, placing multiple venous catheters with the largest bore, shortest length tube will provide the least amount of resistance for rapid, large volume fluid administration, and deposit the fluids as close to the central circulation as possible. Placing the fluid bag under pressure permits rapid volume infusion. Using Y-set infusion adapters allows infusion of multiple types of fluids into a single catheter.

**Crystalloids**
The goal of intravascular fluid resuscitation is to rapidly restore perfusion to chosen end-points (normal heart rate, normal blood pressure, pink mucous membrane color, 1-2 second capillary refill time, adequate urine output) without causing volume overload and its complications. (pulmonary, peripheral and brain edema). Crystalloids alone can be used, however perfusion end-points may be more difficult to reach without the complications of edema.

Replacement crystalloid fluids can be successfully utilized during hypovolemic resuscitation. Buffered solutions, such as Normosol-R®, and Plasmalyte 7.4®, provide a more normal pH level, and may more rapidly and efficiently restore normal pH. These solutions also contain a variety of electrolytes. There are no buffers or added electrolytes contained in 0.9% sodium chloride. Normal saline is therefore appropriate for use in hypovolemic resuscitation during metabolic alkalosis, Addisonian crisis, primary oliguric renal failure, hypercalcemia, hypernatremia, hypochloremia, and head injury. Electrolytes can be added as needed and the pH of the blood must be monitored.
Crystalloid volume and rate of administration depends on a number of factors that can determine the ability of the interstitial space to handle the increased fluid load. Resuscitation volumes are as unpredictable as the response to resuscitation; replacement isotonic crystalloid resuscitation volumes must be titrated to effect. For example, 20-30 ml/kg can be administered during the initial 5-10 minutes followed by reassessment of perfusion. Additional 20-30 ml/kg boluses are administered until the resuscitation endpoints are reached.

Many animals can handle the extra interstitial volume for a short period when large quantities of isotonic crystalloids are rapidly administered. In normal tissues, the lymphatics will return the excess fluid to the vascular space to be excreted by the kidneys. Extreme care must be given when replacing perfusion deficits with crystalloids alone in animals with pathology of the capillaries, kidneys, heart or brain.

Hypertonic saline is a crystalloid that can augment acute volume resuscitation from catastrophic shock. Hypertonic saline provides an additional osmotic attraction for water to flow from the interstitium into the vessel. Hypertonic saline administration is to be used with great caution in animals that are severely dehydrated, hypernatremic, or hyperchloremic. Use in the critically ill animal with little tolerance for interstitial volume increases should also be avoided (e.g., active hemorrhage, cardiac dysfunction, neurological hemorrhage) to avoid diffusion of a high osmotic fluid into the interstitium. Using hypertonic saline with a synthetic colloid may augment intravascular retention of volume. Hypertonic saline is available as a 7.0% solution in water or as a 23.4% concentration that is diluted to 7.5% with synthetic colloids.

By administering colloids in conjunction with crystalloids during fluid resuscitation, less total fluid volume is required, there is less tendency toward fluid overload, and resuscitation times are shorter. Plasma COP can be maintained near normal (20-25 mmHg) with synthetic colloids, favoring intravascular fluid retention.

COLLOIDS

Natural colloids

When the animal requires red blood cells, clotting factors, antithrombin III or albumin, blood products are necessary. Dogs and cats receiving whole blood or a combination of packed red blood cell-colloid transfusion should be blood typed and cross-matched, time permitting. If time is a limiting factor, a universal donor (DEA 1.1 negative) should be chosen for the canine patient. Blood typing or cross matching is always recommended for the cat. Patients receiving plasma transfusions do not require cross-matching. Blood products should be heated in a warm water bath to patient temperature and administered via 18 micron micropore filter.

Modified Biological Colloids

Hemoglobin-based oxygen-carrying solutions contain hemoglobin that bind with pulmonary oxygen and transport it to the tissues where it is off-loaded to the cells. Because of its molecular size, it is smaller than a red blood cell and able to pass through the microcirculation more readily. This may make it the ideal fluid to administer during situations of severe anemia, and/or hypovolemia caused by acute hemorrhage or maldistribution of blood flow.

Oxyglobin®, a stroma-free hemoglobin, is an ultrapure bovine-origin polymerized hemoglobin solution approved in the USA for therapeutic use in dogs with anemia. In addition to acting as a temporary oxygen-carrying substitute for red blood cells, it maintains osmotic pressure and has a vasoconstricting effect that can reduce the volume required for resuscitation. It can be stored at room temperature with a 3-year shelf life, making it more available and transportable than blood transfusions. It has universal compatibility and is less likely to transmit hematogenous diseases. Its limitations include a short half-life (40 hours) once it is administered, interference with enzyme chemistry analyses, and red cell replacement may still be required if significant anemia is present. Rare side effects that may occur include pulmonary edema, vomiting and diarrhea.

Synthetic Colloids

Dextran, and hydroxyethyl starches (HES) are synthetic colloids, each with pharmacology, specific qualities, and potential side effects that make them unique. They provide an increase in COP beyond what is attainable with natural colloids and can be used in conjunction with whole blood or plasma. They are not, however, to be considered a substitute for blood products when albumin, hemoglobin, antithrombin, or coagulation proteins are needed.

HES will retain water longer, maintaining colloid properties as it is broken down into smaller particles prior to elimination. This characteristic is advantageous when sustained volume support is required during increased capillary permeability, and when there is less tolerance of rapid intravascular volume increases (e.g. during brain and pulmonary injury, cardiac insufficiency, or in hypovolemic cats).

Potential side effects of synthetic colloid administration become more important with increased dosages. At recommended doses the activated clotting times may increase up to 50% without evidence of spontaneous bleeding. It has been reported that when hetastarch has been administered in volumes greater than 40 ml/kg/day, there was an associated increase in incisional bleeding. This may be due to an increase in microcirculatory flow and blood pressure, as well as a dilutional and direct effect of hetastarch on coagulation.

Like crystalloids, all of the synthetic colloids are capable of producing volume overload when large volume administration occurs. Colloid administration is always in conjunction with crystalloid administration, although the crystalloid volume is decreased by 40-60%.

FLUID ADMINISTRATION-TYPE, VOLUME AND RATE

Large volume intravascular resuscitation for dogs

Unless there is closed cavity hemorrhage, pulmonary contusions, cardiac dysfunction or head trauma, dogs experiencing shock due to hypovolemia benefit from rapid intravascular volume resuscitation techniques. A 10-20 ml/kg dose of hetastarch can be administered as quickly as possible by IV bolus, in addition to a 10-15 ml/kg bolus of crystalloid. Additional hetastarch can be administered using small volume intravascular resuscitation techniques if perfusion has not improved to the desired end-point after the initial bolus. Whole blood products can be administered by rapid intravenous volume resuscitation techniques in catastrophic hemorrhagic situations, with input at least matching ongoing loss.
Small volume intravascular resuscitation

Small volume resuscitation techniques with synthetic colloids are recommended in the hypovolemic cat. In addition, any animal with intravascular volume depletion combined with closed cavity hemorrhage, head injury, pulmonary contusions, cardiogenic shock, or oliguric renal failure will benefit from careful resuscitation using small volume intravascular resuscitation techniques.

A synthetic colloid or Oxyglobin® is administered at 5 ml/kg increments in the dog or 1-2 ml/kg increments in the cat, over 5-15 minutes while isotonic crystalloids are administered at a rate of 10-15 ml/kg. The perfusion parameters are reassessed and the 5 ml/kg bolus repeated as needed until the end-point of resuscitation is reached. The goal is to administer the smallest volume of colloid possible to successfully resuscitate the intravascular compartment and avoid fluid overload. This minimizes extravasation of fluids into the brain or lungs, titrates the amount of preload stretching a disabled heart, and reduces the probability of disturbing clot formation.

Cats with hypertrophic myocardial disease are particularly susceptible to rapid intravascular volume changes. Therefore, in cats with diagnosed or suspected cardiac compromise (heart murmur, bradycardia, gallop arrhythmia, radiographic pulmonary infiltrate) the colloid titration volume should be decreased to 1 ml/kg increments if they are absolutely required.

Hypothermia, especially in the cat, can significantly limit the cardiovascular response to fluid resuscitation. It has been the author's experience that aggressive volume administration without active warming of the hypothermic cat can result in pulmonary edema despite continued hypotension. Wrapping the hypothermic animal in a blanket or plastic wrap will restrict continued loss of body heat by convective currents. Initial administration of warmed fluids (at room or normal body temperature) using a 5 ml/kg hetastarch bolus concurrently with 10-15 ml/kg warm isotonic crystalloid fluid bolus. Active external warming should occur once fluid resuscitation has been initiated. A continuous infusion of warmed isotonic crystalloids is provided at a rate of 2-4 ml/kg/hr. The goal is to reach a rectal temperature > 98°F within 30 minutes to maximize catecholamine receptor response. Additional resuscitation fluids are rarely necessary when the body temperature has been normalized.

The arterial blood pressure and rectal temperature are frequently reassessed. If a hypothermic cat becomes normothermic, but the systolic blood pressure remains below 70 mmHg, cardiac function should be assessed. Small volume resuscitation efforts are continued up to a total of 40 ml/kg colloid administration if no heart disease is present. If fluid resuscitation has not reestablished the arterial blood pressure >70 mmHg, or should a hypothermic cat (rectal temperature < 98 degrees F) not respond to aggressive warming efforts (generally within 1 hour), vasopressors, such as dopamine, should be considered until body temperature has been normalized.

Volume resuscitation with systemic inflammation

Increased capillary permeability promotes vascular leakage of albumin as a result of inflammatory mediator action during SIRS. The endothelial cells contract and pull away from each other resulting in large interendothelial gaps. Albumin (69,000 daltons) will flux across the capillary membrane into the interstitium at and remote from the injured site as a result of cytokine action. Loss of intravascular albumin decreases intravascular COP and promotes intravascular volume depletion and interstitial fluid accumulation.

When albumin is lost from the intravascular space, the capillary pore size is likely greater than 69,000 daltons in diameter. A colloid should be administered that contains particles larger than the pore size of the capillaries. When there is increased capillary permeability and loss of albumin through the capillary membrane, HES is the colloid of choice for intravascular volume resuscitation. Persisting in giving crystalloids alone will further dilute the COP while raising the intravascular hydrostatic pressure, and accelerate fluid flow across the membrane into the interstitial fluid compartment.

Animals requiring resuscitation by techniques described above will most likely require colloid infusion immediately post-resuscitation, for maintaining intravascular volume (0.8 ml/kg/h).

ADDITIONAL CIRCULATORY SUPPORT

Analgesics

Once fluid resuscitation has been initiated, analgesia is provided when significant pain is suspected. Pain will contribute to the sympathetic response occurring during hypovolemic shock, causing a tachycardia or hypertension. Other than being a humane treatment, low dose narcotics combined with local anesthetics and low dose anxiolytics can remove additional catecholamine reaction caused by pain, providing a more accurate assessment of the baroreceptor response to hypovolemia and resuscitation. Intravenous, reversible agents such as butorphanol, hydromorphone, or fentanyl and benzodiazepines have limited adverse cardiovascular effects in the painful, hypovolemic animal. Their actions are also easily reversed with intravenous antidotes.

Vasopressors

If fluid administration alone is unsuccessful at restoring perfusion end-points during decompenatory shock, administration of vasopressors or positive inotropes may be necessary. 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 cmH2O 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 a cardiac inotropy at lower doses (0.005-1 mcg/kg/min) via beta1 action. However, epinephrine will increase myocardial oxygen demand more than delivery 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 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 other than during resuscitation of the animal in an Addisonian crisis and the animal with gastric dilatation/volvulus. However, low doses of hydrocortisone in humans with hyperdynamic septic shock can be beneficial. Vasopressor infusion in these subjects was able to be significantly reduced with the use of low dose hydrocortisone infusion. Discussion suggests that there may be an inappropriate cortisol production (despite normal serum cortisol levels), and/or corticosteroids may improve the interaction of catecholamines and adrenergic receptors. If this dose is reformulated using intravenous methylprednisone, the dosing would be 0.3 mg/kg every 8 hours. This intervention may be of benefit in animals suffering non-responsive shock from an unknown cause (persistent hypotension and tachycardia, with a CVP 8-10 cmH₂O, PCV>20%, adequate pain control, normal organ function and electrolyte panel).