

Limited Fluid Volume Resuscitation

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Abstract: Volume replacement therapy is crucial to the treatment of hypovolemic shock. In patients with certain conditions, limiting the volume of fluid administered has many potential therapeutic benefits and technical advantages. Hypertonic saline and colloids have characteristics that allow effective treatment of hypovolemic shock using relatively smaller volumes than would be required for isotonic crystalloids alone. This article describes the theory and clinical application of limited fluid volume resuscitation in veterinary medicine.

Hemorrhage is a common cause of hypovolemic shock in veterinary patients and can occur with trauma, coagulopathy, or rupture of a parenchymal mass. In general, affected animals were previously healthy and are acutely hypovolemic due to hemorrhage in the chest or abdomen or along a long bone fracture. The goal of rapid volume replacement in shock is to restore perfusion as quickly as possible by replacing intravascular losses and controlling further bleeding, thus limiting tissue injury that can result in organ dysfunction and

death. However, the decision of whether fluid replacement or hemorrhage control takes priority and which fluid type to use is controversial.

Research has shown improved hemodynamic parameters and outcomes with the use of limited fluid volume resuscitation (LFVR) in patients with hypovolemic shock.¹⁻¹⁰ However, few clinical veterinary trials have been performed. This article reviews fluid distribution in the body, describes the use of LFVR in hypovolemic shock, and summarizes selected experimental and clinical studies of LFVR.

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TABLE 1 Acceptable End Points of Resuscitation^{15,16}

Parameter	Value
Mentation	Alert
Mucous membranes	Pink
Capillary refill time	<2 sec
Temperature	100°F–102.5°F
Heart rate	Cats: 180–220 bpm Small-breed dogs: 100–160 bpm Large-breed dogs: 60–100 bpm
Respiratory rate	20–40 breaths/min
Systolic blood pressure	>100 mm Hg*
Mean blood pressure	>80–100 mm Hg*
Central venous pressure	5–10 cm H ₂ O
Lactate	<2.5 mmol/L
Urine output	At least 1–2 mL/kg/hr

*Active, noncompressible hemorrhage may be the exception, and achieving a mean arterial pressure (MAP) of 70 mm Hg or a systolic arterial pressure (SAP) of 90 mm Hg with improvement of clinical signs during limited fluid volume resuscitation (LFVR) is acceptable until hemorrhage is definitively controlled.

Traditional Versus Limited Fluid Volume Resuscitation

The aim of any fluid therapy regimen for treating hypovolemic shock is resolution of shock, not simply administration of a specific volume of fluid. In addition, volume dosages for any type of fluid must be tailored to the individual patient, and recommended dosages are guidelines only. Treating hypovolemic shock is a dynamic process that requires frequent evaluation of the patient. The end points of optimal resuscitation include alleviation of peripheral vasoconstriction and decreased perfusion, as demonstrated by normalization of vital signs and other objective parameters (**TABLE 1**).

Traditionally, isotonic crystalloids have been used at dosages based on estimated blood volume (90 mL/kg/hr in dogs, 40 to 60 mL/kg/hr in cats) to replace intravascular losses.¹¹ Although they are essential in the treatment of dehydration, isotonic crystalloids can prolong the time needed to restore effective circulating volume, redistribute rapidly into the interstitial space, and contribute to hypothermia. Because <20% of an administered isotonic crystalloid remains in the intravascular space after 1 hour, large volumes of isotonic crystalloids may be required to maintain an effective circulating volume and may result in excessive interstitial edema.¹²

Alternatives to isotonic crystalloids include colloids and hypertonic saline (HS). Colloids and HS are used at much smaller volumes than isotonic crystalloids, enabling faster administration and more rapid repletion of the intravascular space. Colloids are also retained in the intravascular space for longer periods of time than crystalloids and are therefore more effective at maintaining adequate circulating volume and reducing the risk of interstitial edema. Research has shown that HS may have additional benefits, such as restoration of cellular function following traumatic brain injury and immune system modulation.

LFVR, also called *small-volume resuscitation*, differs from hypotensive resuscitation or delayed fluid resuscitation in that it is aimed at achieving normalization of clinical end points. With hypotensive or delayed fluid resuscitation, the patient is permitted to remain hypotensive or fluids are withheld, respectively, until bleeding is definitively controlled. During hypotensive resuscitation, the patient is resuscitated

to a mean arterial blood pressure (MAP) of no greater than 60 mm Hg, which just maintains perfusion to vital organs while minimizing the risk of dislodging vascular clots.^{1,13,14} During delayed fluid resuscitation, no fluids are given until definitive control of hemorrhage is achieved. Once bleeding is controlled in either situation, aggressive fluid resuscitation is initiated.

The goal of LFVR is to use the smallest volume of fluid possible to restore the intravascular compartment and resolve shock while minimizing fluid extravasation into the brain or lungs and the risk of disrupting an incipient blood clot.¹¹ LFVR should be considered in cases with hemoperitoneum, traumatic pulmonary contusions, traumatic brain injury, and other forms of active hemorrhage (**BOX 1**). In patients with active, noncompressible hemorrhage, achieving an MAP of 70 mm Hg or a systolic arterial pressure (SAP) of 90 mm Hg with improvement of clinical signs during LFVR is acceptable until hemorrhage is definitively controlled.^{15,16} Once acceptable clinical parameters have been achieved, the dosage and type of fluid can be adjusted to meet the current and anticipated needs of the patient.

Fluid Distribution and Dynamics

Total body water accounts for approximately 60% to 70% of body weight.¹⁷ Of this water, 66% is located in the intracellular space (including red blood cell mass) and 33% in the extracellular space. The extracellular space is subdivided into intravascular (25%) and interstitial (75%) compartments, which are separated by endothelial cells and a basement membrane.^{11,17} The membrane is permeable to water but not to most solutes, creating differences in osmotic pressure between the compartments. Osmotic pressure is determined by the number of nonpermeable particles in solution.¹¹ A solution that has more, fewer, or an equal number of osmotically active particles per unit of volume or weight compared with intracellular fluid is said to be *hyperosmolar*, *hyposmolar*, or *isosmolar*, respectively.

Water moves across the basement membrane from areas of low solute concentration to areas of high solute concentration via osmosis. Sodium is the most abundant cation in the extracellular fluid and accounts for most of the osmotically active particles in this space. The

QuickNotes

Limited fluid volume resuscitation is particularly beneficial for animals with hemoperitoneum, pulmonary contusions, traumatic brain injury, and other sources of ongoing hemorrhage.

BOX 1

Case Report: A Beagle with Head Trauma

A previously healthy 19-kg [41.8-lb], 3.5-year-old castrated beagle presented to an emergency facility after being hit by a car. The physical findings were consistent with hypovolemic shock (**TABLE A**): lateral recumbency, pale mucous membranes, hypothermia, tachycardia, weak femoral pulses, tachypnea, and a moderate increase in respiratory effort. Other pertinent physical findings included harsh lung sounds bilaterally and signs consistent with head trauma (mild anisocoria, scleral hemorrhage, epistaxis).

Due to signs of head trauma and suspicion of pulmonary contusions, a limited fluid volume resuscitation protocol was implemented. A fluid bolus of 80 mL (4.2 mL/kg) of 7.3% sodium chlo-

ride was administered simultaneously with 200 mL (10.5 mL/kg) of 6% hetastarch IV. Other supportive measures employed included an external passive warming source and supplemental oxygen. Hemodynamic parameters normalized after the bolus (**TABLE A**), and the epistaxis and anisocoria resolved. Supportive care was continued in addition to administration of lactated Ringer's solution, 25 mL/hr (1.3 mL/kg/hr) IV; 6% hetastarch, 4 mL/hr (0.2 mL/kg/hr) IV; and hydromorphone, 0.95 mg (0.05 mg/kg) IV q6h. Thoracic radiography revealed right-sided pulmonary contusions and a small amount of right-sided pleural effusion likely due to hemorrhage (**FIGURES A AND B**). The dog recovered fully and was discharged.

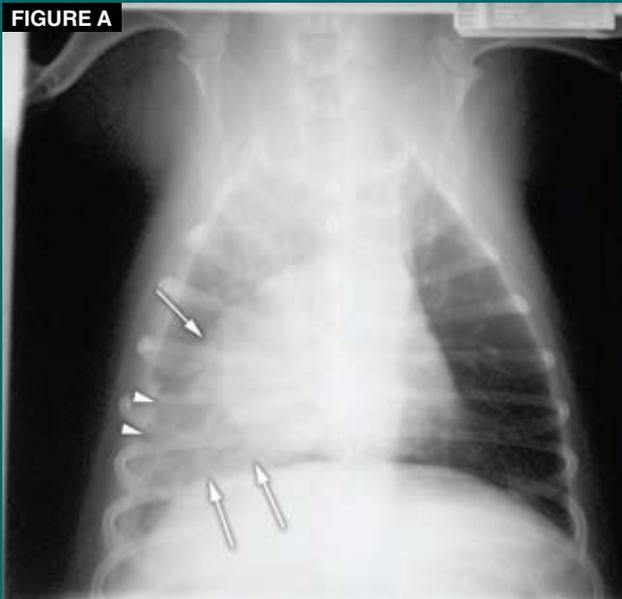
TABLE A Physical Findings on Admission and After Resuscitation

Physical Findings	Temperature (°F)	Heart Rate (bpm)	Respiratory Rate (breaths/min)	Mucous Membrane Color	Femoral Pulse Quality	Systolic Blood Pressure (mm Hg)	Lactate (mMol/L)
Initial	97.5	180	48	Pale	Weak	TLTD	8.6
After resuscitation	99.4	120	28	Pink	Strong	120	1.4

TLTD = too low to determine

Thoracic radiographs of the dog in this case.

FIGURE A



Dorsoventral view. Note the right-sided pulmonary contusions (arrows) and a small amount of right-sided pleural effusion (arrowheads) likely due to hemorrhage.

FIGURE B



Lateral view.

volume of extracellular fluid is determined by total body sodium content, whereas the osmolality and sodium concentration of extracellular fluid are determined by water balance. Regulation of sodium and water balance by the kidneys¹⁸ maintains the volume and osmolality of body fluids within a narrow normal range. In response to the renin–angiotensin–aldosterone system, brain atrial natriuretic hormones, and the posterior pituitary–vasopressin–renal axis, the kidneys maintain extracellular fluid sodium levels and tonicity and contribute to the maintenance of blood pressure.¹⁹

Normally, fluid movement between the intravascular and interstitial compartments depends on membrane pore size and differences between

osmotic, hydrostatic, and colloid osmotic pressure (COP), according to Starling's law of capillary hemodynamics (**BOX 2 AND FIGURE 1**).¹⁷ The major source of intravascular COP is albumin. As the COP increases, fluid movement out of the intravascular space decreases and the amount of plasma fluid retained increases, causing the intravascular hydrostatic pressure to rise. Fluid movement out of the intravascular space occurs in three situations: (1) when the intravascular hydrostatic pressure is greater than the COP, (2) when capillary permeability increases, or (3) when intravascular COP falls

BOX 2

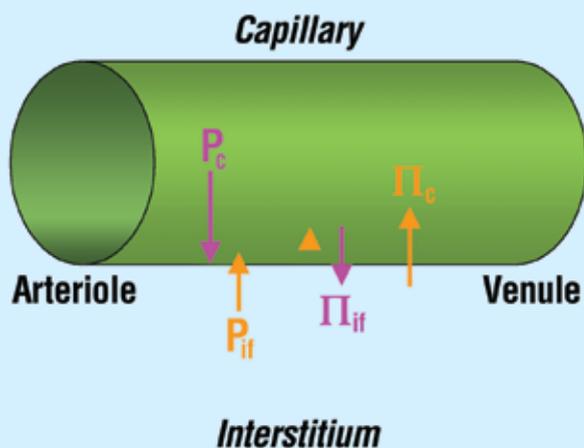
Glossary of Fluid Balance Terms^{11,17,34}

- ▶ **Colloid:** A large molecule that cannot penetrate the capillary membrane and is therefore retained in the intravascular space, creating colloid osmotic pressure.
- ▶ **Colloid osmotic pressure (COP):** Osmotic pressure created at the capillary membrane by colloids and plasma proteins retained within the intravascular or interstitial space.
- ▶ **Hydrostatic pressure:** The natural tendency of water to move out of a fluid compartment, determined by cardiac output and systemic vascular resistance at the capillary membrane and driven by arterial blood pressure against a vessel wall.
- ▶ **Osmolality:** The concentration of a solution in terms of osmoles of solute per kilogram of solution, independent of any membrane.
- ▶ **Osmolarity:** The concentration of a solution in terms of osmoles of solute per liter of solution, independent of any membrane.
- ▶ **Osmotic pressure:** Pressure required on one side of a membrane to oppose the movement of water molecules across the membrane from the other side.
- ▶ **Starling's law of capillary hemodynamics:** States that fluid flux at the capillary level is controlled by a balance between hydrostatic and osmotic pressure gradients between capillaries and the interstitial space.
- ▶ **Tonicity:** A measure of effective osmolality or effective osmolality. A property of a solution in reference to a particular membrane, equal to the sum of the concentrations of the solutes that have the capacity to exert an osmotic force across the membrane.

FIGURE 1

Starling's Law

$$v = k_f [(P_c - P_{if}) - \sigma(\Pi_c - \Pi_{if})] - Q_l$$



v = net filtration, *k_f* = filtration coefficient, *P* = hydrostatic pressure, *c* = capillary, *if* = interstitial fluid, *σ* = membrane pore size, *Π* = oncotic pressure, *Q_l* = lymph flow

Starling's law of capillary hemodynamics states that net fluid movement (*v*) at the level of the capillary is a result of the balance of forces favoring fluid movement out of the vessel (hydrostatic pressure of the vasculature [*P_c*] and the COP of the interstitium [*Π_{if}*]) and forces favoring fluid movement into the vasculature (hydrostatic pressure of the interstitium [*P_{if}*] and the COP of the vasculature [*Π_c*]). Fluid dynamics are also a function of the permeability of the endothelium, which in the Starling equation is the reflection coefficient (*σ*). The last factor that determines net fluid movement is net lymph flow (*Q_l*).

below the interstitial COP¹² (**BOX 3**). Any water-containing fluid (e.g., crystalloids) given intravenously can move out of the vasculature and into the interstitium via any of these mechanisms, and the process may be exaggerated after injury.

In many conditions (e.g., acute pancreatitis, trauma, bite or burn wounds), fluid is lost from the intravascular space via more than one of these mechanisms. Vasculitis causes increased systemic vascular permeability, and plasma proteins and fluid are sequestered into the interstitial space, resulting in interstitial edema.¹⁹ Interstitial edema can also occur as a result of lymphatic obstruction or leakage or when interstitial fluid accumulation exceeds lymphatic drainage.¹²

Fluids Used in Limited Fluid Volume Resuscitation

TABLE 2 summarizes the advantages and disadvantages of the various types of fluids used in resuscitation of hemorrhaging patients, including isotonic crystalloids. Dosing recommendations for the various types of fluids used in LFVR are summarized in **TABLE 3**.

Hypertonic Crystalloids

The most commonly used hypertonic crystalloid is HS containing 7.2% to 7.5% sodium chloride (depending on the manufacturer), although solutions containing 3% to 23.4% sodium chloride are available. HS is best used in previously healthy animals with acute hypovolemia. The high sodium content of HS rapidly pulls fluid from the extravascular space via the osmotic gradient to expand intravascular volume, resulting in rapid resolution of shock at low infusion volumes. When HS is used alone, this effect typically lasts less than 30 minutes. However, when HS is used in combination with colloids, the effect on volume expansion (and therefore cardiac output) is sustained for 2 to 3 hours. HS and colloids can be mixed for simultaneous administration, and the rate of administration should not exceed 1 mL/kg/min. Using HS is advantageous because it more rapidly restores intravascular circulating volume at smaller infusion volumes compared with isotonic crystalloids alone. Shock resolves faster with less personnel time, and the period of hypoperfusion is minimized. It is an ideal solution for resus-

BOX 3

Conditions Causing Fluid Movement From the Intravascular Space Into the Interstitium¹²

Conditions causing intravascular hydrostatic pressure greater than COP

- ▶ Intravascular fluid overload
- ▶ Hypertension
- ▶ Heart failure
- ▶ Anaphylaxis

Conditions causing increased capillary permeability

- ▶ Systemic inflammation
- ▶ Vasculitis
- ▶ Sepsis
- ▶ Immune-mediated disease
- ▶ Excessive vasodilation
- ▶ Trauma

Conditions causing intravascular COP less than interstitial COP

- ▶ Hypoalbuminemia
- ▶ Previous hemorrhage
- ▶ Protein-losing enteropathies
- ▶ Glomerulopathies
- ▶ End-stage hepatic failure

COP = colloid osmotic pressure

citation in transit (e.g., ambulance, battlefield, search and rescue), when there are volume restrictions, or in large animals with acute hypovolemia. HS should never be used as the only fluid therapy because it dehydrates the interstitium. It should be followed by isotonic crystalloids with or without colloids.

HS has many properties that other fluids do not. It has beneficial effects on the heart, including increased inotropy, chronotropy, coronary blood flow, and venous return. Increases in renal, splanchnic, and coronary blood flow have been attributed to a decrease in peripheral vascular resistance and redistribution of cardiac output.⁴ HS has also been shown to decrease leukocyte adhesion and migration, which may help to blunt the inflammatory response and activation of the coagulation cascade.^{20–22} It has been shown to reduce albumin leakage, neutrophil counts in bronchoalveolar lavage fluid, and histopathologic injury compared with resuscitation using lactated Ringer's solution.²³ HS use in hemor-

QuickNotes

Crystalloids cannot maintain intravascular volume or tissue perfusion for extended periods of time and should not be the sole source of intravascular fluid therapy in patients with refractory hypovolemic shock.

TABLE 2 Advantages and Disadvantages of Different Fluid Types in Resuscitation^{11,12,34,39,42,50}

Fluid Type	Advantages	Disadvantages
Isotonic crystalloids (lactated Ringer's solution, 0.9% sodium chloride, Normosol-R, ^a Plasmalyte A ^b)	<ul style="list-style-type: none"> ▶ Low cost ▶ Necessary in dehydration ▶ Widely available ▶ Long storage life 	<ul style="list-style-type: none"> ▶ Large volumes needed ▶ Longer time to resuscitate ▶ Require more technical staff (e.g., placement of multiple, large-gauge IV catheters) ▶ Risk of hypothermia ▶ Risk of interstitial edema ▶ Risk of hemodilution ▶ Risk of rebleeding
Hypertonic saline (7.2%–7.5%)	<ul style="list-style-type: none"> ▶ Low cost ▶ Small volumes needed for rapid resuscitation ▶ Minimizes risks of interstitial edema ▶ Beneficial neurologic effects; decreases intracranial pressure ▶ Immunomodulatory effects ▶ Beneficial cardiac effects 	<ul style="list-style-type: none"> ▶ Short acting when used alone ▶ Transient hypernatremia ▶ Hypotension, bronchoconstriction, or arrhythmias with rapid administration ▶ Risk of volume overload ▶ Possible phlebitis ▶ Hyperosmolar
Synthetic colloids (6% hetastarch, 10% pentastarch, 6% dextran 70)	<ul style="list-style-type: none"> ▶ Smaller volumes needed for rapid resuscitation compared with crystalloids ▶ Minimizes risks of interstitial edema ▶ Longer duration of effect ▶ Increases COP ▶ Less hemodilution 	<ul style="list-style-type: none"> ▶ Higher cost ▶ Risk of volume overload ▶ Exacerbation of coagulopathies ▶ Risk of allergic reactions ▶ Edema with vasculitis ▶ Interference with crossmatching
Hemoglobin-based oxygen carrier (Oxyglobin ^c)	<ul style="list-style-type: none"> ▶ Increases COP ▶ Increases oxygen delivery ▶ Eliminates need to crossmatch ▶ 2-year shelf life 	<ul style="list-style-type: none"> ▶ Higher cost ▶ Risk of volume overload ▶ Possible risk of anaphylaxis with multiple uses ▶ Inability to measure certain blood values after use

COP = colloid osmotic pressure.

^aAbbott Laboratories.

^bBaxter.

^cBiopure.

rhagic shock also prevents immunosuppression after injury by decreasing plasma levels of interleukin-4 and certain prostaglandins and by limiting neutrophil activation, bacterial translocation, and pulmonary lesions.^{24–26}

Hemoperitoneum

Hemoperitoneum is one of the most common emergencies in veterinary medicine. Cases may be due to trauma or may be spontaneous. Most spontaneous cases are caused by rupture of a neoplasm. Most veterinarians agree that the main treatment goals are to reestablish or maintain effective circulating volume, maintain oxygen-carrying capacity, and arrest

ongoing hemorrhage.²⁷ However, which goal takes precedence and which fluid resuscitation protocol to use are controversial. LFVR to achieve specific end points (i.e., SAP ≤90 mm Hg, MAP ≤70 mm Hg, normalization of clinical signs) should be considered in these cases. Until hemorrhage is arrested, the use of small boluses of HS and colloids help to resolve shock and perfuse vital organs. At MAPs of 60 to 70 mm Hg, cerebral and renal blood flow are preserved.²⁷ LFVR also helps minimize the risk of clot disruption caused by sudden increases in intravascular hydrostatic pressure, thereby reducing the risk of rebleeding during resuscitation.

TABLE 3 Shock Doses for Acute Volume Resuscitation^{11,12,36,39,42,50}

Fluid	IV Dosage
Isotonic crystalloids (lactated Ringer's solution, 0.9% sodium chloride, Normosol-R, Plasmalyte A)	<ul style="list-style-type: none"> ▶ Dogs: 90 mL/kg (give 20–30 mL/kg IV over 10–15 min and reassess) ▶ Cats: 45–60 mL/kg (give 10–15 mL/kg IV over 10–15 min and reassess) ▶ Give in 10- to 15-mL/kg increments over 10–15 min with frequent reassessment
Hypertonic saline (7.2%–7.5%)	<ul style="list-style-type: none"> ▶ Dogs and cats: 3–8 mL/kg ▶ Give no faster than 1 mL/kg/min
Hydroxyethyl starches (6% hetastarch, 10% pentastarch)	<ul style="list-style-type: none"> ▶ Dogs: 10–20 mL/kg ▶ Cats: 10–15 mL/kg ▶ Give in 5-mL/kg increments over 10–15 min with frequent reassessment
6% Dextran 70	<ul style="list-style-type: none"> ▶ Dogs: 10–20 mL/kg ▶ Cats: 10–15 mL/kg ▶ Give in 5-mL/kg increments over 10–15 min with frequent reassessment
Oxyglobin	<ul style="list-style-type: none"> ▶ Dogs: 10–30 mL/kg ▶ Not labeled for use in cats ▶ Do not exceed 10 mL/kg/hr

Traumatic Brain Injury

HS is particularly useful in treating patients with traumatic brain injury, cerebral edema, and increased intracranial pressure (ICP). It has been shown to decrease ICP and increase survival following head injury.^{3,28,29} HS is effective at reducing brain volume because it does not cross the blood–brain barrier and mobilizes interstitial fluid from the brain into the intravascular space. Mannitol works in a similar fashion with a longer duration of action, but it also induces an osmotic diuresis, leading to further volume loss.^{30–32}

It is critical to maintain a cerebral perfusion pressure (CPP) above 70 mm Hg in dogs and cats. Given that $CPP = MAP - ICP$ and that normal ICP in dogs and cats is approximately 5 to 10 mm Hg, MAP must be maintained above 80 mm Hg.³³ Hypotension is one of the most important extracranial contributors to secondary neurologic damage with traumatic brain injury.

Fluid therapy should never be withheld in patients with traumatic brain injury, as dehydration only minimally decreases ICP and fluid restriction can result in hypovolemia, compromising CPP. In these patients, the goal is to balance fluid therapy and treat shock (thereby ensuring adequate oxygen delivery) without exacerbating cerebral edema or bleeding. With head injury, adenosine triphosphate depletion leads to retention of sodium in the

intracellular space, which results in intracellular accumulation of water and calcium and extracellular liberation of excitatory amino acids (e.g., glutamine). HS helps to increase extracellular sodium concentrations and restore gradients so that calcium is returned to the extracellular space and glutamate to the intracellular space, limiting secondary injury and neuronal death.^{20,33} It also works to minimize vasospasm, encourage local vasodilation, and limit endothelial cell swelling and permeability by promoting microcirculatory blood flow and improving local oxygen delivery.

Pulmonary Contusions

The management of pulmonary contusions is controversial, with clinical studies yielding inconsistent results. However, pulmonary contusions, which have been reported in up to 50% of animals with thoracic trauma, are another potential indication for LFVR.¹⁶ With pulmonary contusions, the alveolar capillary membranes sustain damage and the alveoli flood with blood, impairing ventilation. HS can be beneficial in these patients, as administration of large amounts of isotonic crystalloids during resuscitation may exacerbate pulmonary parenchymal compromise and further impair ventilation, especially during the first 24 hours after resuscitation. It is recommended that fluid therapy be given to restore

QuickNotes

Hypertonic saline is contraindicated in patients with dehydration, cardiac failure, renal failure, or hyperosmolar conditions (e.g., diabetic ketoacidosis).

and maintain cardiac output and tissue perfusion while avoiding excessive interstitial edema. Although controversial, HS and colloids should be considered the treatment of choice (with judicious use of isotonic crystalloids) until further research suggests otherwise.³⁴

Adverse Effects and Contraindications

Adverse effects of HS administration can include transient hypernatremia, occasional premature ventricular contractions, bradyarrhythmias, temporary hypotension, and bronchoconstriction.³⁵ However, with appropriate patient selection and administration (no faster than 1 mL/kg/min), these effects are rare. In addition to rapid increases in cardiac output and blood pressure, the sodium load of HS may elevate the risk of congestive heart failure in some patients. Also, HS may promote blood loss at the site of vascular injury due to breakdown of a blood clot (i.e., rebleeding). Clinically significant rebleeding has not been observed in studies when current dosing recommendations were followed.^{28,36-38} In fact, the MAP and SAP in experimental swine that experienced rebleeding were found to be 64 ± 2 mm Hg and 94 ± 3 mm Hg, respectively, during treatment, arguably supporting the use of LFVR so that the SAP does not exceed 90 mm Hg.³⁶

Contraindications to HS use include dehydration, preexisting hypernatremia, cardiac failure, hyperosmolar conditions (e.g., diabetic ketoacidosis), renal failure, and intravascular volume overload.³⁹ It is essential to monitor electrolyte levels in patients receiving HS. As with any sudden increase in sodium, there is a potential for neurologic signs due to cellular dehydration and acute neuronal shrinkage. HS

can cause an increase in sodium and chloride concentrations and a decrease in potassium and bicarbonate levels, but these are of minimal clinical importance unless the animal has preexisting electrolyte abnormalities. HS can also increase serum osmolarity by 20 to 30 mOsm in hydrated patients, but this generally normalizes within a few hours.¹⁵

Synthetic Colloids

Colloids exert a prolonged effect on intravascular volume compared with isotonic crystalloids, achieving better tissue perfusion and restoration of blood pressure at lower infusion volumes. In addition to LFVR for acute hypovolemia, colloids may be indicated in animals with hypoalbuminemia, decreased COP, or increased capillary permeability. Colloids can be biologic (e.g., blood, albumin, plasma) or synthetic (hetastarch, pentastarch, tetrastarch, dextran, gelatin, hemoglobin-based oxygen carrier [HBOC]). Biologic colloids are indicated for a variety of conditions but are rarely used as sole fluid support in shock. Synthetic colloids have molecular weights of 69,000 Da (the weight of albumin) or greater. In healthy patients, they cannot pass through the basement membrane of the intravascular space; therefore, they contribute to increases in the intravascular COP. Practitioners should be familiar with the concentrations and molecule sizes of synthetic colloids, which determine the initial amount and duration of intravascular volume expansion, respectively. The properties of synthetic colloids are summarized in

TABLE 4.^{34,40,41}

The use of a bolus of colloids at 5 mL/kg to achieve an SAP of no greater than 80 to 90 mm

QuickNotes

The concentrations and molecule sizes of synthetic colloids determine the initial amount and duration of intravascular volume expansion, respectively.

TABLE 4 Properties of Synthetic Colloids^{34,40,41}

	Molecular Weight Range (Da)	Weight Average Molecular Weight (Da) ^a	Number Average Molecular Weight (Da) ^b	Colloid Osmotic Pressure (mm Hg) ^c
6% Hetastarch	10,000–3,400,000	450,000	70,000	32.7 ± 0.2
10% Pentastarch	10,000–1,000,000	280,000	39,000	40
6% Dextran 70	15,000–160,000	70,000	39,000	61.7 ± 0.5
Oxypolygelatin	5600–100,000	30,000	22,000–24,000	45–47
Oxyglobin	64,000–500,000	200,000	—	43.3 ± 0.1

Da = dalton

^aThe weight average molecular weight reflects viscosity. It accounts for particle size and is therefore exaggerated by the larger particles.

^bThe number average molecular weight is the total weight divided by the number of molecules. Oncotic pressure is determined by the number of particles, not particle size; therefore, this number is a reflection of oncotic pressure. The weight average molecular weight is most commonly used in clinical settings.

^cAs measured on a colloid osmometer.

Hg may be warranted in patients with active hemorrhage during LFVR. It is important to follow colloids with crystalloids because colloids produce a state of relative dehydration in the interstitial space. Colloids can reduce the requirement for maintenance crystalloids by 40% to 60%.⁴²

The disadvantages of using synthetic colloids include cost, increased risk of volume overload compared with crystalloids, potential for anaphylaxis, potential exacerbation of coagulopathies, and interference with crossmatching. However, these side effects are rarely seen clinically in veterinary patients receiving recommended doses.^{34,35} Although often recommended in the treatment of patients with increased capillary permeability, colloids may contribute to the development of edema in animals with vasculitis if the large colloid molecules leak into the interstitial space.¹¹ This is a controversial issue and the topic of ongoing studies.

The effect of colloids on coagulation is likewise controversial, and studies have yielded inconsistent results.⁴³⁻⁴⁵ The hemostatic effects of hydroxyethyl starches are dose dependent and more common with products that have higher molecular weights, a greater degree of substitution (more hydroxyl groups per glucose unit in the molecule), and higher C2/C6 ratios (more hydroxyl groups on the glucose molecule at carbon position 2 compared with position 6).⁴⁶ Studies have shown decreases in circulating von Willebrand's factor and factor VIII, increases in activated partial thromboplastin time (APTT), and hypocoagulable changes on a thromboelastogram with the use of higher doses of these products.^{46,47} Thrombocytopenia has also been reported with the use of hydroxyethyl starches due to blocking of the glycoprotein IIb/IIIa receptor, which is required for platelet activation.⁴⁸ Overall, when used at recommended doses, synthetic colloids have not been associated with clinical signs of bleeding or clinically significant alterations in platelet counts, prothrombin time, APTT, or buccal mucosal bleeding time. Clinical bleeding appears to be rare if doses do not exceed 20 mL/kg/day. However, if massive amounts of synthetic colloids are required for stabilization, concomitant administration of blood products may be warranted to reduce the risk of dilutional coagulopathies.³⁴

Hydroxyethyl Starches

Hydroxyethyl starches are highly branched polysaccharides primarily consisting of amylopectin (e.g., hetastarch [HES], pentastarch, tetrastarch). HES is available as a 6% solution in 0.9% sodium chloride (Hespan, B. Braun Medical, Inc.) or as a 6% solution in a lactated electrolyte solution (Hextend, Hospira, Inc.), which is intended to mimic the principal ionic constituents of normal plasma. Compared with isotonic crystalloids, smaller volumes of HES can normalize and maintain SAP without lowering COP. Rapid administration of boluses may cause nausea in cats, and some experts recommend giving HES at a slower rate in this species.¹¹ The smaller particles in HES are almost immediately excreted in urine, whereas the larger particles are absorbed by the liver and spleen and slowly returned to the circulation for up to 36 hours. The larger molecules are degraded by the reticuloendothelial system and excreted by the liver and kidneys several days later.³⁴ HES can also reverse changes in microvascular permeability caused by oxygen free radicals during reperfusion injury, decrease leukocyte-endothelial cell adhesion, and improve microcirculation.⁴⁹

Pentastarch is available in a 10% solution in 0.9% sodium chloride (Pentaspan, B. Braun Medical, Inc). It is used as a volume-expanding and hemodiluting agent in leukopheresis. In theory, its branched shape may help to plug gaps between separated endothelial cells. Recommended doses of pentastarch are similar to those for HES.³⁴

Tetrastarch is available in a 6% solution in 0.9% sodium chloride (Voluven, Hospira, Inc.). It has a lower molecular weight and degree of substitution than HES and, therefore, causes fewer alterations in coagulation. However, its half-life is shorter, possibly necessitating more frequent dosing. Recommended dosing in people is up to 50 mL/kg/day, although amounts up to 70 mL/kg/day have been used in a research setting without adverse effects.^{46,47}

Dextrans

Dextrans are macromolecular polysaccharides produced by bacterial fermentation of sucrose. Dextran 70 (6% in 0.9% sodium chloride) is beneficial in reperfusion injury because it decreases neutrophil-endothelial interactions. Dosing of dextran 70 is similar to that of HES,

QuickNotes

Overall, when used at recommended doses, synthetic colloids have not been associated with clinical signs of bleeding or clinically significant alterations in platelet counts, prothrombin time, APTT, or buccal mucosal bleeding time.

and life-threatening allergic reactions to dextran 70 in dogs are extremely rare.⁴² Dextran 70 can elevate blood glucose concentrations due to metabolism of the dextran. It has been associated with decreased platelet adhesion and reduction of factor VIII complex activity when very large volumes are infused rapidly for acute plasma volume expansion.⁴³

Oxypolygelatin

A gelatin colloid plasma expander produced from bovine bone marrow (oxypolygelatin) is available, but information about its clinical use is limited. The volume of expansion is double the administered amount, and the clinical effect lasts for 2 to 4 hours.⁴¹ Histamine- and complement-mediated allergic reactions and increases in APTT have been reported with its use, but signs of clinical bleeding have not. In one study, oxypolygelatin caused fewer hemostatic abnormalities compared with dextran 70 when administered to healthy dogs.⁴⁵ Oxypolygelatin can significantly lower serum calcium levels and is currently marketed with supplemental calcium. The manufacturers recommend extreme caution with oxypolygelatin use in animals with coagulation defects, hypoproteinemia, cardiac or pulmonary insufficiency, or renal disease. Due to its small particle size, side effects, and short duration of action, this product is unlikely to gain widespread use versus other synthetic colloids.

Hemoglobin-Based Oxygen Carriers

Hemoglobin binds pulmonary oxygen and transports it to tissues, where it is offloaded to the cells. HBOCs improve oxygen delivery to tissues by increasing hemoglobin levels and circulating volume via colloidal pull. On a gram-for-gram basis, HBOC hemoglobin is more potent than erythrocyte hemoglobin at delivering oxygen to tissues because the molecules are smaller than erythrocytes and are able to pass through the microcirculation more readily. It is thought that HBOCs scavenge nitric oxide in the blood, causing vasoconstriction and increasing systemic vascular resistance.⁵⁰ They allow administration of an effective colloid and oxygen carrier without blood typing or crossmatching and can be stored at room temperature for long periods of time. In veterinary medicine, HBOCs have been investigated mostly for use during canine hypovolemic

shock, hemorrhagic shock, and isovolemic hemodilution. They may also be clinically indicated in the treatment of acute, severe anemia when compatible blood is not readily available or in septic patients to increase oxygen delivery. In animal models of severe, uncontrolled hemorrhage, HBOC infusions resulted in rapid resuscitation and survival with superior cardiac output and oxygen delivery compared with isotonic crystalloids.⁵¹

Oxyglobin (Biopure) is an ultrapurified, polymerized hemoglobin solution of bovine origin in a modified lactated Ringer's solution that is used in veterinary patients. It is approved for one-time use in dogs but should be avoided in animals that are predisposed to volume overload.⁵⁰ A retrospective study on the use of Oxyglobin in cats revealed a high incidence of pleural effusion and pulmonary edema, likely due to acute circulatory overload; therefore, use in cats remains off-label.⁵² Oxyglobin has been suggested for preoperative use in animals with hemoperitoneum to maximize perfusion as part of an LFVR protocol. Approximately 2 to 4 mL/kg is administered with lower doses of crystalloids to raise the SAP just to 80 to 90 mm Hg while minimizing the risk of dislodging clots.⁵³ Side effects of Oxyglobin can include discoloration of mucous membranes, sclera, and urine; mild gastrointestinal upset; and an increase in central venous pressure. Because Oxyglobin has such a strong colloidal pull, concurrent use of synthetic colloids is not recommended. In addition, some clinical laboratory values are temporarily immeasurable after its use, depending on the type of analyzer used. However, Oxyglobin does not interfere with complete blood cell counts, blood typing, co-oximetry, or blood gas analysis.⁵⁰

Research in Limited Fluid Volume Resuscitation

In 1980, it was found that HS resuscitated 100% of dogs in hemorrhagic shock with rapid normalization of MAP, acid-base status, and cardiac output.⁴ Since then, multiple studies have investigated the use of LFVR in hemorrhagic shock. Many studies have shown that HS with or without a colloid is superior to the use of crystalloids alone for resuscitation,¹⁻¹⁰ but others have shown no benefit.⁵⁴⁻⁵⁶ Despite many encouraging findings, strong experimental evidence is still lacking due to con-

QuickNotes

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flicting results, and there are few prospective veterinary clinical studies.

Many of the LFVR studies conducted to date were retrospective and nonstandardized and used animal models of controlled hemorrhage. These studies measured values such as volume expansion or intraabdominal blood loss, not clinically important values such as end points of resuscitation or overall survival. More recent studies^{1,57} have used more realistic animal models with uncontrolled hemorrhagic shock. However, it is challenging to find a humane and clinically realistic long-term method of analgesia that does not interfere with cardiovascular responses.^{1,57}

It is hard to apply human clinical and experimental evidence to veterinary patients. For example, in some human studies of LFVR, the elapsed time from a traumatic event to arrival in the operating room was less than 30 minutes, which often is not feasible in veterinary situations. In veterinary patients with nontraumatic hemorrhage, such as a ruptured hemangiosarcoma, surgery is often delayed for much longer than 30 minutes, and employing a hypotensive or delayed fluid resuscitation technique would prolong hypotension and promote multiple organ dysfunction. Furthermore, some veterinary patients with intraabdominal hemorrhage achieve spontaneous hemostasis and do not require surgery.

Multiple veterinary studies of hemorrhagic shock have shown that resuscitation with HS and 6% dextran (HS/D) returned hemodynamic parameters to baseline more rapidly than large volumes of crystalloids.^{4,9} In addition, the HS/D groups consistently maintained better MAP, cardiac output, and oxygen delivery with superior recovery of splanchnic hemodynamics versus animals receiving crystalloids alone.^{4,9} In studies of dogs with gastric dilatation–volvulus,^{7–9} the HS/D groups maintained higher cardiac output and oxygen delivery than the isotonic crystalloid groups. In addition, treatment time was significantly reduced, limiting the period of shock, gastric ischemia, and technical staff involvement. However, there was no significant difference in overall survival between

the two groups. In a study comparing HS/D to 0.9% sodium chloride and dextran in swine with severe endotoxic shock, the cardiac output, portal blood flow, intestinal mucosal blood flow, and overall survival were significantly higher in the HS/D group.⁶

Conversely, studies using animal models of controlled hemorrhage comparing LFVR with resuscitation using crystalloids alone have found no hemodynamic benefit, and some report no difference in blood loss or blood pressure between the groups.^{54–56} However, increased intraabdominal bleeding and shortened survival time were reported with the use of increasing volumes of lactated Ringer's solution, and significant improvement in oxygen delivery was reported with the use of LFVR.^{54–56} A review of studies in animal models found that LFVR appeared to reduce the risk of death in animal models of severe hemorrhage but increased the risk of death in animals with less severe hemorrhage. However, it also found that hypotensive resuscitation reduced the risk of death in all the trials in which it was used.¹⁰ Overall, some of the results are promising, but more research is needed in the veterinary community.

Conclusion

Clinically, LFVR using HS and colloids is a safe and highly effective alternative to use of crystalloid fluid alone for resuscitation in hypovolemic shock. Previously healthy animals that sustain catastrophic hemorrhage, pulmonary contusions, or traumatic brain injury may benefit most. The use of HS with colloids is superior to the use of isotonic crystalloids alone for vascular volume expansion and may expedite stabilization of hemodynamic parameters while reducing the risk of rebleeding and edema in the lungs and brain. HS may also have immunomodulating and other beneficial properties that alternative fluids do not have. It is important to note that these recommendations apply only to initial shock resuscitation. Treatment must be individualized, and many animals will benefit from combination therapy. Continued research in LFVR is needed in veterinary medicine. **C**

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3 CE
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- In healthy cats and dogs, how much of the body's total fluid is within the intravascular space?**
 - 8.25%
 - 12%
 - 15%
 - 33%
- When isotonic crystalloids are used alone for fluid resuscitation, approximately how much of the administered fluid remains within the intravascular space after 1 hour?**
 - <20%
 - 33%
 - 50%
 - 75%
- In clinical studies, higher doses of synthetic colloids caused all of the following hemostatic changes except**
 - decreased von Willebrand factor antigen.
 - decreased factor VIII.
 - increased APTT.
 - decreased platelet count.
- Which statement regarding synthetic colloids is true?**
 - They are considered to have double the potency of crystalloids for intravascular volume support per milliliter.
 - They are used clinically in doses of 5 to 50 mL/kg/day.
 - They expand intravascular volume by increasing the COP.
 - They can make dogs vomit when given rapidly.
- The recommended dose of 7.2% HS for an animal in shock is _____ mL/kg.**
 - 1 to 2
 - 3 to 8
 - 10 to 20
 - 55 to 60
- HS is not contraindicated in which condition?**
 - dehydration
 - traumatic brain injury
 - heart failure
 - renal failure
- Approximately how long do the resuscitative effects of 7.2% HS alone last?**
 - <15 min
 - <30 min
 - 60 min
 - 1 to 3 hr
- Which is not a benefit of HS administration?**
 - an increased extracellular glutamate level
 - an increased extracellular sodium concentration
 - promotion of local vasodilation and microcirculatory blood flow
 - inhibition of the coagulation cascade
- Which statement regarding HS–colloid combinations is true?**
 - They remain effective in the vascular space for 2 to 3 hours.
 - They can be mixed and given simultaneously.
 - They should not be given faster than 1 mL/kg/min.
 - all of the above
- Which statement regarding Oxyglobin is true?**
 - It is approved for use in dogs and cats.
 - It requires blood typing and cross-matching before use.
 - It will not interfere with any laboratory testing.
 - It should be avoided in animals predisposed to volume overload.

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