Perioperative Fluid Strategies to Prevent Lung Injury

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Fluid therapy and management are important components of the practice of anesthesiology, both in the operating room and in the intensive care unit (ICU). However, choosing the type of fluid, volume, and rate of administration are all questions that need to be addressed when selecting fluid therapy. The physiological goal of maintaining adequate organ perfusion is a constant challenge in clinical practice. With inadequate fluid administration, the patient may be exposed to an increased risk of acute kidney injury, cerebrovascular accident, myocardial injury, and organ hypoperfusion. Conversely, with excessive fluid administration, the patient experiences a shift of the Starling curve to the right, increasing myocardial stress and work. There is a risk of third spacing of fluid leading to peripheral and pulmonary edema. Increased pulmonary edema can predispose patients to decreased functional capacity, pneumonia, and even respiratory failure.[1] Fluid accumulation in the bowel can lead to edema, which in turn may decrease bowel motility or postoperative recovery of bowel function.[2]

Many strategies for the management of fluids in the perioperative setting have been used, attempting to balance maintaining perfusion with avoiding hypervolemia. There is increasing recognition that pulmonary edema, perioperative lung injury, and hypervolemia are modifiable risks of anesthetic care. Strategies that have been used in the past are the traditional liberal strategy incorporating maintenance calculations, fluid deficits, third space losses, and intravascular losses and the more recent development of specific goal-directed management. To determine which management approach may be the most appropriate for an individual patient, a thorough knowledge of the basic physiology behind fluid resuscitation mechanisms is necessary.

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■ Starling Forces

Ernest Starling[3] performed experiments with serum and saline solutions in a canine model, determining that capillaries behave as semipermeable membranes and can absorb fluid from the interstitial space. Krogh et al[4] applied Starling's landmark work to human physiology and found that edema can form with changes in colloid pressure in the capillaries. Curry and Michel[5] further defined this in 1980 with a model of molecular sieving from the capillary wall with a matrix of fibers.

Transvascular fluid exchange theory was then developed, integrating these observations. Factors included were capillary hydrostatic pressure, interstitial hydrostatic pressure, capillary oncotic pressure, and interstitial oncotic pressure. Capillary hydrostatic pressure pushes fluid out of the capillary and into the interstitial space; it is determined by the mean hydrostatic pressures between the arterial and venous systems. Interstitial pressure is determined by the volume and compliance of the interstitium. Capillary oncotic pressure is exerted by plasma proteins, including albumin, and opposes fluid leaking out of semipermeable vessels. Interstitial oncotic pressure is dependent on the protein in the interstitium. The net filtration pressure is a balance of these 4 pressures, and the net balance determines the flow of fluid across a capillary membrane. It has been established that most of the fluid that is found in the extravascular tissue spaces returns to the circulation via the lymphatic system.

■ Endothelial Glycocalyx

This model of transvascular fluid exchange has been further extended to incorporate our understanding of the endothelial glycocalyx layer, as first described by Levick and Michel.[6] The glycocalyx has small pores along the transvascular membrane through which plasma proteins can migrate to the interstitial space and is an important determinant of vascular permeability.[7] The glycocalyx itself consists of endothelial-bound glycoproteins and proteoglycans. Syndecan and glypican proteins along with soluble components contribute to barrier regulation of the endothelial wall. Edema can be caused by partial degradation and loss of glycocalyx function, as has been shown in animal models.[8] Endothelial cells and the junctions between them can also be altered by ischemia, oxidative stress, and cytokine release, although the exact mechanisms are poorly understood.[7] The endothelial glycocalyx influences the transport of water and proteins through tight junctions between endothelial cells. Claudins, which are proteins expressed by the endothelium, form pores and tight junctions in the glycocalyx.[9] These tight junctions and the glycocalyx in concert with hydrostatic and oncotic Starling forces prevent capillary fluid leakage and thus edema formation.

The endothelial glycocalyx is susceptible to damage by many mechanisms. The pulmonary vascular glycocalyx can be injured in ischemia-reperfusion injury during one-lung ventilation. In aortic surgery, elevated levels of glycocalyx components have been measured in the plasma.[10] Endothelial glycocalyx damage can also occur with mechanical ventilation, oxidative stress, and increased fluid load.[7] Injury to the glycocalyx is currently hypothesized to be a major contributing mechanism in the formation of pulmonary edema.

■ Pulmonary Edema

Pulmonary edema may be classified by etiology into high versus low pressure types. Cardiogenic pulmonary edema is caused by increased capillary hydrostatic pressure secondary to elevated pulmonary venous pressure. This can be seen in a wide variety of conditions including systolic or diastolic left ventricular failure, mitral stenosis, left ventricular outflow obstruction, or myocardial infarction. High pressure caused by increased hydrostatic forces, as seen in negative pressure pulmonary edema or transfusion-associated circulatory overload (TACO), can cause a similar clinical picture. As a result of this high pressure, fluid accumulates in the interstitium as well as the alveoli. This causes clinical pulmonary edema.

Noncardiogenic pulmonary edema is caused by injury to the lung parenchyma or vasculature that results in a change in vascular permeability. This is seen clinically as acute respiratory distress syndrome (ARDS), diffuse alveolar hemorrhage, reperfusion injury, transfusion-related lung injury (TRALI), and inflammation. Damage to the endothelial glycocalyx during anesthesia delivery may contribute to postoperative pulmonary edema.[7] A retrospective chart review of 21 patients who developed postpneumonectomy pulmonary edema, compared with age and sex-matched controls, suggested that the mechanism of injury was more consistent with ARDS than with hydrostatic pulmonary edema. Mortality of the study group patients was 100%, and all had histologic evidence of ARDS on autopsy, raising the possibility of a similar underlying pathophysiology of capillary leak.[11] Another study found that patients with postoperative pulmonary edema had elevated protein content in the edema fluid, suggesting a role for altered alveolar membrane capillary permeability in the formation of postoperative pulmonary edema.[12] It may follow that similar pathologic changes in capillary permeability, as seen in ARDS, may occur in postoperative pulmonary edema.

■ Fluid Replacement Strategies

There has been no universal or accepted consensus on optimal perioperative fluid strategy and fluid therapy in anesthesiology or critical

care. Traditional perioperative management of fluid consists of a liberal management strategy based, in part, on calculated needs. Fluid requirements are estimated on the basis of maintenance fluid requirements of 4 mL/kg/h for the first 10 kg of body weight, 2 mL/kg/h for the second 10 kg of body weight, and 1 mL/kg/h for the remainder of the body weight above 20 kg. Multiplying this by the number of hours the patient has been NPO and the duration of surgical time estimates the amount of fluid replacement necessary for a given patient, factoring in a fluid deficit and maintenance rate. The clinician is advised to factor in surgical fluid losses as well. With minimal tissue trauma, 2 to 4 mL/kg/h is to be added to the maintenance rate; for moderate tissue trauma, 4 to 6 mL/kg/h and, for severe tissue trauma, 6 to 10 mL/kg/h. If there is blood loss in the perioperative time frame, each mililiter of blood is to be replaced with 3 mL of crystalloid or 1 mL of colloid or blood products.

Although this liberal fluid strategy is traditionally taught in anesthesiology, it has been questioned. A study of pediatric patients in Africa examined hypovolemic patients who received either no bolus or a 20 to 40 mL/kg bolus of normal saline or albumin. Patients in the no bolus group exhibited a lower mortality at both 48 hours and 4 weeks.[13] The physiological "third space" loss of fluids into the extracellular compartment has been questioned, as has the notion of administering fluid to counteract fluid shifts.[14] Although this study has been critiqued for a lack of a standardized protocol and exact amount of fluid bolused, it prompted further examination of the methodology of liberal perioperative fluid replacement.

Over time, a more restrictive fluid therapy has been developed, consisting of the monitoring of specific static and dynamic measures to incorporate physiological parameters to guide the rational administration of fluid to optimize tissue perfusion. This approach originally utilized measurements of cardiac output, mixed venous oxygen saturation, pulmonary artery pressure, and central venous pressure. More recently, it has reflected widespread adoption of echocardiography and the derivation of dynamic variables reflecting cardiopulmonary interactions such as pulse pressure variation, stroke volume variation, and systolic pressure variation.

■ Liberal Versus Restrictive Strategies

Even though ARDS is more often seen in the ICU as a postoperative problem, the capillary injury pathophysiology may be similar to perioperative lung injury with pulmonary edema. Understanding fluid management in ARDS, therefore, may aid perioperative physicians in fluid management. In the ARDS literature, liberal and restrictive fluid therapies have been compared. In a study from the fluids and catheters

treatment trial evaluating patients with acute lung injury, there was no significant difference in the primary end point of 60-day mortality when comparing restrictive versus liberal fluid strategies. Of note, the conservative fluid management group had a decreased number of days of mechanical ventilation.[15] These authors also conducted a post hoc, subgroup analysis of 244 surgical patients. Patients were randomized to receive conservative or liberal fluid management with guidance from central venous or pulmonary artery pressures. The risk of death did not vary, but ventilator-free days, again, were increased in the conservative group from 13 to 15 days ($P = 0.04$).[16] One other study analyzed risk factors for postoperative ARDS in surgical patients. These authors found that patients receiving > 20 mL/kg/h compared with 10 mL/kg/h were 3.8 times more likely to develop ARDS postoperatively.[17] Intensive care management of ARDS now often involves lung-protective strategies as well as conservative fluid management. Whether such management techniques translate into routine perioperative management remains to be seen.

An observational study in the ICU evaluating fluid overload with the change in extravascular lung water index in mechanically ventilated patients found that patients with an even to negative fluid balance had increased ventilator-free days and decreased mortality.[18] The extravascular lung water index was also decreased in patients with an even to negative fluid balance. A smaller observational study evaluating 27 patients undergoing one-lung ventilation for lateral thoracotomy measured the extravascular lung water index preoperatively and postoperatively in each patient as an indicator of pulmonary function; these authors found that goal-directed therapy using stroke volume variation resulted in no statistical difference in extravascular lung water index from preoperative values.[19] These studies indicate that a decreased amount of fluid administration in the perioperative setting may lead to less capillary leak and possibly decrease pulmonary edema.

In the operative setting, restricted fluid administration may also be beneficial. In the thoracic surgery literature, Evans and Naidu[20] considered the question of whether conservative fluid management in the perioperative management of lung resection reduced postoperative acute lung injury or ARDS. These authors evaluated 67 studies and found the mean fluid volume administered to be significantly lower in patients who did not develop postoperative acute lung injury. They recommended intraoperative and postoperative maintenance fluids at 1 to 2 mL/kg/h, not exceeding a positive fluid balance of 1.5 L. In addition, they suggested that if the patient develops signs of hypoperfusion, vasopressor support could be utilized. In another study evaluating non–small cell lung carcinoma surgical patients, 4 independent risk factors for primary acute postoperative lung injury were identified.[21] These included high intraoperative ventilator pressure index, pneumonectomy, preoperative alcohol use, and intraoperative fluid administration > 1 L. Arslantas et al studied 139

patients who underwent pulmonary resection. The incidence of postoperative pulmonary complications was increased in patients with a higher total amount and a higher infusion rate of fluids within the first 48 hours. The threshold found in this study was 6 mL/kg/h for postoperative pulmonary complications.[22]

When the thoracic anesthesiology and surgery literature are considered, it is suggested that more restrictive fluid strategies may improve postoperative lung injury indices. Although these studies only include a narrow subset of the overall surgical population, thoracic surgical patients, in whom postoperative acute lung injury has a relatively high incidence, may serve as a model for the development of protective strategies that could be applied to more general surgical cases. Indeed, a restrictive fluid administration approach is a component of enhanced recovery after surgery (ERAS) protocols, which are being widely adopted. These call for restricted fluid administration in an effort to help decrease bowel edema and improve postoperative bowel motility in abdominal surgical cases.[2,23,24] Even though studies of ERAS protocols have not evaluated postoperative lung injury, the restrictive fluid strategy is being utilized beyond thoracic surgeries with noted benefits.[23,25–27]

Although no fully agreed upon fluid management strategy exists in the anesthesiology and critical care literature, goal-directed fluid therapy is supported in many meta-analyses when compared with traditional strategies. One meta-analysis of randomized controlled trials suggested that optimization of fluid management may be accomplished with a background rate of crystalloid administration and directed colloid fluid replacement to maintain stroke volume.[28] Another stratified meta-analysis by Corcoran and colleagues evaluated perioperative fluid strategies in major surgeries and compared liberal and goal-directed randomized controlled trials with a combined total of 3861 patients. Patients in the liberal fluid management group had higher risk of pneumonia, pulmonary edema, and longer hospital stays. Liberal fluid use was also associated with increased time to bowel movement.[29] A clinical review of randomized controlled trials in patients undergoing high-risk surgery with an estimated perioperative mortality of over 20%, as compared with lower-risk surgery, demonstrated that goal-directed therapy had a decreased complication rate. This effect was greater in the higher-risk patients.[30] Chappell et al[31] suggest that crystalloid overload and damage to the endothelial glycocalyx can induce fluid and protein shifts to the interstitial space and suggested that replacing fluids in a more restrictive manner may improve clinical outcomes.

■ Type of Fluid

The type of fluid used may be just as crucial a determinant of perioperative lung injury as the volume of fluid administered. There is no

agreed upon best practice management in this area to decrease lung injury. In terms of administering crystalloid or colloid, there is a physiological rationale that the oncotic pressure of a colloid allows it to remain in the intravascular space rather than partitioning to the interstitial space to the same degree as a crystalloid. In the SAFE trial, wherein 6997 patients were randomized to receive either albumin or saline for fluid resuscitation in the ICU, there was no difference in the days of mechanical ventilation.[32] In septic shock patients, Caironi et al[33] randomly assigned 1818 patients to receive either 20% albumin and crystalloid or crystalloid alone; these authors found no difference in either mortality or duration of mechanical ventilation. The CRISTAL trial, which is a randomized multicenter trial conducted in the ICU, asked whether use of colloids or crystalloids alters mortality in patients with hypovolemic shock. They found no difference in mortality; however, there were more ventilator-free days in the colloid group compared with the crystalloid group.[34] Balanced salt solutions, such as PlasmaLyte, have been compared with saline and found to have no difference in terms of the duration of mechanical ventilation.[35] Even though these studies are from the intensive care setting, they may help inform practice in the perioperative setting. In the ICU, these studies provide conflicting results in hypovolemic and septic shock patients and on whether crystalloid or colloid solutions result in better lung mechanics and clinical outcomes.

Blood products are frequently administered in the perioperative setting in addition to crystalloids and colloids. Blood transfusion carries multiple risks, including TRALI and TACO. TRALI often occurs within 6 hours of transfusion, with platelets conferring the highest risk. The incidence is ~1 in every 5000 transfusions.[36] The pathophysiology of TRALI is thought to be from neutrophil sequestration and priming in lung microvasculature secondary to endothelial injury. The neutrophils are then thought to be activated by a factor from the transfused blood product. This in turn releases inflammatory mediators, such as cytokines and oxidases, that further damage the pulmonary capillary endothelium, leading to inflammatory pulmonary edema.[37] Although transfusion of any blood product can result in TRALI, high plasma volume products (plasma, apheresis platelet concentrates, whole blood) confer a greater risk.[38] Unlike the earlier discussion on crystalloid volume, TRALI risk is independent of volume transfused: TRALI may occur with product administration of only 10 to 20 mL.[39] Some studies have found that plasma or whole blood from female donors may result in a higher risk of TRALI compared with plasma or plasma-rich products from male donors.[40–42]

TACO occurs from the transfusion of blood products leading to circulatory overload, which then may result in pulmonary edema. Similar to TRALI, TACO may also occur with any blood product transfused. However, in contrast to TRALI, TACO has a higher risk of occurrence with an increased volume of transfusion.[43] Other predisposing risk factors

include age, history of heart failure, female sex, and history of chronic pulmonary disease.[44]

In order to minimize TRALI and TACO in surgical patients, care must be taken to administer blood products only if necessary and indicated for a patient. In the TRISS trial, Holst et al[45] undertook a multicenter, parallel-group randomized trial in septic patients in the ICU to determine whether different hemoglobin thresholds could benefit or harm patients. These authors randomized patients to a threshold hemoglobin of 7 or 9 g/dL and found no difference in mortality rates or in mechanical ventilation days. In another study comparing liberal with restrictive blood transfusion thresholds, Murphy et al[46] conducted a multicenter parallel-group trial of transfusion thresholds in cardiac surgery patients and postoperative morbidity and mortality. These authors found that in 2007 patients, there was no significant difference in clinically significant pulmonary complications. The best method to decrease the perioperative pulmonary complications of TRALI and TACO may be to transfuse blood products only when there is a clear indication of demonstrated benefit.

■ Conclusions

Although there is no clear agreement on fluid management strategy in the perioperative setting, most studies concur that a restrictive fluid administration strategy may confer better perioperative lung outcomes in patients, especially in thoracic surgery. Studies evaluating fluid administration guided by dynamic variables such as stroke volume variation, [47] pulse pressure variation[48,49], and echocardiographic findings[50,51] suggest that these may be considered when determining whether a patient would benefit from fluid administration.

In terms of best type of fluid to administer, studies have had opposing results, deepening the colloid versus crystalloid debate. Further high-quality studies are warranted to aid in establishing whether the type of fluid administered may influence the development of perioperative pulmonary complications.

Transfusing blood products may also confer a higher risk for acute lung injury in the postoperative period by increasing the risk of TRALI and TACO. One way to avoid imparting this risk to patients may be to allow a lower hemoglobin threshold in patients at high risk for perioperative lung injury. This risk of lung injury has to be balanced with the benefits of blood component therapy.

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