Less is more

*Fluids in critically ill children with acute respiratory failure*

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Summary
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With the emergence of intravenous fluid administration in the 1800s, little was known regarding the consequences of this therapy. Fluid therapy is now extensively used in critically ill patients to treat hemodynamic instability, but is also administered as a vehicle to deliver medication, nutrients and appropriate amounts of water and electrolytes. During critical illness, the drawback of this approach is the potential accumulation of fluid in the body, resulting in fluid overload leading to edema. Especially the lungs are prone to the interstitial accumulation of fluid. Fluid overload is associated with adverse outcome, such as prolonged duration of mechanical ventilation and higher mortality. While in adult patients quite an extensive number of studies have described fluid overload and its consequences, this is not yet the case in critically ill children. This thesis focuses on the pathophysiology, diagnosis and prevention of fluid overload in critically ill children with acute lung injury.

In part I of this thesis, the concept of fluid overload and subsequent interstitial (most notably pulmonary) edema is introduced. Chapter 2 describes the literature on fluid management in children with acute respiratory distress syndrome (ARDS) or pediatric ARDS (PARDS), specifically focusing on the differences between adults and children. ARDS is a syndrome characterized by acute lung injury, pulmonary edema and hypoxia. Studies in adults with ARDS have shown that fluid overload is associated with adverse outcome. Yet, differences between children and adults in the development and consequences of fluid overload in ARDS may exist due to disparities in immunologic response and body water distribution. By systematically reviewing the literature, similar adverse effects associated with fluid overload were seen in children with PARDS as compared with adults. In both patient populations fluid overload is associated with prolonged duration of mechanical ventilation, oxygenation and even mortality. Nevertheless, the size of this effect cannot be compared at this time. Given that there are well-known differences between prevalence and outcome between children with PARDS and adults with ARDS, further study is needed to determine whether there is a need for age-specific fluid management protocols in order to limit fluid overload.
MODELING ARDS: PATHOPHYSIOLOGICAL EFFECTS OF FLUID OVERLOAD

Part II of this thesis explores the pathophysiological mechanisms behind the development of fluid overload and its effects in different age groups by studying two experimental animal models. Chapter 3, describes an experimental rat model of ARDS, in which the effects of two different fluid strategies in both infant and adult rats is compared. Rats were randomized to either a conservative or standard fluid strategy, wherein they received either a little or a normal amount of fluid during a 6 hour period of mechanical ventilation. While a similar hemodynamic response in infant and adult animals was found between both fluid strategies, lung wet-to-dry ratio’s, as an indicator of pulmonary edema, were lower in adult rats receiving the conservative fluid strategy. Interestingly, this effect was not observed for infant rats. Moreover, there were age-related differences in markers of alveolar-capillary barrier disruption and alveolar fluid clearance, although these were unaffected by fluid strategy. Finally, higher cytokine concentrations in adult rats treated with conservative fluid therapy were observed as compared to the standard fluid regimen. Apart from these age-related differences, this also indicates that the choice of fluid strategy is extremely important in animal models. Namely, this may potentially influence the conclusions of experimental studies. As experimental acute lung injury models are often used to increase our knowledge on clinical syndromes, such as ARDS, it is important to realize the effect of specific fluid strategies on outcome. Chapter 4 compares a conservative versus a standard fluid strategy in an ovine model of PARDS. This model incorporates both the resuscitation and maintenance phase of fluid strategies with different protocols for both study arms. In this study, the effect on hemodynamics was studied in more depth, as well as the development of pulmonary edema and inflammatory response. Although significant differences in fluid intake were achieved, the development of pulmonary edema, measured as both extravascular lung water (EVLW) and lung wet-to-dry weight ratios, was not significantly different between fluid strategies. In addition, both fluid strategies succeeded in keeping animals hemodynamically stable. Fluid strategy did not affect lung permeability or inflammation in this short-term model. Nevertheless, microcirculation was significantly diminished at the end of the experiment in the conservative fluid group. While fluid strategy did not prevent the formation of pulmonary edema or lung permeability and inflammation; this unfavourable effect on microcirculation suggests that further adverse effects may ensue if a strict conservative fluid strategy is extended over a longer period of time.

CLINICAL ASPECTS OF FLUID OVERLOAD

Part III of this thesis focuses on the clinical occurrence, prevention and diagnosis of fluid overload. In chapter 5, a cohort of young children with acute respiratory failure due to viral lower respiratory tract disease in need of mechanical ventilation is described. While respira-
tory insufficient, these patients usually have a relatively benign course of critical illness with little cardiovascular instability. Nevertheless, it seems that these patients still develop a large amount of fluid overload with a mean cumulative fluid balance of almost 100 ml/kg on day 3 of mechanical ventilation. This corresponds to a relative fluid overload of approximately 10%. Higher cumulative fluid balance was associated with prolonged duration of mechanical ventilation, yet not with oxygenation indices. This study suggests that avoiding early fluid overload - in the first 3 days of mechanical ventilation - is a potential target to reduce duration of mechanical ventilation in these children. **Chapter 6** takes this notion one step further, by performing a feasibility study in which a similar cohort of mechanically ventilated children due to acute (viral) respiratory tract infection is randomized to either a conservative or a standard, more liberal, fluid strategy. By restricting fluids, the aim is to limit the accumulation of fluid overload, thereby potentially reducing mechanical ventilation duration. In this feasibility study, adherence and safety parameters were assessed. It was observed that in the conservative fluid group, in 75% of the days on mechanical ventilation patients achieved their target fluid intake. No adverse effects on hemodynamics were noted and in both groups an appropriate and similar calorie and protein intake was achieved. Nevertheless, although achieving significantly different amounts of fluid intake, this did not result in a lower cumulative fluid balance in the patients receiving conservative fluids as compared to the standard fluid group. This study therefore suggests that a conservative fluid strategy is safe in this patient cohort, yet did not reduce the degree of fluid overload. These are important results that aid in designing a larger multicenter RCT, in which further redefining of the target fluid strategy is necessary, possibly by further fluid restriction and by early therapeutic stimulation of diuresis to actively lower cumulative fluid balances. In **chapter 7**, it is subsequently described how to potentially detect and monitor the accumulation of fluid in the lungs in patients with acute viral respiratory tract infection by using lung ultrasound. Lung ultrasound is used more often in emergency department and (adult) intensive care settings offering a reliable bedside technique without the disadvantage of radiation exposure. Regarding to fluid accumulation, lung ultrasound may employ a score of so-called B-lines to describe the fluid accumulation in the lung. B-lines are vertical artefacts in the lung generated by fluid-filled interlobular septae. B-line scores are associated with direct measurements of extravascular lung water in different study populations. In critically ill children with viral respiratory tract infection on mechanical ventilation, this technique has not been used before to monitor pulmonary congestion. In this study, serial lung ultrasounds were made on subsequent days to assess the association between B-line scores and cumulative fluid balance, yet did not find an association. Moreover, no association was found between B-line score and oxygenation. Thus, in this specific patient cohort, serial lung ultrasound did not serve as a helpful tool in detecting an increase in pulmonary congestion, as there was no relation with lung ultrasound scores to either fluid balance or oxygenation.
CONCLUSION

In chapter 8, all findings presented in this thesis are discussed in light of recent literature and possible future perspectives.

The main findings of this thesis are:
- Fluid overload is associated with adverse outcome such as prolonged duration of mechanical ventilation, oxygenation and even mortality in critically ill children with PARDS (Chapter 2).
- The choice of fluid strategy is important also in experimental animal models as they may impact results and subsequent conclusions (Chapter 3).
- Conservative fluid management during ARDS seems to lower pulmonary edema in adult animals (rats), yet not in infants (both rats and lambs), indicating that younger animals are less susceptible to the development of fluid overload (Chapter 3 & 4).
- There seems to be little effect of the degree of fluid overload on lung permeability and inflammatory response (Chapter 3 & 4).
- Even in children with a relatively benign acute respiratory disease, being a single organ failure with minor hemodynamic compromise in need of vigorous fluid resuscitation, fluid overload accumulates in large amounts as reflected by a positive cumulative fluid balance associated with a longer duration of mechanical ventilation (Chapter 5).
- Performing a randomized-controlled trial wherein children are randomized to fluid strategy seems feasible and safe, yet requires further refinement for future investigation (Chapter 6).
- Lung ultrasound did not detect an increase in pulmonary congestion in relation to increased amounts of fluid overload in children with acute viral respiratory tract infection on mechanical ventilation (Chapter 7).