Less is more

Fluids in critically ill children with acute respiratory failure

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1 General Introduction and Thesis Outlines
INTRAVENOUS FLUID THERAPY: A HISTORICAL PERSPECTIVE

It was the year 1831, a second cholera pandemic spread from India across Asia and Europe. Little remedy was present to treat cholera patients and mortality was high. As blood from deceased cholera patients was dark and thick, it was believed that removing this diseased blood from the patient was the optimal treatment of choice. Hence, bloodletting was a prime practice in those days. At the same time, a young graduate dr. O’Shaughnessy investigated the constituents of a cholera patient’s blood noting the complete loss of water and saline ingredients from the blood. He suggested the injection of aqueous fluids into the veins to restore the blood to its natural constitution. Dr. Latta took up this idea and injected salty water in large volumes in the basilic vein of patients with terminal cholera achieving remarkable, yet temporal clinical improvement (1). At the time, this was a revolutionary and very controversial treatment and after the cholera pandemic, the treatment was not used often. Yet, by the early 1880s, more evidence rose from Germany where patients with severe haemorrhage were successfully resuscitated with saline infusions. This established fluid therapy as a valid therapy by the end of the 1880s.

Nowadays, fluid loading is widely used in critically ill patients to treat hemodynamic instability (2). In the process of fluid loading, patients receive a high volume of fluid in a short amount of time in the early phase of resuscitation. This has gained much attention in the literature (3-5). Yet, after this phase, fluids are also elaborately administered to provide for water, electrolytes, as a vehicle for the necessary medication administration and feeding (6). After being established as the standard first line treatment, the drawbacks of overzealous use of intravenous fluids in critically ill patients has gained growing attention over the last decades (7).

FLUID DISTRIBUTION

While often life-saving during resuscitation because of restoration of intravascular volume, the main problem of administering fluid intravenously is that fluid will not persist in the vasculature space, giving rise to the formation of edema. Starling’s principle stated the equilibrium of fluid filtration and absorption between vasculature and interstitium to be dependent on pressure gradients between hydrostatic and oncotic pressures of both capillary blood and interstitial fluid. Later, this principle was found to be incomplete, as the intra- and extravascular fluid equilibrium has been shown to be more complex than this. Two independent researchers proposed a revised Starling’s principle (8, 9), suggesting the hydrostatic and oncotic gradients between lumen and interstitium to be dependent on the glycocalyx, a layer of luminal membrane-bound glycosaminoglycans and associated glycoproteins, involved in the maintenance of the integrity of the endothelial barrier, regulation of leukocyte and
platelet adhesion and transmission of shear stress to the endothelium (10). In the case of inflammation, wherein a damaged glycocalyx leads to a leaky vascular wall, fluid therapy may be potentially hazardous.

Fluid therapy may be indicated for various reasons. Firstly, to provide for basic fluid needs, as maintenance therapy. Secondly, to correct for dehydration, when fluid levels are low in the intracellular and extracellular compartment and thirdly, to correct for hypovolemia, when fluid levels are low in the intravascular compartment. When fluid loading leads to an increase in intravascular volume thereby increasing stroke volume and cardiac output the individual is considered a fluid responder. This is however the normal physiological state of every mammal as was described more than a century ago by Patterson and Starling (11). Fluid loading will increase cardiac output in responders but this will only be an adequate therapy when the patient is in need for a higher transport of oxygen. Importantly, all fluids infused distribute themselves over the different fluid compartments depending on the constitution of the fluid. For example, glucose solutions diffuse to both intra- and extracellular areas, while crystalloid solutions mainly distribute to the extracellular spaces and blood infusions (erythrocytes) remain intravascular. Any fluid infusion that is administered is therefore usually distributed over both the intra- and extravascular compartment. Studies show the intravascular remainder of crystalloid and colloid infusions to be significantly decreased in the presence of inflammation wherein increased capillary leakage is caused by the breakdown of the glycocalyx (12).

Age is an important factor to take into account in the context of fluid therapy since the composition of the fluid compartments differs between ages. In children, amounts up to 80% of total body weight is made up of water, compared to approximately 60% in adults (13). Of these fluids, in adults, approximately 20% of total body weight is extracellular water and 40% is intracellular, while in children 45% of total body weight is extracellular water, compared with only 35% intracellular (14). This distribution is also observed in the lungs specifically, as the extravascular water content in the lungs of children is higher as compared to adults when normalized to body weight, although it is age-independent when indexed for height (15). These differences imply the volume of distribution when administering drugs and fluid to be different between ages, which should be taken into account in the treatment of specific patient populations.

**FLUID OVERLOAD AND PULMONARY EDEMA DURING CRITICAL ILLNESS**

During critical illness, damage to endothelial barriers due to inflammatory injury promotes the distribution of fluid into the interstitial compartment. Therefore, a possible consequence of fluid therapy is the development of fluid overload and subsequent interstitial edema. In the lungs specifically, this interstitial edema and even worse; ‘free’ fluid in the alveolar spaces,
may have serious consequences for the gas exchange capacities of the lung, especially in the case of pre-existing lung injury.

Increased amount of fluid overload indeed is associated with adverse outcome such as prolonged duration of invasive ventilation, worsened oxygenation or even mortality in both critically ill adults and children (16-18). In a cohort of adult patients with acute lung injury, a negative cumulative fluid balance was associated with significantly lower mortality and more ventilator-free days (19). More specifically, increased extravascular lung water was associated with mortality in another cohort of adult critically ill patients (20). Similar outcomes were found in several populations of pediatric patients (21-25). Most notably, early fluid overload, occurring in the first 72 hours of invasive ventilation, has been found most deleterious (18). An extensive systematic review of the association between fluid overload in different critically ill children populations found that fluid overload, however defined, was associated with in-hospital mortality, increased risk of prolonged mechanical ventilation and occurrence of acute kidney injury (7). This seemingly overwhelming evidence has led to ongoing discussion concerning the optimal fluid strategy and management.

**ACUTE LUNG INJURY**

Acute respiratory distress syndrome (ARDS), an acute life-threatening pulmonary condition, is a notorious example of extensive acute pulmonary injury with subsequently increased endothelial permeability and pulmonary edema (26). ARDS is characterized by an acute pulmonary injurious state that can be caused by several ‘hits’ either direct (pneumonia) or indirect (trauma, sepsis). It is hallmarked by a dysregulation of the immune- and coagulatory system in combination with altered endothelial and epithelial permeability (26, 27). ARDS was first recognized and described by Ashbaugh et al. (28), and subsequently more precisely defined in 1994 by the American-European Consensus Conference on ARDS in critically ill adult patients, after which several adapted definitions have been formed. The latest of these, the so-called Berlin definition, incorporates timing, chest radiograph, origin of edema and oxygenation status to classify ARDS (29). Pediatric ARDS (PARDS) has been redefined in 2015 by the Pediatric Acute Lung Injury Consensus Conference Group from this adult Berlin definition as pediatric pathophysiology and age-dependent differences were not specified in the Berlin definition (30). The incidence of PARDS lies somewhere between 2.0-12.8 per 100,000 person-years as described by different studies (31-34). While mortality in adults is high (27-45%), mortality in children has been estimated to be lower ranging from 18-35% (32, 35, 36). One of the most prevalent triggers of PARDS in the pediatric population is acute viral respiratory tract infection, or bronchiolitis (37, 38). Bronchiolitis is mostly caused by the respiratory syncytial virus (RSV), and may progress to PARDS in 15-20% of the cases (32, 35,
39, 40). Yet, in a study by Schene et al. 129 of 155 included patients (83%) with RSV-induced respiratory failure fulfilled the criteria for mild to moderate PARDS (41).

One of the important processes that occurs in acute lung injury and (P)ARDS is an alteration in the capillary permeability barrier in the lung with damage to both endothelium and epithelium. This leads to combined (functional or real) hypovolemia and development of peripheral and pulmonary protein-rich edema, with vasoplegia. As briefly mentioned above, the trigger that causes (P)ARDS may be both direct and indirect and instigates a cascade of (local) inflammatory and coagulatory reactions (27). Overzealous fluid administration during and after the initial resuscitation phase of (P)ARDS may lead to further development of (pulmonary) edema. While ARDS has been extensively studied in adult patients, this is not the case in children. Yet, differences in mortality indicate that there may be important differences between children and adults that impact the pathophysiology and outcomes of PARDS.

**THESIS OUTLINES**

Taken together, fluid overload and subsequent pulmonary edema is common in children with acute lung injury and it is associated with adverse outcome such as prolonged duration of mechanical ventilation. This thesis aims to investigate whether fluid overload further aggravates the development of acute lung injury in children and if so, what pathophysiological mechanisms are involved in this process. Subsequently, we may ask ourselves how to prevent and diagnose fluid overload in critically ill children with acute lung injury.

This thesis employs a translational approach, incorporating both bench- and bed-side studies, exploring the occurrence of fluid overload in a PICU setting. Evaluation of the occurrence of fluid overload in mechanically ventilated patients with PARDS and its association with adverse outcome has been reviewed in chapter 2.

In the second part of this thesis, we describe the modelling of (P)ARDS with its pathophysiological aspects in two different experimental animal studies aiming to provide further understanding in the underlying pathophysiological mechanisms of ARDS and subsequent occurrence of pulmonary and extra-pulmonary fluid accumulation. In chapter 3, we describe an ARDS model in rats in which we explicitly research the impact of fluid management on outcomes in animal models. In chapter 4, we go into further depth in an ovine model of ARDS investigating the effect of fluid restriction on extravascular lung water and hemodynamics.

The third part of this thesis, describes the more clinical aspects of fluid overload in a PICU setting. In these studies, pediatric patients with acute lung injury due to bronchiolitis (acute (viral) respiratory tract infection) have been studied. Chapter 5 describes a retrospective cohort of mechanically ventilated pediatric patients with bronchiolitis and investigates the relationship between cumulative fluid balance and outcome such as duration of mechanical ventilation. In chapter 6, we performed a feasibility study in preparation of a larger
multicenter RCT to compare the effect of conservative versus standard fluid (maintenance) regimen in our PICU. Lastly, chapter 7 investigates the possibility of using lung ultrasound to diagnose the occurrence of pulmonary fluid overload in mechanically ventilated patients with bronchiolitis.
Chapter 1

REFERENCES

Introduction


