Volume Management and Resuscitation in Thoracic Surgery

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Abstract Lung injury following thoracic surgery is a major cause of morbidity and mortality. A consistent risk factor is excessive perioperative fluid administration, not only following pneumonectomy, but also after lesser lung resections and esophageal surgery. Recent insights into the pathophysiology of lung injury after thoracic surgery include the role of the endothelial glycocalyx, pulmonary endothelium, lung lymphatics, and right ventricular dysfunction. While a restrictive approach to fluid administration may reduce the risk of lung injury, there are concerns regarding the risks of acute kidney injury with this approach. Goal-directed approaches may be applied to the thoracic surgical population, and lung ultrasound appears to be a promising new technique to further guide perioperative fluid therapy. There is a paucity of data to guide the choice of crystalloid or colloid solution. Further research is required regarding prevention, diagnosis, and treatment of lung injury following thoracic surgery.

Keywords Fluid therapy · Thoracic surgery · Anesthesia · Acute lung injury · Postoperative complications

Introduction

Acute lung injury is a major cause of mortality after lung resection surgery [1], and a principal focus of the thoracic anesthesiologist is prevention of this devastating complication. Fluid therapy is an integral component of the perioperative management of these complex patients [2], and the risks of fluid overload and tissue edema must be balanced against the risk of hypovolemia and end-organ ischemia [3].

Epidemiology and Impact of ARDS After Lung Resection Surgery

Post-pneumonectomy pulmonary edema (PPPE) was first described in 1984 by Zeldin et al. [4], where 10 cases of lung injury following pneumonectomy were described. It has since been recognized that the syndrome may occur after lesser degrees of resection and surgery requiring one-lung ventilation (OLV) without lung resection [5, 6]. PPPE has been found to share histological features with acute respiratory distress syndrome (ARDS) [7], is not of cardiogenic origin [3], and the most severe form of PPPE follows a course indistinguishable from ARDS [5]. Accordingly, the condition may be described as post-thoracotomy ARDS. The American-European Consensus on ARDS criteria [8] has been superseded by the Berlin Consensus on ARDS [9], which may now be used to diagnose classify post-thoracotomy ARDS as mild, moderate, or severe based on timing, chest imaging, origin of edema, and degree of hypoxaemia.

While the incidence of lung injury after lung resection is fairly consistent, between 2 and 4 % [10–12], the mortality rate has decreased from almost 100 % to less than 40 %, largely due to improvements in ICU management [1].

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The risk factors for perioperative ARDS most consistently reported are more extensive resections (such as pneumonectomy) and fluid overload [5, 10]. Other pre- and intra-operative factors have also been implicated, including ASA class [13, 14], alcohol abuse [10, 14], previous radiotherapy [15] low predicted post-operative lung function [16], non-protective ventilation strategies [17], and right pneumonectomy [7, 18].

Fluid Administration as a Risk Factor

In the landmark study by Zeldin et al. [4], patients who received a large fluid load ($4,913 \pm 1,169$ mL, $n = 10$) in the first 24 h following pneumonectomy had a higher incidence of PPPE than those receiving less fluid ($3,483 \pm 984$, $n = 15$ controls). These findings were corroborated by a canine right pneumonectomy model, which compared three groups: a liberal crystalloid load (100 mL/kg bolus preoperatively, followed by >100 mL/kg post-operative balance), a judicious load (50 mL/kg bolus preoperatively followed by <100 mL/kg balance), and a control group (the same fluid regimen as the liberal pneumonectomy group and sham thoracotomy). Pulmonary

edema ensued in all of the liberal pneumonectomy dogs, however in neither of the other groups. This implies that it is not only the volume of fluid administered that predisposes to ARDS, but that the local and systemic changes that occur at lung resection also contribute significantly to the pathophysiology of the condition.

Subsequently, fluid administration, both intra- and post-operatively, has repeatedly been found to be a risk factor for the development of ARDS after lung resection [10, 13, 15–18] (see Table 1). Fluid in excess of 2 L total volume administered during pneumonectomy is linked with negative effects on postoperative respiratory outcomes [3, 13, 15, 17], and similar results have been demonstrated with high perioperative fluid loads and lesser pulmonary resections [3, 10, 16]. In patients with pulmonary fibrosis, higher perioperative fluid volumes and balance are linked to an increased risk of postoperative respiratory compromise after lung resection surgery, a devastating complication [19]. Similar findings have also been demonstrated in esophagectomy, however, in these patients larger volumes of fluid (in the order of 5 L) are implicated [6, 20].

The incremental volume of fluid required to increase the risk of ARDS is not large. It is evident from the study by

Table 1 Fluid administration in lung resection and esophagectomy patients with and without postoperative acute lung injury

Authors (publication year)	Procedure	Number of patients	Study design	Timing	Acute lung injury fluid volume	No acute lung injury fluid volume	<i>p</i> value
Zeldin et al. (1984) [4]	Pneumonectomy	25	Retrospective	24 h postoperative infusion	37 mL/kg	27 mL/kg	<0.05
Parquin et al. (1996) [14]	Pneumonectomy	146	Prospective (observational)	Intraoperative	≥ 2.0 L	<2.0 L	<0.01
Licker et al. (2003) [9]	Pulmonary resection	879	Retrospective	Intraoperative Cumulated intra- and 24 h postoperative Fluid balance 24 h post-operation	9.1 mL/kg/h 2.6 mL/kg/h 2.0 L	7.2 mL/kg/h 2.0 mL/kg/h 1.52 L	0.023 0.003 0.026
Fernandez-Perez et al. (2006) [16]	Pneumonectomy	170	Retrospective	Intraoperative	2.2 L	1.3 L	0.001
Alam et al. (2007) [15]	Pulmonary resection	1,428	Retrospective	Intraoperative and 12 h postoperative	2.775 L	2.5 L	<0.05
Marrett et al. (2010) [12]	Pneumonectomy	1,200	Retrospective	Intraoperative	3.8 L	2.5 L	<0.0001
Mizuno et al. (2012) [18]	Pulmonary resection (pulmonary fibrosis patients)	52	Retrospective	Intraoperative total volume Intraoperative fluid balance	7.71 mL/kg/h 4.99 mL/kg/h	10.3 mL/kg/h 8.00 mL/kg/h	0.049 0.035
Casado et al. (2010) [6]	Esophagectomy	45	Retrospective	Intraoperative fluid balance Fluid balance 5 day postoperatively	5.415 L 7.873 L	4.174 L 5.928 L	0.01 0.03
Tandon et al. (2001) [19]	Esophagectomy	168	Retrospective	Intraoperative	5.0 L	4.4 L	<0.027

Licker et al. [10] that there may be a small margin between a more “liberal” strategy (the volume of fluid administered that is associated with ARDS) and a “conservative” approach (the volume of administered fluid not associated with ARDS) [21]; while there was a significant difference in outcomes between patients receiving larger volumes of intraoperative fluid (9.1 vs. 7.2 mL/kg/h), higher positive fluid balance in the 24 h following surgery (2.0 vs. 1.52 L), and higher accumulated intra- and post-operative fluid volume (2.6 vs. 2.0 L), the differences in the amount of fluids are not great. Furthermore, a “dose-dependent” relationship between perioperative fluid administration and ARDS was demonstrated by Alam et al. [16], who found that for every 500 mL of perioperative fluid administration, there was a significant increase in the rate of primary lung injury (OR 1.2 (1–1.4), $p = 0.02$).

Pathophysiology

A “multiple-hit hypothesis” for lung injury is well described for ARDS [22]. It describes a number of pathophysiological insults, which, in isolation may not result in lung injury, however, when accumulated result in the clinical syndrome of ARDS. The “multiple-hit hypothesis” is likely to also be relevant in perioperative ARDS. The “first hit” is an activation of the systemic inflammatory response by surgical trauma, manipulation, or atelectasis [23], which subclinically injure the lung, rendering it more susceptible to subsequent insults. The successive hits then damage the already vulnerable alveolar-capillary membrane, leading to overt ARDS. The putative second hit may be a variety of known risk factors for post-operative ARDS such as FFP administration [14], mediastinal lymphatic damage [24], non-protective ventilation strategies [17], and oxygen toxicity [25].

This multiple hit model for perioperative ARDS is supported by a rodent pneumonectomy model, which used intratracheal lipopolysaccharide to mimic sepsis-induced lung injury. A small lung injury was observed with either OLV and pneumonectomy, or lipopolysaccharide alone, but an exaggerated injury was triggered when OLV, pneumonectomy, and lipopolysaccharide were combined in one animal [26]. This suggests that the lung is “primed” by the initial insult, and then a subsequent insult will potentially result in a more severe, clinically evident manifestation.

Revised Starling Equation and the Endothelial Glycocalyx

For generations, the axiom guiding trans-capillary fluid behavior was Starling’s model, first proposed in 1896 [27].

The model expresses fluid flux as a balance between opposing hydrostatic and oncotic pressures. Along the length of the capillary filtration is favored at the arteriolar end and reabsorption at the venular end.

However, in vitro and in vivo deviations from the classic Starling principle have been noted [28], such as absence of the venous reabsorption [29] and lymphatic flow [30] required to prevent interstitial edema, and lack of importance of the interstitial colloid osmotic pressure in determining transendothelial fluid balance [31]. This led to further investigation into non-Starling mechanisms of barrier regulation involving the endothelial glycocalyx layer (EGL) [32].

Danielli first proposed the existence of the EGL in 1942 [33]. It is a dynamic, fragile, and complex layer of membrane-bound macromolecules at the luminal surface of the vascular endothelium [32]. The composition and thickness of the glycocalyx change constantly, as it is continually sheared by plasma flow and replaced [34]. Its components have a net negative charge, and therefore, repel negatively charged molecules and blood cells [35].

A primary function of EGL is to regulate and influence vascular permeability [36•]. Together with circulating substances, it forms a barrier that prevents circulating cells and macromolecules from entering the interstitium. In contrast to the original Starling model, which explained regulation of fluid balance occurring across the entire endothelial cell, a revised model has been proposed, whereby the hydrostatic and osmotic forces act only across the EGL surface layer on the luminal aspect of the endothelium [31]. These forces reach equilibrium very quickly, resulting in a much lower fluid flux than predicted by the traditional Starling equation (Fig. 1).

Fig. 1 The glycocalyx model for fluid change between the intravascular and interstitial space. The various components of the glycocalyx model and revised Starling’s forces are shown. In steady state, net filtration into the interstitium occurs and is subsequently removed by the lymphatic system [3]

The EGL has other functions. It regulates blood cell-endothelial interaction by its negative charge, and via specific adhesion molecules for leucocytes and platelets. These are normally hidden deep within the glycocalyx structure, but become exposed following damage to the EGL [36•]. It also protects the vascular endothelium from shear stress and oxidative damage, via nitric oxide-induced vasodilation [37] and scavenging of oxygen free radicals [35].

The EGL may be injured by inflammatory cytokines [38], surgical trauma, and ischemia–reperfusion [39]. Hypervolemia damages the EGL, both by dilution of plasma proteins, and via release of atrial natriuretic peptide, which strips the EGL [39]. Loss of the intact EGL causes increased vascular permeability and fluid extravasation. Loss of plasma proteins further compounds this. Leucocyte adhesion molecules are exposed, promoting cellular adhesion, migration, and further inflammation [40]. This vicious cycle of increased permeability, extravasation, and inflammation leads to pulmonary edema, as is observed in ARDS.

Several empiric strategies, based on animal experiments, have been proposed to protect the EGL, including avoiding hypervolaemia, albumin infusion [41], corticosteroids [42], antithrombin III [43], and direct inhibitors of inflammatory cytokines [44]. Volatile anesthetic agents, when compared with propofol, have been associated with less local release of inflammatory mediators [45, 46•] and less glycocalyx destruction [47].

Pulmonary Endothelial Damage

The alveolar endothelium also plays a role in the regulation of pulmonary interstitial fluid balance. Fluid transport across the endothelium may occur via tight junctions, breaks in tight junctions and vesicular transport [48]. Leaky junctions are associated with cell death, and allow passage of larger molecules. Epithelial sodium channels (ENaCs) are able to enhance the clearance of alveolar fluid [48] and they may be stimulated by beta-adrenergic agonists [49].

Endothelial damage has, therefore, been implicated in the pathogenesis of ARDS after lung resection surgery. Endothelial injury maybe induced by activation of systemic and local inflammatory mediators, related to positive pressure ventilation, “volutrauma”, oxygen toxicity, ischaemia–reperfusion injury, surgical trauma, and pre-existing lung disease [1, 3]. Endothelial cell injury results in disruption of intercellular endothelial cell junctions, cytoskeleton contraction, and cell

death, leading to increased permeability of the alveolar-capillary barrier and decreased lung compliance [1].

Lymphatics and RV Dysfunction

Although fluid overload is well recognized as a risk factor for ARDS after thoracic surgery, there also appear to be other factors at play. ARDS may still occur when very strict fluid restrictive strategies are implemented [50].

Lung lymphatics play a key role in fluid clearance from the lung [48]. Capillary filtrate that enters the interstitium is drained by lymphatics, and when their capacity to drain fluid is exceeded, pulmonary edema will occur [3]. Although lymph flow can increase 7-fold in response to elevated interstitial pressure [51], in the perioperative setting this capacity maybe reduced. Surgical trauma related to lung resection surgery is thought to be an important factor influencing this [3]. Pulmonary lymphatic drainage is not symmetrical: the drainage of the right lung is essentially ipsilateral (>90 %), whereas the left lung has a significant contralateral contribution (>55 %) [52]. Therefore, right pneumonectomy confers a significantly higher risk of pulmonary edema in the left lung, as over half its lymphatic drainage will be lost, which has been demonstrated clinically [7, 18].

Lymphatic drainage may be further impaired by post-operative right ventricular (RV) dysfunction: the resultant elevation in central venous pressure will reduce the drainage capacity of the lymphatic system [53]. RV dysfunction is very common after lung resection surgery, particularly pneumonectomy [54], and is thought to relate to increased RV after load and tachycardia [55, 56].

Risks of Restrictive Approach—Tissue Hypoperfusion and AKI

A restrictive approach to fluid management has been widely adopted to prevent ARDS after thoracic surgery [48]. However, a restrictive fluid regimen may incur the risks associated with hypovolaemia, which include impaired end-organ perfusion, in particular, acute kidney injury (AKI) [3, 48].

Recent data suggest the incidence of AKI after lung resection surgery is 5.9–6.8 % [57•, 58•]. It is associated with increased hospital length of stay [57•] and cardiopulmonary complications [58•]. A link to increased mortality has been inconsistent [55], although a recent study demonstrated a mortality of 19.8 % in those with AKI [58•].

Many risk factors for AKI have been identified. Studies by Licker et al. [1] and Ishikawa et al. [57•], each identified

multiple factors associated with AKI after lung resection surgery. Preoperative patient characteristics include ASA class 3 or 4, FEV1, hypertension, peripheral vascular disease, preoperative renal dysfunction, and preoperative use of angiotensin II receptor antagonists. Intraoperatively, use of vasopressor, duration of anesthesia, use of colloids, and open procedures were implicated. The amount of fluid given intra- and postoperatively was not found to be associated with an increased incidence of AKI. Licker et al. [58•] found that patients with and without AKI received similar volumes of fluid both intraoperatively (4.8 vs. 4.9 mL/kg/h) and on postoperative day 1 (1.1 vs. 1.1 mL/kg/h), respectively. Similarly, Ishikawa et al. [57•] found similar volumes of fluid administered intraoperatively in patients with and without AKI (1,450 vs. 1,276 mL).

Maintenance of adequate perfusion pressure is an important factor in preventing AKI [3], especially in those at increased preoperative risk related to chronic kidney disease, hypertension, or peripheral vascular disease. Hypotension related to excessive anesthesia should be avoided, and depth of anesthesia monitoring may allow more accurate dose titration. Adequate perfusion pressure should be maintained through judicious use of vasopressors, and invasive hemodynamic monitors may provide valuable information to help guide therapy [3].

Esophagectomy

In esophagectomy, the traditional approach involved aggressive fluid resuscitation, due to postulated “third space” losses [3]. The third space, first described in 1961 in major abdominal surgery [59], is classically thought to be a fluid compartment anatomically and functionally separate to the intravascular space, not involved in the exchange of fluid between the vascular space and the interstitium [60]. However, the exact location of this hypothetical compartment, thought to be the gastrointestinal tract or traumatized tissues, has never been fully elucidated. Its existence has recently been challenged due to weak initial evidence, flawed methodology, and the emergence of new data measuring extracellular fluid volume in surgery and hemorrhage [61].

There is an association between fluid balance and postoperative complications after esophagectomy. A link between higher perioperative positive fluid balance and cardiorespiratory complications and death has been demonstrated [62]. Fluid restriction seems protective against respiratory complications following esophagectomy, both as a sole factor [63], and as part of a standardized multimodal regimen including thoracic epidural analgesia, early extubation, and modest fluid restriction [64]. Due to the systemic inflammatory state that occurs following major surgery, and

the increased capillary permeability that ensues, irrational replacement of putative “third space” losses during esophagectomy will lead to fluid accumulation in the interstitial space, and therefore, pulmonary edema [3].

Fluid administration may adversely affect surgical outcomes. There is a growing pool of data suggesting that surgical outcomes [65, 66] including anastomotic complications [67, 68], following gastrointestinal surgery may be improved with a restrictive fluid strategy or multimodal perioperative management protocol that includes fluid restriction. There is no specific evidence of anastomotic protection by a restrictive fluid regimen in esophageal resection, however, extrapolation of these findings suggests that there may be some additional benefit incurred by fluid restriction in esophagectomy, both improving surgical outcomes and reducing the risk of ARDS.

There has been concern regarding use of vasopressors in esophagectomy, due to fear of anastomotic ischemia, a major cause of postoperative mortality. In a porcine model, norepinephrine, when used to treat hypotension caused by hemorrhage, has been associated with severe graft hypoperfusion [69]. However, a small human study found that epinephrine, used to treat hypotension caused by thoracic epidural bupivacaine, restored the resultant decrease in anastomotic blood flow [70]. Similarly, in another small human study, phenylephrine infusion was found to correct epidural bolus-induced reduction of blood flow at the anastomotic end of the newly formed gastric tube [71]. Therefore, it is likely that vasoactive agents, when used to counteract hypotension induced by general or neuraxial anesthesia, can be used without jeopardizing the viability of the surgical anastomosis.

Goal-Directed Approaches

Goal-directed therapy has been used with variable success in cardiac, vascular, orthopedic, and major abdominal surgery. Interest was generated by Shoemaker et al. [72], who demonstrated morbidity and mortality benefits, when a goal-directed approach was applied to the perioperative care of high-risk surgical patients. Some subsequent studies have shown reduced risk of infective complications [73], AKI [74], cardiovascular complications [75], pneumonia, and hospital length of stay [74]. However, others have found no benefit, in abdominal aortic surgery [76] or colorectal surgery [77]. In fact, a goal-directed approach was associated with negative effects on hospital length of stay and readiness for discharge in a subset of aerobically fit colorectal surgical patients [77].

It has been suggested that using clinical assessment of cardiac preload to guide fluid therapy may reduce the risk of ARDS after thoracic surgery [3, 48, 78]: by optimizing

the volume of fluid infused, the risks of both fluid overload and ARDS, and hypovolemia and AKI may be reduced. However, it should be noted that studies of goal-directed therapy in non-thoracic surgery frequently feature more “aggressive” fluid resuscitation in the treatment arm, with patients undergoing goal-directed therapy receiving significantly more fluid than those in the control arms [79–81]. This is at odds to the traditional approach of fluid restriction in thoracic surgical patients already discussed.

Preload estimation is notoriously challenging. Commonly used pressure measurements, such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) are indirect surrogates for LVEDV, and as such are influenced by many other factors, including intrathoracic pressure variation (such as in positive pressure ventilation and OLV), open chest surgery, RV function, and cardiovascular compliance [78]. Most goal-directed strategies utilize monitoring of hemodynamic parameters that predict fluid responsiveness, defined as a significant increase in cardiac output with fluid loading, which theoretically allows maximization of cardiac performance and avoids unnecessary volume administration.

Cardiac Index Estimation

Many goal-directed protocols target cardiac index, which may be measured using a variety of modalities, including the pulmonary artery catheter, transpulmonary thermodilution (e.g., PiCCO monitor), pulse contour analysis (e.g., FloTrac-Vigileo System), and trans-esophageal Doppler measurement. Although use of esophageal Doppler is impractical in esophageal surgery, it has been used with good effect in lung resection surgery. Esophageal Doppler was able to detect a reduction in stroke volume index in lung resection surgery, despite unchanged heart rate and mean arterial pressure, and was used to guide hemodynamic support and fluid therapy [82].

Dynamic Variables—Stroke Volume Variation (SVV) and Pulse Pressure Variation (PPV)

SVV and PPV both use the heart–lung interaction, integrating the effects of preload, respiratory variation, and blood pressure to assess fluid responsiveness [3, 48]. There are some theoretical limitations to the use of these indices during thoracic surgery. Firstly, there has been concern regarding their validity during open chest conditions [83]. Secondly, due to the dependence of these measurements on respiratory variation, their accuracy also is dependent on tidal volume. At relatively large tidal volumes of 8–10 mL/kg during two lung ventilation (TLV), SVV $\geq 12\%$ and PPV $\geq 13\%$ correlate highly with fluid responsiveness [84], however, ventilation with a lung protective strategy may not have the

same correlation. Thirdly, the volume of shunted blood through the non-ventilated lung should not contribute to the generation of SVV and PPV, necessitating a lower threshold value during OLV than that used during TLV [3, 85]. In one study examining SVV during OLV, it was shown only to be acceptably predictive of volume responsiveness with tidal volumes >8 mL/kg, with a threshold for fluid responsiveness of 10.5% [86]. However, another study demonstrated that PPV can predict fluid responsiveness during protective OLV (tidal volumes 6 mL/kg) during thoracotomy, with a threshold value of $>5.8\%$ [85].

SVV has been used successfully to guide fluid therapy in thoracic surgery. A randomized study in thoracoscopic lobectomy found that the goal-directed therapy group, who received fluid boluses guided by SVV using the FloTrac-Vigileo system, had higher PaO₂/FiO₂ ratios at the end of OLV, earlier extubation time, and received less overall fluid ($1,385 \pm 350$ vs. 985 ± 135 mL) [87]. During esophagectomy, SVV accurately predicted hypovolemia, which was useful as a guide to appropriately time perioperative fluid therapy, and correlated better with cardiac output than CVP [88].

Early Detection of Pulmonary Edema

Transpulmonary thermodilution technology has the added advantage of enabling calculation of extravascular lung water (EVLW), and therefore, quantification of pulmonary edema [89]. EVLW has been shown to be an independent predictor of prognosis and survival in critically ill patients [90], and in esophagectomy has been found to correlate with PaO₂/FiO₂ ratio, pulmonary compliance, lung injury score [91], and pulmonary complications [92]. EVLW is derived by subtracting the pulmonary blood volume (PBV) from the pulmonary thermal volume (PTV); there has, therefore, been concern regarding the use of EVLWI after lung resection, as both PBV and PTV may change [93]. However, EVLWI measured by PiCCO has been shown to correlate well with a double-dye technique for up to 12 h after following major lung resection [94]. Another potential limitation in the thoracic surgical setting is the influence of distribution of lung perfusion by position and lung collapse: a spurious increase in measured EVLW has been noted due to regional alterations of pulmonary blood flow [95]. A study assessing a goal-directed approach to fluid management for thoracic surgery requiring lateral thoracotomy and OLV found that their strategy, fluid management guided by SVV, did not result in pulmonary fluid overload as assessed by PiCCO EVLWI [96].

Lung ultrasound has been used to diagnose pulmonary edema with a high degree of sensitivity and specificity (97 and 95 % respectively) by the presence of ultrasound B-lines (previously “ultrasound lung comets”), which appear as hyperechoic, well-defined comet-tail artifacts

arising from the pleural line, and move with lung sliding [97]. B-lines may also be quantified, with good inter-rater reliability [98], and there is a correlation between the number of B-lines and EVLW in patients following cardiac surgery [99]. In ARDS, a significant correlation between ultrasound B-lines score and EVLW was shown, with a B-lines score ≥ 6 indicating a pathologic EVLW >10 mL/kg (sensitivity 82 %, specificity 77 %) [100•]. There is very little data evaluating this technique for quantitative assessment of ARDS [101], and no study to date addresses its application in the perioperative setting. However, lung ultrasound represents a promising non-invasive bedside modality to rapidly assess EVLW of patients at risk of perioperative lung injury, including those undergoing thoracic surgery, and as such warrants further investigation in the perioperative setting.

Fluid Choice

Fluid choice in thoracic surgery remains controversial, with concerns regarding unwanted extravascular distribution of crystalloids to the interstitial space balanced against known adverse effects of the various colloid solutions, including AKI, coagulopathy, and anaphylaxis.

Hyperoncotic colloids have been advocated for use in ARDS, due their potential to promote shift of extravascular lung water into the intravascular space [48]. Some beneficial effects on pulmonary parameters have been demonstrated, including pulmonary permeability [102, 103], histological findings [104], reductions in VILI and pulmonary edema [105], and more rapid hemodynamic stabilization [103]. However, in a large systematic review of burns, trauma, and surgical patients, no outcome benefit of colloids could be demonstrated, and hydroxyethyl starch (HES) was found to possibly increase mortality [106].

There is particular concern regarding HES and the risk of AKI: in a multicenter RCT of patients with severe sepsis, HES was shown to increase risk of mortality and use of renal replacement therapy [107]. These findings were seemingly confirmed when a recent systematic review and meta-analysis of HES in critically ill patients found that HES use was associated with a significantly increased risk of AKI, use of renal replacement therapy, and death [108].

Due to concerns regarding synthetic colloid therapy, interest in human albumin has been renewed, as there is no evidence of adverse effects on renal function, and it is generally felt not to affect coagulation [109]. The SAFE trial [110] failed to demonstrate any difference between 4 % albumin and saline therapy in a variety of outcomes in a mixed population of critically ill patients. A recent systematic review and meta-analysis comparing albumin to

saline therapy in patients with ARDS found no significant mortality difference, but improved PaO₂/FiO₂ in the first 48 h and after 7 days in patients receiving albumin [111•]. However, an overall paucity of evidence was noted, and there is clearly a need for more randomized controlled trials to address this question.

A strong evidence base to guide transfusion practice in thoracic surgery is lacking. The risk of adverse effects of transfusion, including immunomodulatory effects, must be balanced against the effects of perioperative anemia. A dose-dependent adverse effect of intraoperative blood transfusion on a variety of outcomes in thoracic surgical patients has been demonstrated [112]. Immunomodulation may be harmful in oncological surgery: an unfavorable impact on clinical outcomes has been demonstrated [113–115]. A meta-analysis of 5,915 lung cancer resection patients has demonstrated a negative association between transfusion and overall and disease-free survival [116]. Conversely, in lung transplantation, the immunomodulatory effect of transfusion may have a favorable effect on outcomes: allogeneic blood transfusion is associated with lower rate of acute cellular rejection [117].

Recommendations for Clinical Practice

The following principles are suggested for the management of patients undergoing thoracic surgical procedures:

- (1) Fluid administration should account for maintenance requirements and insensible losses
- (2) Blood loss should be replaced initially with albumin, then with allogeneic packed red blood cell transfusion to maintain hemoglobin >70 – 80 g/dL
- (3) There is no third space
- (4) Urine output >0.5 mL/kg/h is unnecessary in the early perioperative phase, unless there is a high risk of acute kidney injury
- (5) Appropriate invasive hemodynamic monitors may be used to guide more complex therapy with vasopressors, inotropes, or fluid administration

Conclusion

Post-operative ARDS is a devastating complication of thoracic surgery. New insights into its pathophysiology include the multifactorial risk profile and the role of the EGL. Excessive fluid administration is harmful, and the risk of ARDS may be reduced by fluid restriction, without jeopardizing end-organ perfusion. Several new concepts will continue to be explored, including goal-directed

therapy and bedside assessment of EVLW, and further data are required to guide appropriate fluid selection.

Compliance with Ethics Guidelines

Conflict of Interest Catherine Ashes and Peter Slinger declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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