Colloid Osmotic Pressure in Health and Disease*

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ABSTRACT: The use of synthetic colloids has become commonplace in the treatment of critically ill animals. The theoretical benefits of colloid compared with crystalloid fluid therapy for increasing plasma volume include a more rapid and longer-lasting fluid resuscitation with colloids, a lesser fluid volume necessary to achieve the same level of resuscitation, and reduced risk of edema formation. These benefits are achieved, in part, by increasing or maintaining the patient's colloid osmotic pressure (COP) to retain fluid within the vasculature and limit extravasation of fluid into the interstitium. COP, and ultimately fluid balance, are normally highly dependent on the concentration of albumin within the vasculature. Understanding how COP is affected in different conditions (e.g., hypovolemia, sepsis, systemic inflammatory response syndrome, acute and chronic hypoalbuminemia) can guide clinicians in the appropriate uses of colloid therapy.

Maintenance of fluid homeostasis requires a delicate balance between hydrostatic and oncotic gradients. Of the forces involved, intravascular hydrostatic pressure and plasma COP are the most significant. Intravascular hydrostatic pressure is the main force promoting fluid extravasation from vessels, while plasma COP is the pressure that prevents fluid movement from the intravascular to the interstitial compartments. Starling's equation (Figure 1) relates these forces such that fluid flux is determined by the difference in hydrostatic and oncotic gradients found between the intravascular and interstitial compartments. The forces favoring filtration of fluid out of the intravascular space are capillary hydrostatic pressure and interstitial oncotic pressure. These forces are opposed by intravascular COP and interstitial hydrostatic pressure. In most biologic systems, there is always a net fluid flow out of the vascular system and into the interstitium. The excess interstitial fluid is eventually returned to

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The intravascular hydrostatic pressure, \( P_c \) is the intravascular oncotic pressure, \( \pi_c \), means that its synthesis is sensitive, which represents the permeability of the membrane or pore size. The arrows indicate the direction of each force.

Two additional factors responsible for modulating the impact of Starling’s forces on fluid flux are the reflection coefficient and the filtration coefficient:

- The **reflection coefficient** (\( \sigma \)) represents the permeability of the membrane to macromolecules. Mechanisms affecting macromolecular permeability include differences in size and charge of the molecules and route of transport. Macromolecules cross the microvascular membrane through large pores on the venous side of the capillary, and their transport is also influenced by the charge of endothelial cells and the composition of glyocalyx close to the endothelial membrane.

- The **filtration coefficient** (\( K \)) represents conductance or relative ease of fluids to cross the membrane, and \( \sigma \) is the reflection coefficient, which represents the permeability of the membrane or pore size. The arrows indicate the direction of each force.

The interplay of Starling’s forces is dynamic and varies considerably among organ systems. For example, the permeability of capillary membranes to albumin is quite high in the lungs. As a result, an effective oncotic gradient cannot be maintained and therefore COP is less important in controlling fluid extravasation in this system. To compensate, lymphatic drainage is enhanced, preventing accumulation of filtered fluid. This explains why pulmonary edema is more common in situations of high hydrostatic pressures, such as fluid overload and congestive heart failure (CHF), but relatively uncommon in hypoproteinemia. In contrast, the capillary permeability to albumin is low in the subcutaneous interstitium, which helps to account for the greater tendency to develop peripheral edema in hypo-oncotic states. This edema formation may be countered in clinical practice with support wraps, which increase the interstitial hydrostatic pressure.

### GENERATION AND MAINTENANCE OF COLLOID OSMOTIC PRESSURE

Albumin is the principal contributor to COP, accounting for approximately 80% of plasma COP. Other proteins (e.g., immunoglobulins, fibrinogen) also contribute to COP. These plasma proteins are marginally permeable through the capillary membranes and are therefore concentrated within the vasculature. Because of the poor permeability of these osmotically active proteins (i.e., albumin, immunoglobulins, fibrinogen), a concentration gradient is created across the membrane, generating most of the COP.

Another property that is a significant contributor to COP is the Gibbs-Donnan effect. Most proteins, including albumin, are negatively charged molecules surrounded by noncovalently bound cations such as sodium. These sodium ions act independently from their own concentration gradients and further increase the water-retaining effect of COP within the vasculature. This effect is additive and increases disproportionately with increasing albumin concentration. Acidemia, which is common in critically ill patients, decreases the relative negative charge of albumin, limiting the Gibbs-Donnan effect and reducing the effective COP.

Generation and maintenance of the COP (and albumin in particular) are important in healthy animals. The relationship between albumin synthesis and COP is incompletely understood. Albumin synthesis takes place exclusively in hepatocytes. In situations of adequate nutritional status and ample supply of amino acids, albumin synthesis is thought to be regulated by hepatic plasma COP. However, other factors independent of COP may also be involved in albumin synthesis. For example, albumin is known as a negative acute-phase reactant, which means that its synthesis is suppressed in response to inflammation. Controversy exists as to whether the administration of natural or artificial colloids could, in fact, suppress albumin synthesis. A recent in vitro study demonstrated significant decreases in albumin synthesis by isolated hepatocytes when the cultures were incubated with solutions of albumin and hetastarch.
A low plasma COP has been associated with increased mortality in critically ill humans. Critically ill veterinary patients have also been recognized as having abnormally low COP, but actual correlation to outcome has not been established. Perhaps more important than the actual plasma COP is the ratio between plasma and interstitial COP. Conditions resulting in acute hypoalbuminemia dramatically decrease intravascular COP relative to interstitial COP and can result in hypovolemia, decreased tissue oxygenation, and systemic edema formation. For example, in a case in which there is significant acute blood loss followed by massive crystalloid infusion, the decrease in intravascular COP promotes edema formation. Although peripheral edema may not have serious consequences in most patients, intestinal edema could be life-threatening in cases of intestinal surgery due to an increased risk for anastomotic dehiscence. In cases of chronic hypoalbuminemia, as seen with protein-losing enteropathy and protein-losing nephropathy, COP is decreased in both the interstitium and the intravascular space, and therefore the ratio between these two compartments is preserved and fluid balance is maintained. These patients would have a low COP but no signs of edema unless crystalloids were administered. In the absence of peripheral edema, colloid therapy would offer little benefit in these chronic cases.

OTHER MEASURES OF FLUID BALANCE

As discussed, COP counterbalances hydrostatic pressure. Hydrostatic pressure is dependent on arterial blood pressure, precapillary and postcapillary resistance, and venous pressure. Clinically, it is difficult to measure hydrostatic pressure, although pulmonary capillary wedge pressure (PCWP; measured via a Swan-Ganz catheter) and central venous pressure (CVP) might be useful as clinical correlates of hydrostatic pressure. A PCWP–COP gradient has also been shown to accurately predict the presence of pulmonary edema in critically ill humans, although no such relationships have been demonstrated in veterinary medicine and PCWP is not routinely measured. In addition to hydrostatic and oncotic forces, increased vascular permeability has a major impact on fluid balance.

MEASUREMENT OF COLLOID OSMOTIC PRESSURE

Colloid osmotic pressure may be predicted or directly measured. Because the concentration of plasma proteins in part determines COP, predictive equations of COP based on total protein concentrations have been proposed. Although these equations provide values that correlate well with COP in healthy humans, they are unreliable in critically ill patients. This is due in part to changes in blood pH, particularly acidemia, which influence the Gibbs-Donnan effect. Attempts to apply these equations to dogs and cats have not produced reliable results. Although new formulas have improved the ability to use total protein to predict COP, direct measurements remain the method of choice for determining COP in clinical patients. A commercial colloid osmometer can be used to directly measure COP in the clinical setting, providing rapid and reliable results (e.g., Wescor® 4420, Logan, UT; Figure 2).

Some authors have cautioned that certain conditions can alter the reading of the COP by a colloid osmometer. Such artifacts as severely hemolyzed samples can reportedly falsely elevate COP readings through the addition of free hemoglobin, while the use of liquid anticoagulants in sample collection can cause a dilutional effect and falsely lower the COP measurement. Normally, immunoglobulins are only minor contributors to COP. In cases of severe hypergammaglobulinemia (e.g., multiple myeloma, feline infectious peritonitis), however, COP can be dramatically elevated. The consequences of an abnormally elevated COP are unclear, although high COP could inhibit albumin synthesis and result in hypoalbuminemia. Pathologic changes associated with hypergammaglobulinemia are usually attributed to increases in blood viscosity and the deposition of immunoglobulin complexes but apparently not to the altered COP.

![Figure 2](image-url)
Several studies have established normal values of COP in veterinary patients using colloid osmometry. Normal canine plasma COP values range from 14 to 27 mm Hg, whereas normal feline plasma COP values can range from 21 to 34 mm Hg. The reported mean COP in whole blood was 19.9 ± 2.1 mm Hg in dogs and 24.7 ± 3.7 mm Hg in cats. However, just as with any laboratory test, a reference range should be established for the particular colloid osmometer and protocol used.

**FLUID BALANCE IN DISEASES**

The normal dynamics of various fluid compartments are altered during different disease states. Changes may include the following:

- Increased vascular permeability
- Acute or chronic decreases in albumin (and COP)
- Increased intravascular hydrostatic pressure

Increased vascular permeability is one of the more challenging conditions encountered in critically ill patients and is one in which the use of synthetic colloids is perhaps most controversial. Diseases associated with increased vascular permeability include the systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), pneumonia, sepsis, vasculitis, reperfusion injury, pancreatitis, and anaphylaxis. Additionally, envenomation (e.g., bees, wasps, rattlesnakes), trauma, burns, smoke inhalation, and multiple blood transfusions are also associated with increased vascular permeability. Inflammatory cytokines can induce changes in endothelial cells that increase microvascular permeability and lead to capillary leakage. For example, during reperfusion of hypoxic tissue, the endothelial junctions in capillary membranes separate, increasing the number and size of the pores in the capillary membranes. In sepsis, it is thought that endothelial damage occurs as a result, in part, of the action of activated, degranulating neutrophils. Subsequently, the increased capillary permeability is responsible for albumin leakage and a decrease in plasma COP. With a decrease in plasma COP, fluid filtration from the intravascular compartment is enhanced and leads to edema formation and fluid loss into third spaces. The subsequent loss of plasma volume contributes to the cardiovascular dysfunction and tissue hypoperfusion in sepsis.

In patients with ARDS, inflammatory cytokines are released in response to septic and inflammatory stimuli and cause deranged capillary permeability. These patients usually receive aggressive fluid therapy, resulting in elevated pulmonary hydrostatic pressure. The combination of these effects favors filtration of fluid into the pulmonary interstitium and may impair pulmonary gas exchange. With the increased permeability, the oncotic gradient between the pulmonary vasculature and interstitium is diminished, causing COP to become less significant in affecting fluid flux. This increase in permeability also presents a problem for patients receiving synthetic colloids. Although there are some data to suggest that medium-sized macromolecules could attenuate some of the increased permeability, most artificial colloids are heterogeneous solutions containing various-sized macromolecules. For example, hetastarch contains molecules ranging from 20 to 2500 kD (6% hetastarch in 0.9% sodium chloride, Abbott Laboratories, North Chicago, IL). The smaller particles may easily pass through capillary membranes and extravasate into the pulmonary interstitium. This could potentially lead to worsening of pulmonary edema.

When hypoalbuminemia results from nephrotic syndrome, the exact mechanism of fluid retention and edema formation remains controversial. A pervasive theory states that renal sodium and water retention occur as a response to low intravascular volume caused by the transudation of fluid from the plasma to the interstitial compartment due to a low plasma COP. However, some studies have cast doubt on this theory, and edema formation in nephrotic patients is now thought to occur as a result of primary renal mechanisms of sodium and water retention, independent of COP. Therefore, the use of colloids to raise the COP in this patient population may not be warranted. Similarly, increases in pulmonary hydrostatic pressure are often seen in CHF. Colloid fluid therapy is usually avoided in animals with CHF due to concerns about intravascular volume overload and subsequent worsening of pulmonary edema or pleural effusion.

**COLLOID FLUID THERAPY**

Treatment of critically ill animals typically entails correction of dehydration and hypoperfusion via the administration of intravenous fluids to compensate for fluid losses and to maintain cardiovascular homeostasis. Intravenous fluids are categorized as either a crystalloid solution or a colloid solution based on their composition. A crystalloid is an aqueous solution with small particles that are normally osmotically active in body fluids and that can easily pass through the capillary membrane. Examples include 0.9% saline, lactated Ringer’s solution, and hypertonic saline. A colloid is an aqueous solution containing both small and large particles (larger than 30 kD), with the larger molecules being too large
to filter through capillary membranes. Colloids can be either natural (e.g., whole blood, plasma, albumin solutions) or synthetic (e.g., dextrans, hydroxyethyl starches, hemoglobin-glutamers [Oxyglobin® Biopure Corporation, Cambridge, MA]). Colloid therapy and products have been recently reviewed. Parenteral nutrition components such as amino acid solutions, lipid emulsions, and dextrose solutions behave similarly to crystalloids and have COP measurements less than 1 mm Hg.

Colloid therapy is employed based on the principle that the patient’s COP can be influenced by the administration of either natural or synthetic colloids. Properties of the different colloids may help predict their in vivo effects. For example, the inherent COP of synthetic colloids ranges from 29 to 65 mm Hg, and therefore the degree of COP change will depend on the type and volume of colloid used. Other factors, such as the half-life of each particular colloid and the duration of effect, are thought to also influence the effect on COP. The expected increase in COP associated with particular dosages and types of colloids has not been established.

While there are many benefits to colloid therapy (e.g., more rapid and longer-lasting resuscitation), there are potential side effects associated with synthetic colloid administration. These rare side effects can be dose-dependent, such as fluid overload and changes in coagulation parameters, or the more unpredictable anaphylactic/anaphylactoid reactions and acute renal failure. To minimize the occurrence of some of these effects, general recommendations have been made, including dose recommendations for various colloids (e.g., 20 ml/kg/day for hetastarch) and monitoring COP during colloid therapy. Some authors have advocated using the COP to guide colloid administration (e.g., administering colloids until the patient’s COP is at least 15 mm Hg). However, this therapeutic goal may not be optimal in all situations. In our experience, standard colloid therapy (20 to 40 ml/kg/day of hetastarch) results in only modest changes in COP of 4 to 5 mm Hg posttreatment in most animals. Administration of synthetic colloids does not appear to increase COP in a predictable manner, although a general dose-dependent effect is seen. The benefit of COP monitoring during colloid therapy may be clearer when observing trends rather than attempting to achieve a certain COP level. As with any laboratory test, the actual value is meaningless when taken out of context with respect to the clinical assessment of the patient.

Increased transcapillary leakage of fluid and proteins is often seen in critically ill patients. Continued use of crystalloids for fluid therapy in these patients could result in significant fluid losses from the intravascular space. Reducing vascular permeability may be of value to counteract the resultant tissue edema and hypovolemia. In some studies, the use of dextrans and hetastarch was shown to attenuate macromolecular leakage by presumably occluding some of the endothelial “gaps” associated with some conditions (e.g., ischemia, sepsis). However, there are concerns over the use of heterogeneous colloid solutions in states of increased permeability because the smaller colloid particles will extravasate into the interstitium and potentially promote edema. Furthermore, the clearance of these small, osmotically active particles from the pulmonary interstitium is particularly slow, and so colloids should be used with judicious care in cases of increased pulmonary vascular permeability.

**COLLOID OSMOTIC PRESSURE MEASUREMENTS IN CLINICAL CASES**

The three cases in Box 1 illustrate how measurement of COP could impact clinical decisions in both the diagnosis and treatment of veterinary patients. In Case 1, the acute decrease in COP associated with blood loss, coupled with increased hydrostatic pressure from aggressive fluid administration and possible increased vascular permeability from massive blood transfusions, favored edema formation. Restoration of the intravascular/interstitial COP gradient with synthetic colloids may have facilitated edema clearance.

In Case 2, a similarly low COP was measured, yet no edema was noted. This was due to the chronicity of protein loss that allowed equilibration of protein distribution between the intravascular and interstitial compartments, thus preserving the normal gradient. This illustrates that edema cannot be predicted solely by the COP.

In Case 3, the presence of generalized edema with a normal COP supports either an increase in vascular permeability or the inability to clear interstitial fluid, as may be seen with lymphatic obstruction associated with neoplasia as the cause for edema. Lymphatic obstruction was unlikely in this case because of the distribution of edema, leaving vasculitis as the main diagnostic differential. The normal COP also helped determine that colloid therapy was not indicated in this case. Knowledge of the COP can help in classifying and diagnosing diseases associated with edema as well as determining the appropriate situations in which synthetic colloids might be used. Colloid osmotic pressure is an important concept in understanding the pathophysiology of edema, fluid resuscitation, and colloid therapy.

**FUTURE RESEARCH**

As the intricacies of COP in both health and disease are further elucidated, an individual patient’s COP
could potentially be used as a prognostic indicator. Although some studies have related low COP to an increased risk of developing pulmonary edema in humans, no such studies have been conducted in veterinary medicine. Measurement of COP can also be used as a guide for colloid therapy. However, an optimal level of COP achieved with colloid therapy in various clinical settings has yet to be determined. Because COP is so dependent on plasma albumin concentrations, the impact of nutritional support, either parenteral or enteral, on overall albumin synthesis needs to be evaluated. Development of newer synthetic colloids with decreased side effects and increased intravascular persistence holds much promise for the treatment of critically ill patients. As our understanding of COP in health and disease continues to develop, direct measurements of COP in clinical patients could become an indispensable tool in the monitoring and treatment of critically ill animals.

Box 1. Clinical Cases

Case 1
A 10-year-old, intact male, 26-kg weimaraner was presented for acute weakness and hematemesis. Initial packed cell volume (PCV) was 32%, serum total solids (TS) were 4.2 g/dl, and initial COP was 16.4 mm Hg (reference range, 17 to 23 mm Hg). The dog was tachycardic and weak and had pale mucous membranes and poor pulse quality. Hypovolemic shock was aggressively treated over 3 hours with 5 L (200 ml/kg) of lactated Ringer's solution, but severe hematemesis continued and PCV, TS, and COP continued to drop precipitously (PCV, 13%; TS, 2.1 g/dl; COP, 10.3 mm Hg) with no improvement in hemodynamic signs. During resuscitation, multiple blood transfusions (7 units of packed erythrocytes) were administered. The dog became extremely edematous, especially on its limbs and face. At surgery, a large gastric ulcer was identified and attributed to NSAID therapy for arthritis. The peripheral edema began to resolve only after several days of supportive care, including colloid therapy with hetastarch and fresh-frozen plasma. Following colloid therapy, COP had increased to 14.6 mm Hg, while TS were 4.3 g/dl.

Case 2
A 5-year-old, neutered, 24-kg Labrador retriever was presented for an 8-week history of small-bowel diarrhea and weight loss. The standard gastrointestinal workup included a complete blood cell count (CBC), biochemical profile, multiple fecal examinations, abdominal imaging studies, and endoscopy with biopsies. Based on clinical findings and histologic characteristics, the dog was diagnosed with severe lymphocytic-plasmacytic inflammatory bowel disease. Despite a low serum albumin of 1.4 g/dl (reference range, 3.0 to 4.2 g/dl) and a low COP of 10.6 mm Hg, no edema was detected.

Case 3
A 7-year-old, spayed, 31-kg Doberman pincher was presented for lethargy, inappetence, and edema extending from the face to all four limbs. A diagnostic workup was performed, and no abnormalities were noted on the CBC, urinalysis, thoracic radiography, or abdominal ultrasound. On a biochemical profile, the albumin concentration was 3.0 g/dl (reference range, 3.0 to 4.2 g/dl) but was otherwise unremarkable. Systolic blood pressure (130 mm Hg), CVP (3 cm H$_2$O), and COP (21.8 mm Hg) were within normal limits. Given the normal COP, the edema could not be explained by low oncotic pressure. Titters for ehrlichiosis, leptospirosis, and antinuclear antigen were negative. Skin biopsies demonstrated neutrophilic infiltration of vascular walls, consistent with vasculitis. Since no inciting cause was identified, prednisone (20 mg q12h PO) was initiated. After 2 weeks of therapy, the edema completely resolved and the dog showed no other signs of illness. Prednisone was gradually discontinued.
REFERENCES


1. Intravascular COP
   a. is generated by interstitial albumin and other proteins.
   b. preserves fluid within the vasculature and opposes extravasation of fluid into the interstitium.
   c. is a negligible Starling force in biologic systems.
   d. is preserved despite losses of albumin encountered in many different diseases.

2. Starling’s equation
   a. can be accurately calculated using CVP and plasma.
   b. relates fluid shifts in terms of reflection and filtration coefficients.
   c. relates fluid flux as a difference in hydrostatic and oncotic gradients found between the intravascular and interstitial compartments.
   d. is the relationship of forces regulating fluid homeostasis and is constant among all organ systems.

3. Albumin
   a. is the main contributor to COP.
   b. synthesis is solely regulated by hepatic COP.
   c. is completely impermeable through capillary membranes.
   d. is an acute-phase protein, and its synthesis is increased in response to inflammation.

4. One rationale for administering synthetic colloids is to increase
   a. endogenous albumin synthesis.
   b. lymphatic drainage.
   c. plasma COP.
   d. total protein.

5. The Gibbs-Donnan effect
   a. refers to increased membrane permeability due to inflammation.
   b. contributes to COP by attracting immunoglobulins and other osmotically active proteins to albumin.
   c. increases COP by attracting sodium ions to albumin against their concentration gradient.
   d. is the difference between the oncotic and hydrostatic gradients.

6. Increased vascular permeability
   a. is counteracted by increased protein synthesis.
   b. can be easily reduced by administering synthetic colloids.

7. Measurement of COP
   a. is inaccurate in acemic patients; therefore, predictive formulas of COP based on total solids should be used.
   b. can be used to guide colloid therapy and help evaluate causes of edema.
   c. can be falsely reduced in hemolyzed samples.
   d. is useful in calculating the exact dose of colloid therapy.

8. Plasma COP values above the reference range
   a. have significant implications for colloid therapy.
   b. can be seen with severe hypergammaglobulinemia associated with feline infectious peritonitis or multiple myeloma.
   c. can be used as a therapeutic endpoint of colloid therapy.
   d. predispose patients to pulmonary edema.

9. Animals with chronic hypoproteinemia
   a. are best treated with natural rather than with synthetic colloids.
   b. should be treated with synthetic colloids until COP is restored to normal.
   c. do not require treatment because COP is maintained at normal levels by other molecules.
   d. may not require treatment if clinical signs (e.g., edema) are absent.

10. Desirable characteristics of newly developed synthetic colloids include
    a. increased antigenic stimulation and uniform particle size.
    b. a shorter half-life than current synthetic colloids.
    c. decreased side effects and increased intravascular persistence.
    d. decreased intravascular persistence and the ability to increase vascular permeability.