

Restricted, optimized or liberal fluid strategy in thoracic surgery: A narrative review

ABSTRACT


Perioperative fluid balance has a major impact on clinical and functional outcome, regardless of the type of interventions. In thoracic surgery, patients are more vulnerable to intravenous fluid overload and to develop acute respiratory distress syndrome and other complications. New insight has been gained on the mechanisms causing pulmonary complications and the role of the endothelial glycocalyx layer to control fluid transfer from the intravascular to the interstitial spaces and to promote tissue blood flow. With the implementation of standardized processes of care, the preoperative fasting period has become shorter, surgical approaches are less invasive and patients are allowed to resume oral intake shortly after surgery. Intraoperatively, body fluid homeostasis and adequate tissue oxygen delivery can be achieved using a normovolemic therapy targeting a “near-zero fluid balance” or a goal-directed hemodynamic therapy to maximize stroke volume and oxygen delivery according to the Frank–Starling relationship. In both fluid strategies, the use of cardiovascular drugs is advocated to counteract the anesthetic-induced vasorelaxation and maintain arterial pressure whereas fluid intake is limited to avoid cumulative fluid balance exceeding 1 liter and body weight gain (~1-1.5 kg). Modern hemodynamic monitors provide valuable physiological parameters to assess patient volume responsiveness and circulatory flow while guiding fluid administration and cardiovascular drug therapy. Given the lack of randomized clinical trials, controversial debate still surrounds the issues of the optimal fluid strategy and the type of fluids (crystalloids versus colloids). To avoid the risk of lung hydrostatic or inflammatory edema and to enhance the postoperative recovery process, fluid administration should be prescribed as any drug, adapted to the patient’s requirement and the context of thoracic intervention.

Key words: Acute lung injury; cardiac output; glycocalyx; normovolemia

Introduction

Historically, empiric intravenous (IV) fluid dosing protocols have been applied in surgical patients with the assumption that a “third fluid compartment” was generated by

trauma-induced capillary injuries that justified a high volume or liberal IV fluid therapy to maintain an adequate circulatory volume.^[1,2] Yet, this concept has been challenged by two observations: 1) the neuroendocrine stress response always

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leads to fluid retention and peripheral vasoconstriction,^[3] 2) capillary lesions causing fluid exudation are transient and limited to the operative site in the absence of sepsis.

Currently, prescriptions of IV fluids vary largely, between institutions and between physicians within a same department. For instance, at the John Hopkins Hospitals, over a 4-year period, the median crystalloid volume that was infused during lung surgery was 11.3 mL/kg/h with large variations between anesthesiologists.^[4]

Mounting evidence indicates that fluid balance influence clinical outcome in critically ill patients admitted in the intensive care unit (ICU) and those undergoing major surgery.^[5,6] Therefore, attention should be paid to prescribe IV fluids as any other drug to target three important goals: 1) volume resuscitation to restore intravascular volume in case of fluid deficits due to hemorrhage, prolonged fasting, polyuria, vomiting or diarrhea, 2) volume replacement to compensate external fluid losses (e.g., oozing, perspiration, digestive secretions and urinary output), 3) nutritional support of cellular function with energetic compounds, proteins, essential fats, vitamins and correction of acid-base and electrolyte disturbances whenever oral intake is not allowed or possible.

During acute stress such as trauma and surgery, restoration and maintenance of oxygen delivery (DO_2) by normalizing gas exchange and circulatory flow are key treatment goals to support cellular oxygen uptake (VO_2) and organ function.^[7] In anesthetized surgical patients, the administration of fluids and cardiovascular drugs are titrated to compensate the loss of body fluids as well as the changes in intravascular volume and fluids shifts to interstitial space due to anesthesia-induced vasorelaxation and inhibition of the sympatho-adrenal activity.^[8] In contrast with the awake condition where thirst, tachycardia and cutaneous vasoconstriction herald the onset of hypovolemia, under general anesthesia or thoracic epidural anesthesia, the diagnosis of hypovolemia is based on the onset of gradual and parallel reductions in mean arterial pressure (MAP), stroke volume (SV) and cardiac output (CO) that are accompanied by increased pulse pressure variation (PPV) or stroke volume variation (SVV) in mechanically ventilated patients.^[9] Noteworthy, intraoperative prolonged low DO_2 or CO conditions are associated with splanchnic and renal vasoconstriction as well as lactic acidosis that are predictive factors of postoperative organ failure, cognitive dysfunction, delayed wound healing and infections.

As with any other drug therapy, prescription of fluids should consider: 1) their indications, contraindications and side

effects, 2) the volume and content of fluids, 3) the rate and duration of administration guided by estimation of fluid deficits (fasting, bleeding, urine) or monitoring physiological and biological parameters (CO, MAP, tissue oximetry, pH, electrolytes, lactate).

In this review, we provide physiologic insights in fluid homeostasis and highlight the impact of fluid management on postoperative pulmonary complications in patients undergoing thoracic surgery.

Physiology of Fluid Balance

Body fluid compartments and Starling principle

Water comprises about 60% of body mass, with two-third of body water distributed within the cells and one-third around the cells, in the interstitial and intravascular spaces (IS 15% and IVS 5%; Figure 1).^[10] In laboratory conditions, dilution tracer techniques enable physiologists to measure total body water (with deuterium or tritium), extracellular fluid content (with radiolabeled sulphate or bromide) and IVS (with Evans blue or radiolabeled albumin).

In healthy individuals, the daily fluctuations in total body water are minimal (<0.5%) and are precisely regulated by the renin–angiotensin–aldosterone (RAS), antidiuretic and atrial natriuretic peptide hormone systems that regulate fluid intake (~1.0-1.5 ml/kg/h in normothermic individuals) and urine output. The IVS includes the “stressed” volume that contribute to the venous return flow according to the pressure gradient between peripheral veins and the right atrium whereas the “unstressed” volume corresponds to the remaining blood volume [Figure 1].

The capillary endothelium is freely permeable to water and electrolytes but impermeable to large molecules (>35 kDa, albumin), while small proteins are continuously leaking.^[11] Therefore, when 1 L of glucose 5% or 1 L of saline solution are infused, only 7-10% of glucose 5% and 20-30% of crystalloids are retained within the IVS, the remaining part being transferred to the IS and cleared by the kidney over the following hours.^[12] According to the classical Starling concept, the fluid shifts between IVS and IS are determined by the opposite hydrostatic and colloid osmotic pressure gradients (ΔP and $\Delta \pi$), the integrity of the endothelial cells (ECs), the endothelial glycocalyx layer (EGL) and the clearance capacity of the lymphatic system [Figures 2 and 3].^[13] The pre- and post-capillary resistances and the resulting capillary hydrostatic pressure (P_c) are modulated by sympathetic reflexes, angiotensin II (AT-II), as well as by vasoactive drugs and mediators released during ischemia-reperfusion and inflammation (paracrine and

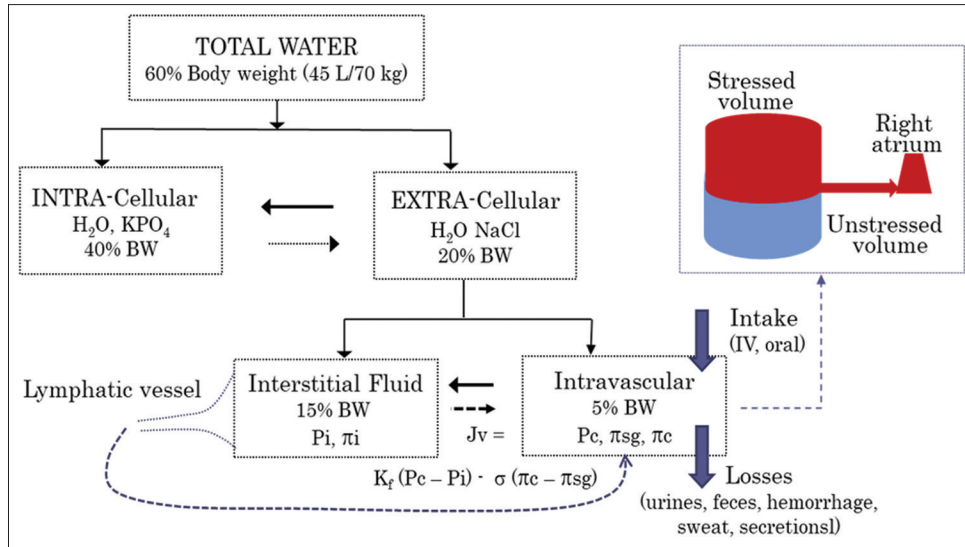


Figure 1: Body fluid compartments

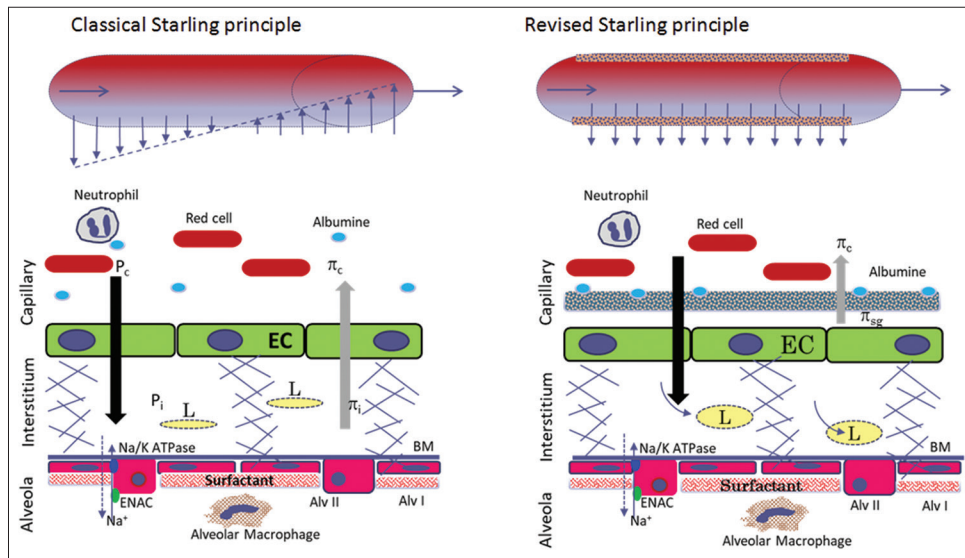


Figure 2: Fluid shifts between intravascular, interstitial and alveolar spaces

autocrine effects). The net effect of ΔP on fluid transfer is modulated by the filtration coefficient (K_f) that reflects the hydraulic permeability and the available microvascular surface area. On the other hand, the fraction of the $\Delta\pi$ is modulated by the vascular permeability factor or reflection coefficient (σ) which for water-soluble solutes has values between 0 and 1.0 (0, freely permeable membrane to protein; 1, non-permeable membrane). To ensure an efficient seal, tight junctions are formed between ECs with occludins, claudins and junctional adhesion molecules. In the lungs, additional mechanisms involving epithelial sodium channels (ENaC, on the apical side of EC) and sodium/potassium adenosine triphosphatase (Na/K ATPase, on the basal side of the EC) ensure that alveola are kept “dry” by continuous extrusion of sodium, chloride and water towards the interstitial space.^[14,15]

Endothelial glycocalyx layer

The EGL represents a meshwork of glycosaminoglycans, glycoproteins and proteoglycans in which various active compounds are embedded (e.g., anti-thrombin, superoxide dismutase, adhesion molecules, growth factors and angiotensin-converting enzyme [ACE]).^[16] The EGL plays a pivotal role in transcapillary fluid movements, in modulating the inflammatory response and in promoting tissue blood flow. With the presence of sulfated glycosaminoglycans, the EGL acts as a barrier repelling negatively charged cells, namely erythrocytes, leukocytes and platelets. In the revised Starling equation, the EGL is considered an integral structural and functional part of the IVS, besides plasmatic and cellular components. As circulating albumin molecules are partly absorbed over the EGL to form a soluble layer, a low $\Delta\pi$

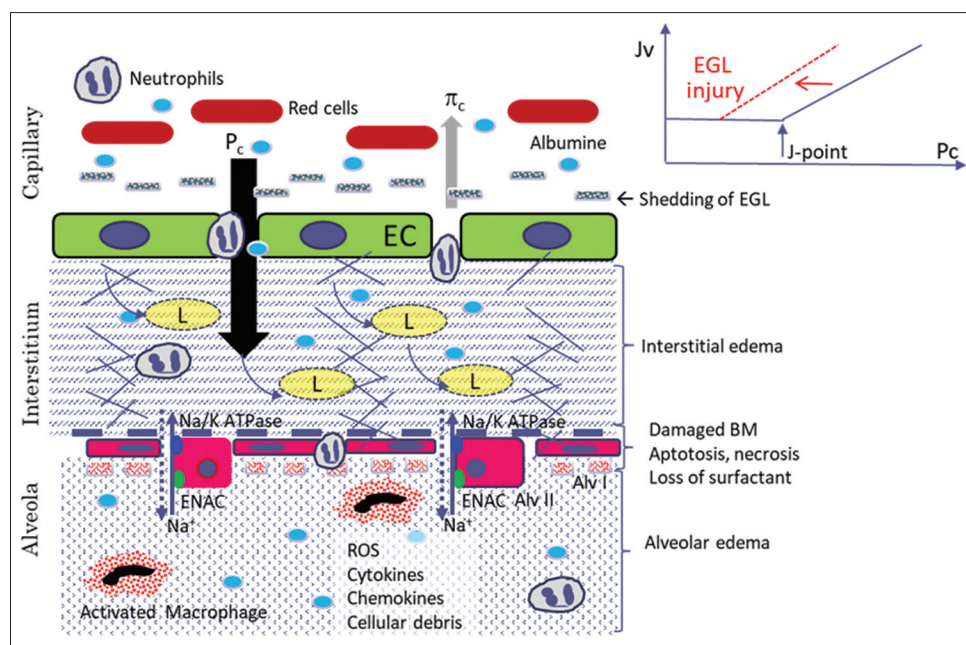


Figure 3: Edema formation in acute lung injury

gradient prevails in the protein-free subglycocalyx space. Accordingly, in contrast with the classical Starling concept where outwards and inwards fluid shifts are balanced owing to opposite changes in ΔP and $\Delta\pi$ along the capillary, in the revised Starling concept, the $\Delta\pi$ is considered negligible and the outward fluid movements are almost exclusively driven by the hydrostatic gradients, the accumulation of fluids in the IS being prevented by efficient clearance through the lymphatic vessels and recycling into the systemic circulation.^[13] In the lungs, lymph flow has been shown to increase by up to 2- to 10 fold, from 10-20 ml/hr at baseline to 50-100 ml/hr, although its role in ARDS has been poorly explored.^[17]

Tissue trauma, circulatory shock, ischemia-reperfusion, inflammation and sepsis may all damage the EGL resulting in excess circulatory plasmin activity, plugging of leucocytes and platelets to the activated ECs and capillary fluid leakage causing impaired tissue blood flow and interstitial edema.^[18] Interestingly, in patients undergoing lung transplantation, the amount of EGL breakdown products released after reperfusion of the lung graft has been shown to predict organ acceptability and the development of primary graft failure.^[19]

Although the damaged EGL can be regenerated over 6-8 h, it may take several days in pathological conditions, depending on the extent of shedded glycocalyx and the ongoing traumatic and inflammatory insults.^[20] Ageing, sedentarity, high-sugar diet and smoking are predisposing factors to EGL injuries.^[16] Furthermore, the presence of hypoalbuminemia and hyperglycemia as well as excessive vascular shear stress caused by rapid infusion of large volumes of acidic crystalloids

or the induction of hypervolemia with IV colloids have been shown harmful to the EGL and in turn, generate or worsen interstitial edema.^[21]

Post-thoracotomy Respiratory Failure and Acute Lung Injury

Definition

The diagnosis of acute respiratory failure is based on documentation of inadequate gas exchange (low ratio of arterial oxygen pressure to inspiratory oxygen fraction, $[PaO_2/FIO_2]$) poorly responsive to inhaled oxygen therapy and requiring mechanical support with non-invasive or invasive ventilation.^[22] The underlying mechanisms of inefficient pulmonary oxygen uptake are related to impairments in cardiovascular, pulmonary and/or muscular functions. After lung surgery, pneumonia, acute respiratory distress syndrome (ARDS) or ALI, broncho-pleural fistula with empyema, IV fluid overload, new/worsening heart failure (e.g., arrhythmias, myocardial ischemia) and weakness of respiratory muscles may all be incriminated in causing low PaO_2/FIO_2 , with or without hypercapnia.^[23]

Rather than a single pathological disease, ARDS/ALI represents a syndrome with different phenotypes and etiologies that share common mechanisms and inflammatory pathways. Distinctive clinical, radiological and functional characteristics allow physicians to differentiate ARDS from hydrostatic lung edema according to the Berlin definition criteria that were issued by the European Society of Intensive Care Medicine, the American Thoracic Society, and the Society of Critical

Care Medicine [Table 1].^[24,25] Noteworthy, ALI is defined on the same clinical and radiological criteria than ARDS, with a $\text{PaO}_2/\text{FIO}_2$ threshold at <300 mmHg (40 kPa).

Mechanisms

Overall, pulmonary edema results from the interactions between several pathological processes, namely:

1. alveolar mechanical stress defined by deformation and increased pressure on the epithelial cells (AEC) caused by mechanical ventilation,
2. dysregulated inflammatory responses in the alveola with activation of coagulation system, leucocytes and platelets,
3. activation of ECs and increased capillary permeability due to endogenous inflammatory mediators and/or exogenous toxic products,
4. alveolar surfactant deactivation due to ventilatory-stretch and deformation of AEC type II cells.^[26]
5. increased hydrostatic capillary pressure due to cardiogenic failure or fluid overload.

In ICU, the triggering events leading to ARDS are pneumonia (35–50%), non-pulmonary sepsis (30%) followed by inhalation of gastric content (10%), and trauma (10%).^[25] In these critically-ill patients, ventilatory settings (high driving pressure and tidal volume), plasma transfusion, infection, positive fluid balance and low serum protein levels have been identified as independent risk factors for ARDS whereas weight gain exceeding 10% was associated with a higher mortality rate.^[27-30]

Regardless of the origin, ARDS encompass common pathologic pathways, namely: Overexpression of pro-inflammatory factors (e.g., interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor alpha, E selectin, angiopoietin-2, vascular and intracellular adhesion molecules), the loss of surfactant and the release of apoptotic factors and reactive oxygen species (ROS) that contribute to disrupt the alveolar-capillary barrier and in turn, to increase vascular permeability.^[31] A growing body of evidence has also highlighted the role of the RAS in ARDS: The classical cascade, represented by ACE and AT-II exert vasoconstrictor, pro-inflammatory and profibrotic effects whereas the alternate cascade, involving ACE-2, angiotensin 1–7 and the Mas receptors, mediates the vasodilatory, anti-inflammatory and anti-fibrotic actions.^[32]

Thoracic surgical patients exhibit different phenotypical signatures with endothelial, epithelial or combined insults.^[23] In the multiple hit model of post-thoracotomy ALI, intraoperative ventilatory-induced lung injury (e.g., high FIO_2 , high V_T , high driving pressure or power) and gastric aspiration could be the initiating/triggering factors whereas preoperative patient's condition (e.g., lung inflammation, depressed immune defenses, genetic footprint), IV fluid strategy and postoperative complications (e.g., atelectasis, pneumonia) may act as “primers” or second (third) “hit (s)” to fuel the pulmonary inflammatory response.^[33,34] In addition, disruption of the lymphatic vessels by preoperative chemo-radiotherapy or surgical dissection may prevent proper interstitial fluid clearance and therefore increase the

Table 1: Diagnostic criteria for postoperative lung edema

	Acute Respiratory Distress Syndrome	Hydrostatic edema
History	Trauma or surgery, pneumonia or other infection, transfusion, shock	Known cardiac disease (CAD, HF, valvular, arrhythmia), renal dysfunction
Timing	Acute onset, <1 week of known insult. 1-3 days (early) or > 3 days (delayed) after surgery	Acute or subacute onset after surgery
Chest X-Rays	Bilateral opacities (or unilateral after pneumonectomy), Not fully explained by alveolar collapse, nodules or effusions	Increased cardio-thoracic ratio Blood diversion to upper lobes Peri-bronchial cuffing, Kerley lines Air space opacification, air bronchograms Pleural effusion
Chest ultrasounds	B-lines + + +, non-homogenous distribution, spared areas Pleural effusions +/-	B-lines + + +, homogenous Areas of consolidations + + Pleural effusions +/-
Origin	Respiratory failure not fully explained by cardiac failure or fluid overload (pulmonary artery wedge pressure $\geq 15-18$ mmHg, unchanged ventricular function at TTE)	<i>Cardiogenic</i> cause, based on: increased blood levels of biomarkers (BNP, NT-proBNP) depressed left ventricular function <i>Hydrostatic</i> , non-cardiogenic, based on: Positive fluid balance, with normal ventricular function
Grading severity	$\text{PaO}_2/\text{FIO}_2$ ratio 200-300 mmHg (27-40 kPa), PEEP/CPAP ≥ 5 cm H_2O Mild 100-200 mmHg (13.3-27 kPa), PEEP ≥ 5 cm H_2O Moderate <100 mmHg (13.3 kPa) with PEEP ≥ 5 cm H_2O Severe	$\text{PaO}_2/\text{FIO}_2 < 300$ mmHg (40 kPa) with PEEP/CPAP ≥ 5 cm H_2O

BNP: Brain natriuretic peptide; NT-proBNP, N terminal pro-brain natriuretic peptide; CPAP, continuous positive airway pressure; $\text{PaO}_2/\text{FIO}_2$, ratio of arterial oxygen pressure to inspiratory fraction of oxygen; PEEP, positive end-expiratory pressure; TTE, transthoracic echocardiography

risk of lung edema, making these patients more vulnerable to fluid loading.

Clinical expression and diagnostic tools

Based on retrospective cohort analysis, two main clinical patterns of post-thoracotomy ALI can be distinguished corresponding to different pathogenic triggers: 1) ALI developing within 48–72 h after lung resection (primary ALI), 2) a delayed form triggered by postoperative transfusion and adverse events such as inhalation of gastric content, pneumonia or other infections.^[34]

Besides anesthesia and surgery-induced reduction in lung volumes, the presence of interstitial and alveolar edema further contributes to increase lung elastance (or stiffness), with consequent increase in the work of breathing and impairment in gas exchange when respiratory muscle fatigue occurs.^[22]

Oxygen desaturation and rapid shallow breathing are common findings of pulmonary complications. Routine examination of chest X-rays and drainage output may document or rule out the presence of atelectasis, pneumothorax, alveolar infiltration, broncho-pleural fistula, cardiogenic edema or ARDS. Further chest imaging (ultrasounds, CT-scan) and transpulmonary thermodilution (TPTD) techniques as well as blood measurements of cardiac biomarkers (BNP, NT-proBNP) and microbiological analysis of blood/sputum (or broncho-alveolar lavage) samples are helpful tools for rapid and accurate diagnostic guidance.^[35-37] Bedside ultrasound lung scanning may reveal distinctive characteristic features of hydrostatic edema (e.g., uniform distribution of interstitial edema associated with >3 B-lines) and ARDS (e.g., reduction of lung “sliding”, consolidation areas, pulses, air bronchograms, pleural thickening).^[37,38] Interestingly, documentation of increasing numbers of B-lines has been shown to correspond to weight gain, elevation in blood levels of natriuretic peptides and decreased PaO₂/FIO₂ ratio in the early days after major lung resection.^[37,39]

By computing the indicator loss through pulmonary capillaries, the TPTD quantifies the amount of extravascular lung water, intrathoracic blood volume and global end-diastolic volume.^[35] When lung water content is increased, the TPTD-derived pulmonary vascular permeability index is a helpful marker to discriminate between hydrostatic and inflammatory edema.^[40]

Perioperative Fluid Optimization

Glycocalyx sparing therapies

In experimental settings, several treatment options have been shown effective to rebuilt or protect the EGL through the

administration of hydrocortisone or nitric oxide in isolated heart preparations, heparin in septic shock, plasma protein in haemorrhagic shock and albumin in heart transplantation.^[41] In the clinical field, preliminary results indicate that insulin therapy in diabetics is effective to enhance EGL formation and attenuate leukocyte-endothelial cell interactions along with the development of micro- and macro-angiopathy.^[42]

Regarding anesthetic agents, the current scientific literature has yielded mixed results. Although in cellular preparations and animal models of ischemia-reperfusion sevoflurane has demonstrated protective effects on the EGL, in humans, exposure to volatile anesthetics has failed to attenuate tourniquet-induced release of glycocalyx injury markers EGL after knee surgery and after thoracic surgery under one-lung ventilation.^[43,44]

Perioperative fluid strategies

Postoperative outcome

With modern surgical and anesthesia care including minimally-invasive approaches, protective mechanical ventilation and avoidance of excessive hydration, the risk to damage the capillary-alveolar barrier is attenuated as shown by limited shedding of the EGL, small increase in extravascular lung water and in permeability vascular index after thoracic procedures.^[45,46]

In all types of surgery, including lung resection, a U-shaped distribution curve best describes the relationship between intraoperative IV fluid dosing and the occurrence of major postoperative complications, namely mortality, infections, ALI/ARDS, wound dehiscence and acute kidney injury [Figure 4].^[47] The nadir on the x axis associated with the lowest risk of postoperative complications, refers to the optimal fluid volume required to maintain normovolemic condition (not a “magic number” in ml/kg/h) while avoiding both hypovolemic and hypervolemic circulatory conditions (leftwards and rightwards, respectively). The absolute rate of fluid infusion depends on the extent of tissue insult and the integrity of the capillary endothelial barrier. Accordingly, the averaged IV fluid infusion usually ranges between 5 and 9 ml/kg/hr in open upper abdominal surgery and in patients with active inflammatory/infectious conditions whereas lower infusion rates (e.g., 2 to 5 ml/kg/hr) are required during Video-Assisted Thoracic Surgery (VATS) or laparoscopic interventions to maintain hemodynamic stability and adequate oxygen supply [Figure 1 and Table 2].^[48,49]

Type of fluids

Although being more expansive and potentially deleterious (renal and hemostatic effect), colloids offer some advantages in perioperative fluid resuscitation. In

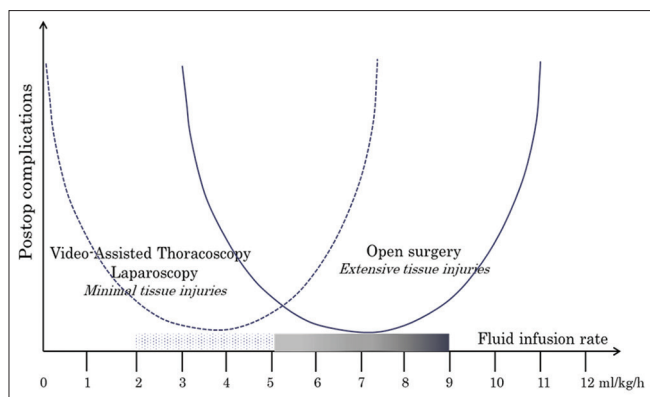


Figure 4: Relationship between perioperative fluid therapy and postoperative complications

conditions of hemorrhagic or septic shock, resuscitation with crystalloids has been shown ineffective to restore the EGL whereas fresh frozen plasma, albumin and to a lesser extent artificial colloids such as hydroxyethylstarch (HES) have demonstrated protective endothelial properties that result in reduced vascular permeability along with enhanced tissue blood flow.^[50] As far as the EGL is intact, colloids with their high molecular weight molecules (HES, gelatins or albumin) are almost exclusively distributed into the IVS. In hypovolemic conditions, restoration of circulatory volemia with colloids infusion is achieved faster and requires a smaller volume than with crystalloids. Indeed, by increasing π_c , the administration of colloids causes greater volemic expansion and reduce the

Table 2: Studies analyzing the clinical impact of intravenous fluids in thoracic surgery

Authors, year	n	Type of surgery	Perioperative fluid administration		Study endpoint (incidence, %)
			With complications	No complications	
Parquin F ^[63] 1996	146	P	1'039 ± 938 ml	729 ± 859 ml	PE (15%)
Rufini E ^[71] 2001	1'221	LS,	No association with PPCs intraoperative IV Fluids: 2100 ml (range 1550-3200)		ALI/ARDS (2.2%)
Bernard A ^[75] 2001	639	P	Crystalloids over 12-24 h associated with complications (median 20 ml/kg/h [range 10-200]) over first 12 hours)		CVC & PPC (38%) ARDS (3%)
Moller AM ^[69] 2002	107	P	Intraoperative fluid balance ≥ 4 L = RF		CVC & PPC (29%) ARDS (3%)
Licker M ^[34] 2003	879	LS	9.1 ± 4.1 ml/kg/h	7.2 ± 4.2 ml/kg/h	ALI/ARDS* (4.2%)
Fernandez-Perez ER ^[77] 2006	170	P	2.2 (IQR 1.4-3.7) L	1.3 (IQR 0.9-2.7) L	ALI/ARDS
Alam N ^[73] 2007	152	LS	2.8 L (95%1.4-5)	2.5 L (95%1.4-4.5)	ALI/ARDS* (3.1%)
Blank RS ^[76] 2011	129	P	2.7 L (95%2.0-4.0) L	1.8 L (95%1.5-2.5)	All PPC
Marret E ^[67] 2010	129	P	3.8 L ± 1.5*	2.5 L ± 2.0	APC
Ishikawa S ^[64] 2012	1'129	LS	1'450 ± 655 ml	1'276 ± 607 ml	AKI
Mizuno Y ^[78] 2012	52	LS	7.7 ± 3.1 ml/kg/h	10.3 ± 3.7 ml/kg/h	Exacerbation of pulmonary fibrosis
Matot I ^[62] 2013	102	LS	RCT: 2 ml/kg/h vs 8 ml/kg/h 2131 ± 850 ml vs 1035 ± 652 ml Similar incidence of complications in the two groups		APC, urinary output
Arslantas MK ^[74] 2015	139	LS	6.6 ± 3.6 ml/kg/h	4.6 ± 2.3 ml/kg/h	PPCs
Ahn HJ ^[72] 2016	1'442	LS, Oeso	4.8 ± 1.8 ml/kg/h	4.8 ± 2.0 ml/kg/h	AKI
Oh TK ^[70] 2020	2'412	LS	Intraoperative IV HES = RF if preop renal dysfunction OR 7.6 (95%CI 1.5-58) Cumulative 24 h positive fluid balance OR 2.42 (95%CI 1.2-4.9)		AKI
Wu Y ^[79] 2019	446	LS	Restrictive 7.9 ± 1.3 ml/kg/h OR 2.2 (95%CI 1.2-4.1) Liberal > 11.9 ml/kg/h OR 2.6 (95%CI 1.3-5.3) Euvolemia: 9.4 to 11.8 ml/kg/h		Unplanned hospital re-admission (8.3%)
Kim HJ ^[66] 2019	287	LS	No association between IV colloids/ crystalloids & AKI		PPC (38%)
Jo JY ^[65] 2019	892	Oeso	8.1 ± 3.8 ml/kg/h	5.7 ± 2.3 ml/kg/h	AKI
Kim JA ^[67] 2020	1'031	LS	Fluids, kg/h OR 1.48 (95%CI 1.15-1.35) HES/crystalloids ratio, OR 2.12 (95%CI 1.5-3.0)		ALI (2.8%)
			Restrictive 2.4 ± 0.8 ml/kg/hr; High 6.9 ± 1.2 ml/kg/h Intermediate 4.4 ± 0.5 ml/kg/h OR 0.54 (95%CI n.a.)		APC (30%)
			No association between Intermediate rate and AKI		ALI/ARDS (2.9%)

ALI/ARDS: Acute lung injury/acute respiratory distress syndrome; AKI, acute kidney injury; APC, all postoperative complications; CI, confidence interval; CVC, cardio-vascular complications; HES, hydroxyethylstarch; L, lobectomy; LS, lung surgery; P, pneumonectomy; PE, pulmonary edema; PPC, postoperative pulmonary complications; Oeso, oesophagectomy; OR, odds ratio

transcapillary passage of water, compared with crystalloids that diffuse freely in the IS.

In contrast with the first generations of high molecular weight HES that were shown to increase bleeding by interference with platelets and coagulation factors (e.g., von Willebrand factor and fibrinogen), the third generation of HES has a lower-molecular weight (130 kd), a molar substitution ratio of 0.5 and is suspended in a balanced salt solution at a lower concentration (6%) that altogether confer a safer risk profile while keeping the volemic expansion advantage with prolonged IVS persistence and lesser positive fluid balance.^[51]

Current physiologically-based guidelines recommend to compensate external fluid losses (e.g., sweat, perspiration, urine, digestive secretions, capillary leakage) with IV crystalloids whereas for volume resuscitation and restoration of IVS, clinicians may use either crystalloids or colloids in the majority of patients except those with preexisting renal dysfunction, ongoing septic or acute inflammatory conditions where colloids are contraindicated.^[52-54]

Perioperative IV strategy

Whenever the “stressed” circulatory volume is reduced as a result of bleeding or capillary leakage, the rate of IV fluids should be increased whereas the administration vasopressors (or inotropes) should be preferred in case of anesthesia or inflammatory-mediated vasorelaxation (or cardiac depression). Although there is agreement on maintaining a near-normal blood pressure level, scientists and experts advocate two different fluid strategies: 1) a goal-directed hemodynamic therapy (GDHT) to achieve maximal SV, CO or DO₂ according to the Frank-Starling relationship between cardiac preload and CO, 2) a restrictive normovolemic therapy (RNT) to maintain “near-zero fluid balance, minimize postoperative weight gain and the risk of lung edema. The GDHT requires a close monitoring of blood flow and tissue oxygen availability whereas RNT relies on direct evaluation of bleeding, other external losses and the severity of tissue trauma. In both approaches, the vasodilatory effects of anesthetic agents and central neuraxial block are reversed with vasopressors, -instead of fluids-, to restore the “stressed” blood volume and improve blood venous return.

The application of transesophageal Doppler, continuous noninvasive blood pressure, arterial pressure wave analysis and near-infrared spectroscopy (NIRS) provide useful physiological markers (e.g., SV, CO, PPV, SVV, StO₂) to timely adjust fluids and cardiovascular drug therapy to the procedural approach (open vs minimally invasive), the

ongoing tissue trauma and the patient’s cardiovascular response. In unstable hemodynamic conditions and high-risk procedures, GDHT offers the advantage of a more personalized approach to titrate IV fluids, vasopressors and inotropes whereas in low/moderate risk cases, maximizing CO and achieving supra-normal DO₂ values could result in fluid overload.

So far, both GDHT and RNT in non-thoracic surgery have shown favorable effects on early postoperative morbidity and hospital length of stay compared with liberal fluid protocols.^[55,56] Yet, the impact of GDHT on clinical outcome has been reduced with the implementation of standardized perioperative interventions included in the enhanced recovery after surgery (ERAS) protocols.^[57] The 2018 ERAS guidelines for perioperative care in colorectal surgery have focused the indications of GDHT only to high-risk patients, instead to all patients, as stated in the 2012 guidelines.^[58] Interestingly, the GDHT algorithms are largely heterogenous^[59] and, in studies comparing GDHT and RNT, no significant difference in clinical and functional outcome has been demonstrated so far.^[60,61]

In thoracic surgery, a single RCT was designed to compare two fixed fluid regimen (2 versus 8 ml/kg/h) in patients undergoing lobectomy via VATS and it showed that a low infusion rate of Ringer’s lactate solution at 2 ml/kg/h was not associated with impaired renal function.^[62] Over the last 25 years, cohort studies involving thoracic surgical patients suggest a link between the amount IV fluids and the occurrence of postoperative ALI/ARDS, other complications and unplanned re-admission [Table 2].^[34,62-79] Accordingly, RNT targeting a near-zero fluid balance can be adopted in the majority of cases (low/moderate risk) with utilization of noninvasive monitoring tools to ensure stability of circulatory volume and adequate DO₂/VO₂ matching (PPV/SVV, SV, NIRS, bioimpedance/bioreactance monitors).^[80-82] In patients with severe cardio-pulmonary dysfunction and those undergoing complex procedures, more advanced hemodynamic monitoring is preferable with direct measures of arterial pressure, SV, tissue oximetry, extravascular lung water and cardiac filling pressure, (arterial and central venous lines, transesophageal Doppler, TPTD) with application of GDHT algorithms.^[83,84]

Conclusions

Given the lack of large and well-designed RCT in the field of thoracic surgery, current hemodynamic protocols are driven by physiological understanding, interpretation of retrospective cohort analysis and expert opinions. In line with the guidelines for enhanced recovery after lung surgery

issued by the European Society of Thoracic Surgery,^[85] the following strategy could be adopted regarding perioperative fluid management:

- 1) To allow oral fluid intake up to two hours before surgery with carbohydrate loading (100 g the evening before, 50 g the day of surgery) with the aim to improve patient well-being (less nausea), avoid dehydration and maintain a metabolically fed state,
- 2) To start the infusion of buffer/balanced salt solution, at a rate of 2-5 ml/kg/h in minimally invasive surgery and 4-8 ml/kg/h during open thoracotomy; additional crystalloids in 2-3:1 ratio (or colloids 1:1 ratio) can be given to compensate blood losses and a loading dose of fluids after anesthesia induction is not deemed necessary if the preoperative fasting period is shortened,^[86]
- 3) Vasopressors should be prescribed to counteract the anesthetic-induced vasorelaxation, restore peripheral venous tone and in turn, improve CO; caution should also be exercised at proper patient positioning, with a slight head-down table tilt to enhance blood venous return.
- 4) As heart rate, blood pressure, urinary output and central venous pressure are weak indicators of volume status, estimation of ongoing fluid losses (by the surgeon and anesthesiologist), use of dynamic indices of fluid responsiveness (PPV/SVV) and brain tissue oximetry is indicated in the majority of cases whereas more advanced hemodynamic monitoring (transesophageal Doppler, TPTD, pulmonary arterial catheter) should be considered in high-risk patients and complex procedures (e.g., resection of the trachea, pleural mesothelioma).
- 5) Postoperatively, IV fluids should be limited (0.2-0.5 ml/kg/h hypotonic glucose solution) until oral intake is resumed, the cumulative fluid balance should not exceed 1-1.5 L over the first 24 hours, with a weight gain less than 1-1.5 kg of body weight and diuretic should be prescribed to clear any excess in extracellular water. Administration of inhaled salbutamol may enhance the resolution of lung edema and improve oxygenation by accelerating sodium transport as a result of increased activity of sodium and chloride channels and the ATPase in the alveolar epithelium.^[87]

Avoidance of hypo/hypervolemia, maintenance of blood pressure and support of adequate DO_2/VO_2 matching are important goals shared by all anesthesiologists. The perioperative hemodynamic strategy depends on patient's baseline physiological conditions, external fluid losses and variable response to the surgical stress. Ensuring body fluid homeostasis and tissue oxygen delivery can be achieved using RNT in the majority of cases or GDHT in patients with DO_2/VO_2 mismatch.

Over the last three decades, the old paradigm “keep the lungs dry and clean” still holds true and both thoracic surgeons and anesthesiologists still strive for a safer hospital patient journey by implementing individualized protective interventions as included in enhanced recovery protocols.

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Conflicts of interest

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