To the author’s knowledge, it has been more than 20 years since the JAVMA published an article entitled perioperative fluid therapy.1 That report focused on fluid types, fluid additives, and recommendations for their administration. In the meantime, IV therapy has undergone a renaissance of interest in both human and veterinary medicine.2,3 Major topics have included transmembrane fluid movement, fluid kinetics, under- and over-resuscitation, fluid efficacy, fluid overload, and the development of dynamic monitoring methodologies. Despite this reawakening, many veterinarians consider the type, rate, and volume of fluid administered challenging.4 The administration of perioperative fluids can be difficult because fluids are capable of producing diverse pharmacodynamic effects dependent upon their composition, osmotic potential, kinetics, and dose. Appropriate dosing requires an understanding of body fluid compartments, fluid balance, and the administered fluids’ behavior in the body. Anesthetic drugs and general anesthesia produce CNS, neuroendocrine, and macro-/microvascular hemodynamic effects. These effects modulate the response to IV fluid administration and promote interstitial fluid accumulation, third-space fluid loss, and fluid overload. This narrative review discusses current knowledge regarding anesthesia-associated physiologic and IV fluid kinetic changes that influence the efficacy of IV fluid administration during the intraoperative period. A rationale for intraoperative fluid dosing that addresses intraoperative hypotension, blood loss, and practices that promote fluid overload is provided. Intraoperative IV fluid administration should be individualized and monitored by dynamic goal-directed methods that evaluate fluid responsiveness.

Hemodynamics and Blood Volume Distribution

Arterial blood pressure (Pa) and vascular capacitance are acutely regulated by the sympathetic nervous system (SNS). Splanchnic veins and venules are 30 times more compliant than arteries, contain 5 times more adrenergic receptors, and are responsible for most of the active capacitance changes associated with alterations in SNS activity.9 Alterations in Pa are traditionally discussed in terms of the hydraulic equivalent of Ohm’s law (ie, $Pa = CO \times R$), where CO and R represent cardiac output and systemic vascular resistance, respectively. Although R is not the only hemodynamic factor responsible for the opposition to blood flow, it is the major component. Cardiac output is determined by the amount of blood pumped (ie, stroke volume [SV]) during each heart contraction (ie, heart rate [HR]; $CO = SV \times HR$). Changes in SV, however, are also influenced by SNS, HR, R, venous return (VR), cardiac contractile function (contractility [CC]), and blood volume (BV). Consequently, Pa is dependent upon SNS activity, CO, R, SV, HR, VR, CC, and BV.

BV is generally considered to be normal (eg, 80 mL/kg for dogs; 55 mL/kg for cats; 90 mL/kg for horses) in most healthy animals subjected to anesthesia for elective surgical procedures. Total BV is unevenly distributed between veins and arteries, with a 5- to 6-fold difference in venous and arterial volumes (Figure 1).10 This implies that as little as a 1% increase in venous vascular compliance (Cv; distensibility) in a 15-kg dog could result in a redistribution of over 8 mL of arterial blood to the venous system (80 mL/kg X 15 kg = 1,200 mL; 1,200 mL X 0.70 = 840 mL; 1% x 840 mL = 8.4 mL). This shift of arterial blood to the venous circulation reduces arterial volume by approximately 7% (10% [0.1] X 1,200 = 120 mL; 8.4 mL/120 mL = 0.07
Fluid that is filtered across the capillary endothelium returns to the circulation via the lymphatic system. Interstitial fluid is transiently reabsorbed into the capillary during an acute decrease in Pc or a marked increase in plasma osmolality, but only until a new steady state is established. The GCX model and no-reabsorption rule provide an explanation for why hyperosmotic and hyperoncotic solutions are only temporarily and not always effective in decreasing interstitial edema. 

Volume Kinetics

The administration of IV fluids increases extracellular fluid (ECF) first by expanding the plasma volume (PV) followed by gradual expansion of some portion of the interstitial fluid (IF) volume. Water balance is primarily maintained by renal excretion (Figure 3). The term volume kinetics (VK) describes the dynamic changes in vascular volume expansion over time by quantifying the fractional plasma hemoglobin dilution. Different contemporary fluids disperse at different rates from Vc into a peripheral volume (Vp) representing some portion of the remaining ECF volume. Fluid returns to Vc via the lymphatic system and is removed from Vc by insensible losses and renal excretion. Fluid that does not return to Vc in a reasonable time or is unavailable for renal excretion is considered lost to a third space. Rate constants (k) for removal and return of fluid to Vc are used to represent capillary leak (k12) and fluid redistribution (k13), respectively. Redistribution (k13) correlates with lymphatic flow in the thoracic duct. Rate constants for fluid removal from Vc and fluid that is slow in returning to Vc represent renal elimination (kF) and third-space loss (kS), respectively (Figure 4).

Volume kinetic analysis has been employed to simulate and calculate the plasma and interstitial volume, expanding effects of various fluids and fluid administration techniques in both conscious and anesthetized humans and anesthetized rabbits, pigs, and sheep. Limited data, however, are available from conscious or anesthetized companion animals. A study investigating the VK of a balanced isotonic crystalloid solution in conscious healthy cats reported a plasma half-life of 49 minutes, rapid distribution (ie, 3 to 4 times faster), and slower elimination compared with conscious humans, thereby providing

The Revised Starling Principle

Earnest Starling's observations in 1896 led to the promotion of the Starling principle and foreshadowed the development of the familiar Starling equation: 
\[ Jv = Kc \left( (Pc - P) - \sigma (\pi_c - \pi_i) \right), \]
where Jv equals transcapillary fluid flux; the subscripts c and i represent intraluminal and interstitial, respectively; P and \( \pi \) equal hydrostatic and oncotic pressures, respectively; \( K_c \) equals the filtration coefficient (ie, \( K_c = membrane hydraulic conductivity [Lp] \times the surface area [S] \)); and \( \sigma \) equals the macromolecular reflection coefficient. The Starling principle has remained unchanged for over a century and describes fluid filtration across capillary walls as a function of opposing hydrostatic (P) and oncotic (\( \pi \)) pressures. Traditional interpretations suggest that Pc prevails at the arterial end of the capillary, forcing fluid into the interstitium while Pc predominates at the venous end of the capillary (ie, \( \pi_c > \pi_i \)), resulting in fluid reabsorption into the capillary (Figure 2). Skepticism of this interpretation has led to the conclusion that fluid is not normally reabsorbed from the venous end of the capillary during steady-state conditions; this conclusion is known as the no-reabsorption rule. Additionally, it has been determined that Jv is primarily dependent upon Pc throughout the length of the capillary, and Jv is less than originally hypothesized. These discoveries, in conjunction with the identification of a carbohydrate-rich layer lining the vascular endothelium (glycocalyx [GCX]) and its associated absorbed serum proteins (eg, albumin), have resulted in revision of the Starling equation (Jv = Kc [(Pc - P) - \( \sigma (\pi_c - \pi_i) \)], where \( \pi_0 \) equals the sub-GCX osmotic pressure). The GCX acts as a molecular sieve regulating endothelial permeability, mechanotransduction (ie, flow-related changes in vascular tone), and leukocyte transmigration. Recent studies have determined that the GCX is not the sole determinant of endothelial fluid permeability since targeted enzymatic degradation of the GCX does not increase capillary membrane permeability. Fluid that is filtered across the capillary endothelium returns to the circulation via the lymphatic system. Interstitial fluid is transiently reabsorbed into the capillary during an acute decrease in Pc or a marked increase in plasma osmolality, but only until a new steady state is established. The GCX model and no-reabsorption rule provide an explanation for why hyperosmotic and hyperoncotic solutions are only temporarily and not always effective in decreasing interstitial edema.

Figure 1—Blood volume distribution. Blood volume is disproportionately distributed among the heart and lungs (approx 15%), arteries (approx 10%), capillaries (approx 5%), and veins (approx 70%). Arterial resistance vessels (ie, arterioles) regulate the distribution of blood flow to capillaries, and venous smooth muscle regulates the compliance and capacitance of the venous circulation. Arterial blood pressure (P) is determined by arterial blood flow (Q) and vascular resistance (R).

or 7%). An anesthesia-associated shift in arterial blood to the venous circulation therefore decreases Pa by increasing Cv.
evidence for species differences and cats’ predisposition to fluid overload. These data highlight the value of VK studies and emphasize the need for additional animal studies to develop safe and effective species-specific guidelines that avoid IV fluid therapy related adverse events including fluid overload.

Anesthesia: Hemodynamics, the Starling Principle, and Volume Kinetics

Hypotension is one of the most frequently encountered and concerning adverse events that occur in anesthetized animals and is associated with increased morbidity and mortality. General anesthesia produces important and often underemphasized changes in BV distribution, transcapillary fluid flux, and VK in addition to its more publicized dose-dependent CNS, autoregulatory (eg, baroreceptor reflex), and cardiorespiratory depressant effects. Anesthetic drugs (eg, propofol, isoflurane) decrease Pa by increasing venous (eg, splanchnic veins, venules) Cv and redistributing BV from arteries to veins. Relatively small anesthetic-induced increases in venous capacitance redistribute arterial blood to the venous circulation, lowering Pa without blood loss. Increased Cv is responsible for decreased VR and preload with resultant reductions in SV, CO, and Pa even if R does not change, since CO and Pa are directly related (Figure 1). Evidence supporting this mechanism is provided by experiments in anesthetized dogs and pigs wherein extremely low doses of norepinephrine and phenylephrine improve CO and
Pa by decreasing Cv. Pa therefore is determined by all the aforementioned variables (ie, SNS activity, CO, R, SV, HR, VR, CC, BV) and Cv.

General anesthesia also modifies transcapillary fluid exchange. Pc is the principal determinant of transcapillary fluid flux and is determined by Pa and the ratio of precapillary arteriolar (a) and postcapillary venular (v) resistances (Ra/Rv). Decreases in Ra or increases in Rv increase Pc, and since Ra/Rv is normally large, transcapillary fluid flux is more dependent upon a change in Rv than Ra. The effects of clinically relevant concentrations of most anesthetic drugs on Ra/Rv and Jv have not been determined; however, drugs that decrease Ra (eg, acepromazine, most inhalants) would be expected to increase Pa and Jv. Some anesthetic drugs, including isoflurane, would be expected to increase Pc and Jv. Potential mechanisms include anesthetic-induced increases in vascular endothelial growth factor, nitric oxide–induced vasodilatation, and anesthetic-coupled increases in membrane fluidity. Propofol and inhalant anesthetics, particularly isoflurane, increase membrane fluidity and reduce lymphatic pumping.

In summary, the proportion of infused fluid that stays in Vc during general anesthesia is determined by Pa, Ra/Rv, Pc, and membrane permeability. General anesthesia increases IF accumulation (ie, increases Vp and k_b) in proportion to the decrease in vascular endothelial growth factor, nitric oxide–induced vasodilatation, and anesthetic-coupled increases in membrane fluidity. Propofol and inhalant anesthetics, particularly isoflurane, increase membrane fluidity and reduce lymphatic pumping.
in renal elimination (ie, decreases $k_f$). Anesthetic-induced decreases in $P_a$ result in a greater fraction of the infused fluid remaining in $V_c$ (ie, fluid efficacy: normally 20% to 30%), but the anesthetic-associated increase in capillary membrane permeability and decrease in redistribution (ie, $k_{r1}$) promote IF accumulation and tissue edema.\textsuperscript{15-17,24} Notably, fluid type (eg, colloids, crystalloids), infusion rate, and the total volume of fluid administered also influence IF accumulation (ie, greater infusion rates and fluid volumes increase IF). General anesthesia also prolongs compensatory plasma volume restitution following hypotension or hemorrhage.\textsuperscript{25} These effects combined with adjunctive fluid infusions (eg, lidocaine, fentanyl) exacerbate IF accumulation (ie, “fluid creep”) and the development of fluid overload.\textsuperscript{26}

**Fluid Types**

IV fluids possess important inherent properties that include osmolarity, tonicity, electrolyte concentration, colloid osmotic pressure, strong ion difference, viscosity, and caloric content. Commercially available fluids can be divided into 2 broad categories, crystalloids and natural (eg, albumin) or synthetic colloids.\textsuperscript{27} Crystalloids are salts (eg, Na\textsuperscript{+}, Cl\textsuperscript{−}, K\textsuperscript{+}, Mg\textsuperscript{2+}, Ca\textsuperscript{2+}) of water soluble molecules and are the diluents for colloidal solutions. They include “normal” or “physiologic” saline (ie, 0.9% NaCl\textsuperscript{−}), 5% dextrose, and “balanced” electrolyte solutions that contain organic anions (eg, lactated, acetate, gluconate).\textsuperscript{27} Balanced crystalloid solutions are defined as fluids “that contain an electrolyte composition that is similar to that found in plasma,” “maintain or normalize acid-base balance,” and are “isosmotic and isotonic (ie, do not induce inappropriate fluid shifts) with normal plasma.”\textsuperscript{28} Balanced solutions aid in normalizing acid-base balance by having an in vivo electrolyte content, after metabolism of their organic anion, that produces a strong ion difference between 24 and 29 mEq/L.\textsuperscript{4,28} Balanced crystalloid solutions are the fluid of choice for perioperative administration.\textsuperscript{27,28} Excessive crystalloid administration can result in damage to the endothelial GCX, interstitial edema (eg, pulmonary and gut edema), hemodilution, reduced oxygen delivery to tissues, and prolonged recovery from anesthesia.\textsuperscript{8} Colloids (eg, natural: albumin, synthetic: hydroxyethyl starch) are large-molecular-weight molecules (ie, > 30 kD) that exert a colloid osmotic pressure.\textsuperscript{27} The benefits of their perioperative administration remains unresolved, and caution is advised in high-risk animals due to reports of dose-dependent renal impairment, coagulation abnormalities, and the absence of a survival benefit.\textsuperscript{27} A third category of fluids, called hemoglobin-based oxygen carriers binds transport and releases oxygen to tissues, but they are not currently available in the US.\textsuperscript{29}

**Clinical Implications**

IV fluid is frequently recommended for the treatment of anesthesia-associated hypotension and surgically induced blood loss, but is it effective?\textsuperscript{24} The ability of hemodynamic parameters to improve in response to a fluid challenge or bolus, also called fluid responsiveness, is largely dependent upon health status (ie, ASA category), anesthetic drug selection, and anesthetic depth. Large doses of anesthetic drugs and deeper stages and planes of anesthesia impair or prevent the response to fluid administration (ie, fluid nonresponsive) even when high infusion rates of fluid are administered (eg, 60 mL/kg/h).\textsuperscript{30} The revised Starling principle GCX model and no-reabsorption rule, increased capillary permeability, and fluid nonresponsiveness during anesthesia help to explain why published crystalloid-to-colloid ratios required to achieve similar hemodynamic effects range from 3:1 to 5:1 (ie, 3 to 5 mL of crystalloid for 1 mL of colloid or blood loss) during anesthesia, whereas this ratio is closer to 1.5:1 or 2:1 in conscious human subjects.\textsuperscript{12,21-23} Colloids distribute inside the endothelial surface layer, providing better initial plasma volume expansion than crystalloids, which distribute to the endothelial wall (Figure 4). The benefit of the initial colloidal distribution however is translated to improved outcome.\textsuperscript{27} Colloids have a longer half-life and therefore enter the interstitium at a slower rate than crystalloids (ie, longer half-life).\textsuperscript{16} The distribution and accumulation of colloids in the interstitial space slows the removal of IF, promoting IF accumulation.\textsuperscript{32}

The assessment of popular static hemodynamic parameters (eg, central venous pressure, $P_a$) are now known to be unreliable or misleading indicators of fluid responsiveness compared with dynamic parameters, which include pulse pressure variation, $SV$ variation, plethysmography variability index, and central venous oxygen saturation.\textsuperscript{33} Dynamic markers evaluate fluid responsiveness and help to reduce the risk of fluid overload but require controlled mechanical ventilation and may be misleading during spontaneous respiratory efforts, cardiac arrhythmias, right heart failure, and elevated intra-abdominal pressures.\textsuperscript{33} Definitions for fluid responsiveness include “the ability for hemodynamic parameters to improve in response to a fluid challenge or bolus” and “the positive reaction of a physiologic parameter of a certain size to a standardized volume of a certain type of fluid (or other type of induced preload change) within a certain amount of time and measured within a certain interval.”\textsuperscript{15,34} Importantly, more than 30% of healthy normotensive isoflurane-anesthetized dogs were reported to be nonresponsive to a fluid challenge even when dynamic parameters of fluid responsiveness were employed.\textsuperscript{35} These results suggest that judicious anesthetic selection, attentive monitoring of anesthetic depth, multiple monitoring modalities, and hemodynamic support (eg, dobutamine) are required to improve fluid responsiveness.

**Perioperative Fluid Administration**

Perioperative fluid therapy progresses through 3 distinct periods: preoperative, intraoperative, and postoperative. Each period includes 1 or more of 4 phases: resuscitation (R), optimization (O), stabilization (S),...
evacuation (E). Faster rates and larger volumes of IV fluid can be safely administered to conscious animals, compared with those that can be administered to anesthetized animals.8,16–18,36 The difference is primarily explained by the detrimental effects of anesthetic drugs and general anesthesia on Pa, transmembrane fluid flux, fluid redistribution (k_r), and renal elimination. Surgical procedures should be performed in normally hydrated and hemodynamically stable animals when possible. Current perioperative recommendations suggest implementation of veterinary anesthesia medical quality standards, adoption of enhanced recovery strategies, and utilization of dynamic goal-directed monitoring methods.33,37,38

Preoperative Fluid Considerations

The success of perioperative IV fluid administration depends upon the patient’s preoperative physical status (ie, ASA score), key blood (eg, PCV, lactate) and hemodynamic (eg, Pa) parameters, and fluid responsiveness. Immediately prior to anesthesia, PCV and Pa should be determined in all senior animals and those with an ASA score > 2. Food should be withheld for up to 6 hours before surgery in adult animals. Water should always be available. Preoperative oral liquid nutrition (eg, electrolytes, carbohydrates), crystalloid administration, or coloading crystalloid with colloid fluids immediately prior to anesthetic induction have not reduced the incidence or severity of hypotension in humans.39 Preoperative fluid boluses immediately prior to anesthetic induction however have decreased the incidence of significant blood pressure drops within 15 minutes of induction to anesthesia in humans.39 A randomized clinical trial in septic dogs evaluating the effects of preoperative IV lactated Ringer solution administration (ie, 5 or 10 mL/kg/h) for 2 hours before propofol or isoflurane anesthesia demonstrated that 75% of all dogs were fluid responsive and suggested that dogs that were administered 10 mL/kg/h during isoflurane anesthesia maintained a higher intraoperative Pa.40 This study did not report the incidence or severity of postinduction or intraoperative hypotensive episodes and did not contain a control group that did not receive preoperative fluids. General anesthesia inhibits heat-producing responses (ie, shivering) and disrupts the regulation of core temperature, predisposing smaller animals (ie, < 5 kg) to hypothermia, and all animals to surgical site infection, hemorrhage, impaired immune function, and prolonged recovery. The administration of warmed IV fluids did not reduce the incidence of perioperative hypothermia or improve recovery time in small dogs, although it did slow the rate of heat loss in rats.41,42

Intraoperative Fluid Administration

Intraoperative fluid dosing during anesthesia should be based on knowledge of the animal’s normal BV and guided by serial determinations of PCV, Pa, and fluid responsiveness. Most healthy anesthetized animals do not begin to demonstrate significant hemodynamic, tissue perfusion, or oxygen delivery impairment until BV, PCV, and Pa have decreased from normal values by more than 10% to 20%.43 Fluid infusion rates of 10% to 15% BV/h (eg, dog BV, approx 80 mL/kg [8 to 16 mL/kg/h]; cat BV, approx 55 mL/kg [6 to 8 mL/kg/h]; horse BV, approx 90 mL/kg [9 to 18 mL/kg/h]) are not likely to produce measurable benefits or signs of significant side effects in anesthetized animals with an ASA score ≤ 2.13,44,45 The routine administration of normal saline (ie, 0.9% NaCl) during anesthesia and surgery should be discontinued.28,46 Hypotensive animals (ie, Pa < 55 to 60 mm Hg) that have not suffered significant blood loss (ie, < 15% to 20% BV) should be administered a balanced crystalloid fluid bolus of 15% BV/kg followed by an infusion rate of 5% to 10% BV/h. A second fluid bolus of 15% BV/15 to 20 min can be repeated if the animal remains hypotensive and is fluid responsive. A 20-kg dog with a BV equal to 80 mL/kg or a total BV of 1,600 mL can be administered at 240 mL over 15 to 20 minutes (80 mL/kg X 20 kg X 0.15 = 240 mL). Animals that are deeply anesthetized or sick (ASA score of > 2) may not respond to fluid administration.30,33 Anesthetic drug concentrations should be reduced, and analgesic (eg, lidocaine, fentanyl) and vasoactive drugs (eg, norepinephrine) should be administered to animals that do not respond to fluid administration.43

Intraoperative Blood Loss

Acute blood loss in healthy animals subjected to elective surgical procedures should be replaced with 1.5 to 2.0 times a balanced crystalloid for each 1 mL of lost blood.47 Animals that have acutely suffered 30% or greater blood loss should be administered whole blood or packed RBCs. Total crystalloid fluid volumes > 30% BV (eg, 20-kg dog BV, approx 80 mL/kg [80 mL/kg X 20 X 0.3 = 480 mL/kg]) predispose to hemodilution, impair coagulation, and distribute a greater amount of the administered fluid to the interstitial space. The rapid administration of larger amounts of crystalloid (> 40% BV) also predisposes to hypothermia and fluid overload.48,49 Crystalloid fluid volumes that increase body weight by more than 10% in 24 hours are associated with increased morbidity and mortality in humans and are likely to produce the same effects in animals.49 Red blood cells regulate blood flow distribution in addition to their oxygen-carrying capabilities. Optimal tissue perfusion and systemic oxygen delivery are achieved at PCV values ranging from 27% to 33% and become impaired when the PCV falls below 20%, reaching a critical point below 9% to 12%.50 The PCV in healthy animals normally ranges from 35% to 45%, and values < 30% dysregulate the distribution of blood flow and impair tissue oxygen delivery to vital organs (eg, kidney). Methods for estimating the allowable hemodilution produced by crystalloid administration (ie, the amount of fluid that will decrease the PCV by a predetermined amount) provide a guide for the total amount of fluid that can be administered before considering a whole blood transfusion.51 The minimum
amount of crystalloid required to acutely reduce the PCV from baseline to a predetermined minimum value can be determined by $L = V (H_o - H_i) (3 - H_{avg})$, where $L$ is the volume of the noncellular replacement fluid, $V$ is the estimated initial BV, $H_i$ is the initial PCV, $H_o$ is the lowest acceptable Hct, and $H_{avg}$ is the average PCV ($H_{avg} = (H_o + H_i)/2$). The minimal amount of crystalloid or colloid required to decrease PCV from 45% to 30% in a 20-kg dog is approximately 624 mL (dog BV, approx 80 mL/kg; $L = [20 \times 80] X [0.45 - 0.30] X [3 - (0.45 + 0.30)/2]) = 240 \times 2.6 = 624$ mL or = 39% BV). A similar calculation for a 450-kg horse yields a value of 17,820 mL (horse, 90 mL/kg; 39% [0.39] X 90 mL/kg X 450 kg = 15,795 mL).

Conclusions and Future Directions

Perioperative fluid administration supports the maintenance of tissue perfusion, oxygen delivery, and cell viability. Perioperative IV fluid administration is based upon a working knowledge of physiologic principles, body fluid compartments and their volumes, BV and its distribution, and macro- and microvascular hemodynamics. Fluid dosing should be guided by the animal’s normal BV, physical status (ie, ASA score), the selected fluids VK, and goal-directed dynamic measures of fluid responsiveness. The continued administration of IV fluid to animals that are fluid nonresponders results in increases in tissue fluid accumulation, third-space loss, and fluid overload. Utilization of medical quality standards and dynamic goal-directed monitoring techniques in conjunction with team-centered cooperative protocols and procedures has improved outcomes in human patients and has the potential to do so in animals.37,50

Paraphrasing 1 author’s opinion, “fluid therapy (during the perioperative period) may be more difficult (and more important) than you think.”

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