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Purpose of review

Early Adult Respiratory Distress Syndrome (ARDS) in characterized by protein rich inflammatory lung edema often associated with an hydrostatic component. Mechanical ventilation with positive intra-thoracic pressure furtherly induces salt and water retention, while impairing the pathways designed for edema clearance. In this framework we will review the recent findings on fluid strategy and edema clearance in ARDS.

Recent findings

Consistently, conservative strategies lead to better oxygenation and reduces the length of mechanical ventilation. A possible drawback associated with conservative strategy is the impaired cognitive function. Echography may be used for safer use of furosemide/ hemofiltration therapy during edema clearance. Albumin and furosemide techniques may accelerate edema clearance when pulmonary capillary permeability is restored. Beta-2 agonist therapy does not accelerate edema clearance and is potentially dangerous.

Summary

Lung edema is likely the single pathogenic factor more relevant for ARDS severity and outcome. Fluid overload must be avoided. Several monitoring technique are available to reach this target. No specific studies are available to recommend a given fluid composition in ARDS. In our opinion, the general recommendations for fluid composition suggested for severe sepsis and septic shock should be applied to ARDS which may be considered as an organ-confined sepsis.

Key-word

Acute respiratory distress syndrome, fluid management, lung edema

Introduction

Adult Respiratory Distress Syndrome (ARDS) is a near-whole lung parenchymal reaction to pulmonary and extra-pulmonary insults which leads to extravasation of protein-rich fluids (inflammatory pulmonary edema) into the interstitial space. The lung weight increases producing compression atelectasis with impairment of lung mechanics and gas exchange. In full-blown ARDS, pulmonary hypertension may be easily associated with increased pulmonary capillary pressure and/or cardiac failure. Both conditions may add an hydrostatic component to the edema formation. Moreover, the physiological consequences of the increased intra-thoracic pressure due to mechanical ventilation are the activation of all feedback system designed to maintain intravascular volume and arterial pressures [1]. In particular the renal aldosterone-angiotensin system is activated leading to water and salt retention. Therefore, in ARDS, to the original inflammatory protein-rich edema an hydrostatic component is usually over-imposed and there is a tendency to retain the infused fluids with further water accumulation.

In addition, while all the mechanisms causing the increased edema are operating, the pathways for its clearance are impaired. In fact, the three ways for edema clearing (i.e. pleural effusion, lymphatic flow and capillary reabsorption into the venous side of the pulmonary capillary network are all dumped by the positive intra-thoracic pressure associated with mechanical ventilation).

The physiology of fluids behavior in ARDS has been extensively studied in the late ’70 and ’80. While discussing the more recent literature, we would like to suggest reading two old studies which, among many others, most impressed us: the first one, published in Anesthesiology [2], which reported the effects of 2 days of spontaneous breathing, mechanical ventilation or mechanical ventilation with PEEP on fluids distribution and on water retention in dogs; the second one was

published in Chest [3] by Schuster et al. This author was the one who mostly underlined the need of edema measurement in ARDS due its paramount importance in pathogenesis and outcome. In the present report we will group the most recent literature in two main items related to edema formation and clearance: what's new in the strategy of fluid infusion and which are the techniques available to enhance edema clearance.

Strategy of fluid infusion

The landmark study in this field is the FACTT trial [4]. In this study, the fluid management was based on measuring central venous pressure or pulmonary capillary wedge pressure. Patients with a central venous catheter received therapy to maintain a target central venous pressure of less than 4 mmHg in the conservative group compared with 10–14 mmHg in the liberal treatment group. Patients with a pulmonary artery catheter had a target central venous pressure of less than 8 mmHg in the conservative group compared with 14–18 mmHg in the liberal strategy. The rate of death at 60 days was 25.5 percent in the conservative-strategy group and 28.4 percent in the liberal-strategy group (P=0.30). The cumulative fluid balances during the first seven days were strikingly different: –136±491 ml in the conservative-strategy group and 6992±502 ml in the liberal-strategy group (P<0.001). As compared to liberal strategy, the conservative strategy improved significantly the oxygenation index, the lung injury score, the number of ventilator-free days and decreased the length of stay in the intensive care unit. All these advantages were obtained without significant increase of side effects as non-pulmonary organ failures. Of note, the need for dialysis was almost significantly reduced in the conservative arm (P=0.06). These results were confirmed in a post hoc subgroup analysis which focused on surgical patients more likely presenting under-resuscitation or therapeutic dehydration [5].

However, the brain dysfunction has been recently recognized as a possible risk of conservative fluid strategy in ARDS patients, as reported in a further post-hoc analysis of the FACTT trial [*6]. Out of 406 eligible survivors, 122 subjects were tested within one year for cognitive and psychiatric morbidity. The authors found that both hypoxemia and conservative strategy were independently associated with long term neuropsychological impairment. In our opinion, as every post hoc analysis, this one too is an interesting hypothesis generator and the data must be confirmed in a larger population sample.

To date, all the randomized trials evaluating fluid management strategies in mechanically ventilated patients in intensive care unit found that the conservative fluid management improved oxygenation and shortened mechanical ventilation [4,7-9].

Without exception all the restrictive strategies rely on high dosage furosemide to achieve and maintain diuresis. The possible impact of acute kidney failure, however, has not been evaluated. A recent post-hoc analysis of the FACTT trial patients investigated whether positive fluid balance and diuretic therapy, after acute kidney failure are independently associated with mortality in patients with ARDS. Three-hundred six patients previous enrolled in FACTT trial who developed acute kidney failure within the first 2 days were analyzed [10]. Hundred-thirty-seven were in the fluid-liberal arm and 169 in the fluid-conservative arm (P=0.04). The authors found, in all the analysis they performed, that positive fluid balance was significantly associated with mortality. To be noted, although in the crude analysis high dosage furosemide was associated with better survival, this association appeared to be mediated by the fluid balance which remained the strongest predictor of outcome.

The definition of acute kidney failure, however, relies, in part, on the creatinine levels which, in turn, may be affected by the fluid balance. To assess whether the fluid accumulation may delay the recognition of acute kidney injury by diluting the creatinine levels, another interesting analysis of the FACTT trial was published in 2011 [11]. The main result of this study was that, depending on the correction of creatinine levels, the conservative strategy was associated with significantly higher incidence of acute renal failure (no correction of creatininemia) or with significantly lower incidence of acute renal failure (correction of creatininemia). Although the concept is appealing, in our opinion, the algorithm for creatinine correction, is questionable as it relies on several assumption.

To address the question whether a conservative fluid management strategy in the perioperative management of lung resection patients is associated with a reduced incidence of postoperative ARDS in the recovery period, Evens and Naidu reviewed fourteen paper out of sixty-seven found through a medline search [*12]. Two retrospective case-control studies showed a direct positive association between liberal fluid intake and the incidence of ARDS. In fact, the patients who did not develop ARDS following lung resection had lower intraoperative fluid infusion volume [1.22 l (1.17–1.26) vs 1.68 l (1.46–1.9) P = 0.005], lower postoperative fluid balance [1.52 l positive (1.44–1.60) vs 2.0 l positive (1.6–2.4) P = 0.026] and lower overall fluid infusion [2.0 ml/kg/h (1.7–2.3) vs 2.6 ml/kg/h (2.3–2.9) P = 0.003]. On this best evidence, the authors recommend intra-and postoperative maintenance fluid to be administered at 1–2 ml/kg/h and that a positive fluid balance of 1.5 l should not be exceeded in the perioperative period. The authors conclude that, if the fluid balance exceeds this threshold, a high index of suspicion for ARDS should be adopted and escalation of the level of care should be considered. In our opinion, there is always a risk in defining with a single number a safety threshold, however this study further supports the concept that fluid overload may be an important additional cause for edema

development, particularly in patients after major surgery in whom the mechanism of water/salt retention are generally activated.

The possible importance of fluid retention “per se” in dictating outcome was also tested in a post hoc analysis in 313 children with [13]. Positive fluid balance (in increments of 10 mL/kg/24 h) was associated with a significant increase in both mortality and prolonged duration of mechanical ventilation, independent of the presence of multiple organ system failure and the extent of oxygenation defect. These relationships remained unchanged when the subgroup of patients with septic shock (n = 39) were excluded.

So far we discussed the fluid management focusing on the amount infused instead of the fluid composition (different crystalloids solutions, starches, albumin, gelatin). This issue has been highly debated in the recent years but mostly concentrated on patients with severe sepsis or septic shock [14-17]. Most of these patients, however, may present ARDS. Therefore, although specific studies are scanty, some of the issues raised is severe sepsis and septic shock for fluid management should be considered also for ARDS which, in our opinion, in nothing else that “organ confined severe sepsis”. The pro- and con- of the different solutions have been nicely reviewed elsewhere [**18].

In a non-septic model of experimental ARDS in pigs, induced by lung lavage associated with high tidal volume ventilation, 25% of the estimated blood volume was drawn while initiating protective ventilation [19]. Thereafter, animals were randomly assigned to be resuscitated with Ringer Acetate, Gelatin-Polysuccinate or Hydroxy-Etil-Starch (6% 130/0.42). In this model of ARDS the intravascular volume expansion with starches led to less lung damage than ringer acetate

and less kidney damage than gelatin. The results of this study are in sharp contrast with the current thinking which pose the starches at possible greater level of danger than crystalloids in sepsis [14]. However, it must be emphasized that this model of ARDS (lung lavage associated 40 ml/Kg tidal volume for about 4 hours) is mostly due to a surfactant depletion where capillary permeability and glycocalix are likely conserved. In fact, the needed amount of ringer lactate (2500 ml) were about 3 folds than gelatin (704 ml) and starches (837 ml), indicating an intact permeability barrier. Actually in human severe sepsis and ARDS the amount of crystalloids or colloids needed to reach similar hemodynamics are near similar [16]. Therefore, in our opinion, it is very difficult to translate the results in human ARDS scenario.

Enhancing edema clearance

The most rough attempt to decrease the lung water is the use of high dosage furosemide and/or hemofiltration. The inherent risk of these maneuvers is to induce organ hypoperfusion, including kidney failure instead of reducing the lung edema. Allyn et al. [*20] tried to find an index which could safely guide the edema-clearance by furosemide or hemofiltration before inducing organ hypoperfusion. They designed a prospective and observational study to evaluate the possibility of an echocardiography/echodoppler index (E/Ea ratio) [21,22] to predict the tolerance of negative fluid balance in patients with ARDS. This index is the ratio of the mitral inflow E wave to early diastolic mitral annulus velocities and is a marker of left ventricular filling pressure. Forty-five ARDS patients were enrolled. Echocardiography was performed before inducing negative fluid balance and again after 24 hours. Tolerance of negative fluid balance was evaluated by the presence of hypotension, acute kidney injury, or need for fluid expansion. Two patient groups were obtained (tolerating (65%) and not tolerating (35%) negative fluid balance). Negative fluid balance was 1950 [1200-2200] ml within 24 hours in the tolerant group. After univariate and multivariate logistic regression analyzes, 2 criteria were independently associated with poor tolerance: mitral

inflow E wave to early diastolic mitral annulus velocities ratio (E/Ea ratio; odds ratio, 2.02 [1.02-4.02]; P = .04) and weight gain (odds ratio, 1.2 [1.03-1.4]; P = .02). The area under receiver operating characteristic curves was 0.74 for E/Ea and 0.77 for weight gain. According to the results obtained, the authors concluded that the ratio of E/Ea accurately predicts tolerance of negative fluid balance in patients with ARDS. This study suggests that there is some space for an attempt to the lung edema clearance when the hydrostatic component is also present. In this particular study the reduced E/Ea ratio suggests a cardiac dysfunction which may be, in part, mitigated by volume depletion. The approach to artificial clearing of edema, however, must not be oversimplified as a possible cardiac dysfunction is only one part of the problem.

A second possibility to accelerate the lung edema clearance is to use albumin to promote the water movement from the interstitial to the intravascular space by raising the oncotic pressure associated/followed by the use of furosemide to remove the excess of water from plasma. Martin et. al [8] were the first to promote this technique in hypoproteinemic ARDS patients. The patients treated with albumin and furosemide showed, compared to controls, improvement of oxygenation with better hemodynamic and fluid balance. The results were successively confirmed in a trial comparing the efficacy of furosemide plus albumin compared with furosemide alone [9]. It is important to stress, however, that both studies excluded patients with hemodynamic instability and/or cardioactive drugs suggesting that the full-blow phase of ARDS was already overcome in the enrolled patients. In an editorial accompanying the first study [23] we computed that this technique accelerates the edema clearance, as estimated by the amount of diuresis and the improvement of the oxygenation index, by 3 to 4 days compared to its natural evolution. Actually, this technique requires a near intact or a newly restored lung capillary permeability. In normal lung the reflection coefficient for albumin is approximately 0.6; it is possible that this level is necessary to restore the normal intravascular/interstitial equilibrium. In full ARDS, as well as in severe sepsis or septic

shock, the reflection coefficient is close to zero making the use of albumin as oncotic agent more a wishful dream than a reality.

To specifically determine the effects of colloid therapy compared to crystalloids on mortality and oxygenation in adults with ARDS a systematic review and meta-analysis has been published [24]. Unfortunately only 3 randomized controlled trials out of 4130 potential trials found in the databases could be selected. In the 206 patients analyzed, the authors found an improved oxygenation with albumin without survival benefit. It is difficult, in our opinion, to make any conclusion from this kind of analysis but that, as the author also suggest: "further studies are necessary".

Finally, an appealing way to enhance the edema clearance is the use of beta-agonists to pump sodium (and water) out of the alveoli. Perkins et al [25] were the first to demonstrate that the infusion of salbutamol compared to placebo for 7 days in ARDS patients was able to reduce significantly the extravascular lung water with improvement of oxygenation and respiratory mechanics although outcome benefits were not shown. Unfortunately, the promises were not maintained in successive trials. In fact, a trial of 326 ARDS patients, intubated and mechanically ventilated randomly assigned to salbutamol or placebo was terminated early due to excess mortality in the group receiving IV salbutamol [26]. In addition the ALTA trial (Albuterol Treatment for Acute Lung Injury) [27], comparing aerosolized albuterol or saline/placebo failed to demonstrated difference in ventilator free days and was stopped early for futility.

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