Fluid management in Acute Respiratory Distress Syndrome: A narrative review

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INTRODUCTION

Since its initial description in 1967 by Ashbaugh et al. [1], Acute Respiratory Distress Syndrome (ARDS) remains a serious and frequent challenge in modern intensive care units. Despite great improvement in management, mortality and morbidity continues to be significant [2], with mortality of 45% in the severe form [3]. Newer therapeutic modalities are needed, requiring better understanding of the underlying pathophysiology as well as better refinement of the tools currently at our disposal.

One of the interventions used in the management of ARDS patients is fluid therapy. This therapy poses a special dilemma as a double-edged sword. On one hand, it is frequently needed in patients with ARDS, particularly when evidence of hypoperfusion exists. On the other hand, fluid infusion and resultant volume overload leading to pulmonary edema can exacerbate the pre-existing gas exchange abnormalities.

This review includes a general overview of the management of ARDS, with a focus on fluid management. We review the underlying pathophysiology and its effect on fluid movement across the alveolar-capillary membrane, as well as the large trials that addressed the optimal fluid therapy in this syndrome.

DEFINITION AND CLINICAL PICTURE

After two decades of using the 1994 American/European Consensus Conference definition of ARDS [4], a new, revised definition was adopted [3]. Known as the Berlin definition, it requires that ARDS develop within 1 week of a known clinical insult, with bilateral radiographic opacities. The pulmonary opacities must not be related only to mechanical ventilation. Bilateral radiographic infiltrates are present, frequently indistinguishable from those seen in cardiogenic pulmonary edema [11]. Computed tomography most often reveals consolidation with alveolar filling, predominantly in the dependent zones [12]. In later stages, interstitial opacities with bullae formation may also develop. Complications may include pulmonary hypertension, right ventricular failure [13], and the development of pneumothorax [14].

Acute Respiratory Distress Syndrome remains a major source of morbidity and mortality in the modern intensive care unit (ICU). Major advances in the understanding and management of this condition were made in the last two decades. The use of low tidal ventilation is a well-established therapy. Conservative fluid management is now another cornerstone of management. However, much remains to be understood in this arena. Assessing volume status in these patients may be challenging and the tools available to do so are far from perfect. Several dynamic measures including pulse pressures variation are used. Ultrasound of the lungs and the vascular system may also have a role. In addition, the type of fluid to administer when needed is still open to debate. Finally, supportive measures in these patients, early during their ICU stay and later after discharge continue to be crucial for survival and adequate recovery.

Key Words: acute lung injury; fluid replacement; mechanical ventilation

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Pathophysiology

Hydrostatic and oncotic pressures across the capillary wall govern fluid movement between the capillary and the interstitial space, as described by the Starling's equation:

\[ Q_f = K_f [(P_C - P_I) - \sigma (\pi_C - \pi_I)] \]

where \( Q_f \) is flow across the membrane, \( K_f \) is capillary filtration coefficient, \( P_C \) is capillary hydrostatic pressure, \( P_I \) is interstitial hydrostatic pressure, \( \sigma \) is oncotic reflection coefficient, \( \pi_C \) is capillary colloid osmotic pressure, and \( \pi_I \) is interstitial colloid osmotic pressure.

These pressures dictate the direction and the amount of fluid movement. In general, the net force favors ultrafiltration at the arteriolar end of the pulmonary capillaries, whereas reabsorption typically occurs at the venular end. Accumulated fluid in the interstitium is removed by the lymphatic system. In addition, tight junctions between the alveolar epithelial cells normally act as a barrier preventing alveolar flooding.

Based on the above, an increase in the capillary hydrostatic pressure or a disruption in the integrity of the alveolar–capillary membrane (with increased permeability) may result in interstitial and alveolar flooding. ARDS is an example of the latter, characterized by alveolar edema/flooding that occurs in the presence of normal capillary hydrostatic pressure. The flat type I cells (typically making up 90% of the alveolar surface area) are injured. The cuboidal type II cells, typically more resistant to injury, would eventually differentiate into type I cells, restoring the normal alveolar architecture if the ARDS resolves [13]. The membrane injury results in massive amount of fluid and plasma proteins leaking into the alveolar space, with subsequent formation of hyaline membranes. Fluid removal from the alveolar space is also impaired.

Activated inflammatory cells, primarily macrophages and neutrophils, accumulate in the interstitium. Proinflammatory cytokines, including interleukin (IL)-1β, IL-8, and tumor necrosis factor (TNF)α, are also released into the lungs [15, 16] and are thought to play a role in the cellular response and microvascular injury as well as the extra pulmonary organ failures seen in ARDS [16].

Surfactant activity and composition is also affected, resulting in elevated surface tension and alveolar collapse [17], decreased lung compliance [18], impaired gas exchange, and increased pulmonary arterial pressures [19, 20].

Interstitial inflammation and fibrosis become the dominant pathologic findings by day 7. In a subset of patients, pulmonary fibrosis develops. It appears the presence of such fibrosis closely correlates with mortality in established ARDS [21].

General management

Recognition and treatment of the underlying etiology, such as infection, should always be a priority. In addition, adequate nutrition and prophylaxis against thromboembolic events should be considered [22].

Mechanical ventilation

The vast majority of ARDS patients require endotracheal intubation and mechanical ventilation, primarily to correct the severe hypoxemia encountered in this setting. Special attention should be paid to tidal volume to avoid ventilator-induced lung injury.

Based on a large ARDSnet study (861 patients) [23], comparing tidal volumes of 12 and 6 mL/kg of predicted body weight (plateau pressure ≤ 30 cm of H2O, low tidal volume is now considered the standard of care in patients with ARDS. In this study, mortality was lower in the group treated with 6 mL/kg (31.0% vs. 39.8%, p = 0.007). In a porcine model of pulmonary edema, low tidal volume (6 mL/kg) was associated with lower extravascular lung water (EVLW), as measured by the double indicator method, compared with a tidal volume of 12 mL/kg [24].

Analyzing data from nine randomized trials, Amato et al. [25] found that the driving pressure, defined as the ratio of the tidal volume and the respiratory-system compliance, correlated best with survival in ARDS, even in patients receiving protective ventilation. This suggests that the driving pressure may be a better therapeutic target in future trials.

The use of low tidal volume may result in CO2 retention and respiratory acidosis. This permissive hypercapnia can be managed with a higher respiratory rate.

Positive End Expiratory Pressure (PEEP) is used primarily to improve oxygenation, by increasing the functional residual capacity, preventing small airways and alveoli from collapsing, and improving the ventilation–perfusion (V/Q) matching [26–28]. The effect of PEEP on the EVLW as measured by transpulmonary thermodilution appears to be mild or negligible [29]. Side effects associated with PEEP are primarily circulatory depression and barotrauma.

Several trials were conducted to determine whether higher levels of PEEP are associated with better outcomes [30–32]. No mortality difference was seen in these trials, suggesting that the lowest PEEP associated with acceptable oxygenation and airway pressure may be used. Nevertheless, the 2016 Surviving Sepsis Campaign guidelines suggest using higher PEEP over lower PEEP in adults with sepsis-induced moderate to severe ARDS (weak recommendation, moderate quality of evidence) [33].

Finally, a recent trial showed worse outcome with a strategy that included lung recruitment and titrated PEEP according to respiratory system compliance compared with a strategy of low PEEP [34].
Prone position
The use of prone position in moderate to severe ARDS results in oxygenation improvement [35, 36]. The reasons for this improvement are unclear [16, 37, 38], but they likely include an increase in lung volume with a decrease in the amount of atelectasis and shunt fraction, better V/Q mismatch, and release of the effect of the heart weight on the left lung. Interestingly, a small study found that the ETLW index measured by the transpulmonary thermodilution technique increased after proning (12.7 ± 4.7 vs.14.8 ± 7.8 mL/kg), but the increase remained of no clinical relevance [39]. Although early studies did not show an effect on mortality [40, 41], a more recent trial in patients with severe ARDS (PaO$_2$/FiO$_2$ < 150 mm Hg) showed a lower 28-day mortality when prone position was used for at least 16 consecutive hours [42]. Based on that, current evidence supports its use in severe ARDS, including patients with sepsis-induced ARDS and a PaO$_2$/FiO$_2$<150 mm Hg [33].

Other supportive therapies
Inhaled Nitric Oxide (iNO), a powerful vasodilator, improves the ventilation–perfusion mismatching, with a dose-dependent improvement in oxygenation [43]. In a small animal model of acute lung injury, iNO reduced edema formation secondary to fluid resuscitation [44]. Its use in ARDS was evaluated in multiple clinical trials [45–48]. The results are consistent with improvement in oxygenation, with no firm effect on mortality. As with any other salvage therapy, iNO may be considered in patients with refractory hypoxemia, keeping in mind the potential for side effects and the fact that any benefit is likely time limited.

Iloprost, a stable prostaclin analogue, improves gas exchange in patients with ARDS and pulmonary hypertension [49]. However, unlike iNO, iloprost did not attenuate lung edema in an ovine model of lung injury [50].

The use of steroids in ARDS remains one of the most controversial issues. Over the last few decades, studies have reached different conclusions when assessing the effect on mortality [51–55]. Recent guidelines from the Society of Critical Care Medicine and European Society of Intensive Care Medicine suggest their use in patients with early moderate to severe ARDS (PaO$_2$/FiO$_2$ < 200 mm Hg and within 14 days of onset) (conditional recommendation, moderate quality of evidence) [56]. Any possible benefit should be weighed against the potential for adverse effects, including infections and neuromuscular weakness.

Extracorporeal Membrane Oxygenation (ECMO) uses an extracorporeal circuit to directly oxygenate and remove CO$_2$ from the blood [57]. It can be used as salvage therapy in patients with severe ARDS, but well-designed controlled trials showing clear survival benefit are lacking. A recent international trial showed that in patients with very severe ARDS, the 60-day mortality was not significantly lower with ECMO compared with a conventional mechanical ventilation strategy that included ECMO as salvage therapy [58]. More studies are needed to define ECMO’s potential role in ARDS.

High-frequency oscillatory ventilation, delivering very small tidal volumes at very high rates, was studied in ARDS. Based on a trial showing that in moderate-to-severe ARDS, its early application did not reduce, and may increase, inhospital mortality; its use cannot be recommended in ARDS [59].

Neuromuscular blockade in ARDS results in improved oxygenation. A 2010 French trial found that the early use of Cisatracurium in severe ARDS (onset within 48 h) improved the adjusted 90-day survival without increasing muscle weakness [60]. More studies are needed to confirm this finding and to determine whether this survival benefit is seen with other neuromuscular blocking agents.

Edema clearance is dependent on active Na transport, with water following the Na gradient [61]. In hydrostatic pulmonary edema, fluid clearance is usually maximal or submaximal in a majority of patients compared with ARDS [62]. Therefore, enhancing fluid removal from the airspace in ARDS is another attractive therapeutic modality. This process can be upregulated by catecholamine-dependent and independent mechanisms [63], including beta-2 adrenergic agonists. A single-center small randomized trial found that treating ALL/ARDS patients with intravenous salbutamol resulted in lower lung water and plateau pressure [64]. However, in another ARDS network trial, aerosolized albuterol (5 mg, every 4 h up to 10 days) was compared with saline placebo in patients with ALL [65]. No improvement in clinical outcomes was seen with albuterol in this trial. Therefore, the routine use of beta2-agonists in these patients for the sole purpose of alveolar edema clearance cannot be recommended.

Fluid management and responsiveness
Fluid management in ARDS is a complicated and delicate issue. Frequently, these patients require fluid administration, such as in cases of sepsis or septic shock. However, the underlying pathophysiology of normal pressure pulmonary edema makes it evident that fluid administration may increase the left atrial and pulmonary venous pressures, can worsen the alveolar flooding, decrease the PaO$_2$/FiO$_2$; therefore, it needs to be performed with close monitoring of the gas exchange and hemodynamic parameters. On the other hand, studies showed that induced hypotension, accompanied by a reduction in the cardiac output and the pulmonary blood flow (as seen during hemorrhagic shock), results in increased alveolar and physiological dead space [66]. This leads to worsening gas exchange, with an increase primarily in the PaCO$_2$. In addition, therapy and/or conditions that result in the lowering of the pulmonary arterial pressure, such as vasodilator treatment for pulmonary hypertension, typically increase the intrapulmonary shunting and worsen hypoxemia [67]. This suggests that maintaining adequate volume status in these patients is paramount.

Accurate determination of the intravascular fluid status and the degree to which impaired cardiac function is contributing to the oxygenation issues is difficult to obtain clinically. Chest X-ray and blood gases are of limited value for quantifying pulmonary edema [68]. Balancing the two competing priorities (tissue perfusion and tissue oxygenation) is often challenging. Therefore, finding the optimal intravascular volume-pressure with the best risk–benefit ratio is difficult.

Optimal volume status
The optimal intravascular volume maintains adequate tissue perfusion while minimizing alveolar flooding. Theoretically, if ARDS patients are kept dry, improvement in the pulmonary status including gas exchange could potentially result in improved outcomes. In fact, some retrospective studies suggested that this is indeed the case [69–72]. Alsous et al. [69] showed that in patients with septic shock, at least 1 day of negative fluid balance in the first 3 days was associated with better survival when adjusted for age, APACHE II scores, SOFA scores on days 1 and 3, and the need for mechanical ventilation. Five patients also had ARDS/ALI by day 3 [69]. In another retrospective analysis a decade earlier, Humphrey [70] found that lowering the pulmonary artery wedge pressure (PAWP) was associated with increased survival in ARDS. Using logistic regression analysis, Simmons et al. [71] found an association between weight loss and negative fluid balance and survival in ARDS. Another observational study based on prospectively collected data found that excessive fluid administration in trauma-related ARDS patients was associated with increased mortality [72]. Independent variables in this study included demographics, severity score, injury-admission delay time, first 24-h transfusion, and septic and organ failure complications. These studies were not prospectively randomized and included patients with different definition of ARDS.

A large prospective, randomized controlled trial compared conservative and liberal fluid management strategies in 1000 patients with ALI [73]. Patients were simultaneously randomized to receive either a pulmonary–artery catheter or a central venous catheter. Management was based on four variables: central venous pressure (CVP) or PAWP, depending on catheter assignment, the presence or absence of shock, oliguria, or ineffective circulation. Fluids, diuretics, or inotropic agents were used to achieve the desired variables. During the first 7 days, the mean cumulative fluid balance was -136 ± 491 mL in the conservative strategy group and 6992 ± 502 mL in the liberal strategy group.
As compared with the liberal strategy, the conservative strategy had improved oxygenation index, lung injury score, and number of ventilator-free days. There was no difference in shock, use of dialysis, or in the primary outcome of 60-day mortality (25.5% in the conservative-strategy group vs. 28.4% in the liberal-strategy group, \( p = 0.30 \)). In addition, the percentage of patients receiving vasopressors did not differ significantly between the two groups. Overall, it was felt that these results support the use of a conservative fluid management strategy in patients with ALI.

Assessing volume status/fluid responsiveness

CVP/PAWP

CVP and the PAWP have traditionally been used to guide fluid management in a variety of clinical scenarios, including ARDS. However, one has to remember that the relationship between these pressures and the cardiac preload is variable [74]. And even though measuring these pressures to guide therapy could theoretically result in outcome improvement, there is a very poor relationship between CVP and blood volume, and the CVP does not predict the hemodynamic response to fluid challenge [75].

Despite the central venous catheters (CVC) limitations in this setting, Wheeler et al. [76] compared its benefits and risks to those of pulmonary-artery catheters (PAC) in ALI. PAC-guided therapy did not improve survival or organ function but was associated with more complications than CVC-guided therapy, predominantly arrhythmias. Other PAC complications included air embolism, catheter malfunction and insertion-site bleeding. This suggests that PAC should not be routinely used for the management of ALI.

Pulse pressure variation

Pulse pressure (PP) is the difference between the systolic and diastolic pressure, and it reflects the ventricular stroke volume. Pulse pressure variation (PPV) is the difference between the maximal (PPmax) and the minimal values (PPm) divided by the mean value over a single respiratory cycle (Figure 2). Appropriate measurement requires a tidal volume \( \geq 8 \text{ mL/kg} \), the presence of sinus rhythm, and the absence of spontaneous triggering of the ventilator. This variation during positive pressure ventilation is thought to depend on the patient’s position on the Frank-Starling curve, with fluid-responsive patients being on the steep part of the curve. Patients who are fluid responsive are expected to have a significant PPV while mechanically ventilated (>10–12%) [77]. However, its value in ARDS patients treated with protective ventilation is poor, partly owing to insufficient changes in the pleural pressure [78]. Other factors limiting its performance include the presence of arrhythmia or the presence of spontaneous respiratory efforts.

Lung/central vascular ultrasound

Lung ultrasound represents a relatively new modality to assess the EVLW, using reverberation artifacts (B lines) arising from the pleural line (Figure 3), which are believed to originate from interlobular septal thickening caused by fluid [79]. The presence of these B lines was not found to be predictive of the PAWP [80]. This is not surprising since pulmonary edema can result from cardiogenic as well as non-cardiogenic etiologies. On the other hand, the presence of horizontal reverberation pattern (A lines) was found to predict a low PAWP (<18 mmHg) with a sensitivity and specificity of 50% and 93%, respectively [80].

A B-line score (BLS) aimed at measuring the EVLW was found to correlate with radiological EVLW scores in patients admitted to the medical and cardiac intensive care units [81]. In patients undergoing hemodialysis (HD), the BLS measured 1 h after HD decreased by 2.7 B-lines for each 500 mL removed (\( p = 0.02 \)) [82], indicating that lung ultrasound can be used as a repeated measure to track the resolution of pulmonary edema related to hypervolemia. In another study, patients with high altitude pulmonary edema were found to have a higher BLS score compared with control subjects (31 ± 11 vs. 0.86 ± 0.83), and their oxygen...
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Fluid type

Studies assessing the optimal fluid type to be used specifically in ARDS are lacking. In the ARDS network trial comparing conservative and liberal fluid strategies, although the protocol specified the volume of fluid to be administered, clinicians were free to select any type of fluid including: isotonic crystalloid, albumin, or blood products [73]. Hydroxyethyl starch (HES, 6%) was compared with 0.9% saline for resuscitation in a large ICU population [91]. The study did not specify the proportion of patients with ARDS. No difference in the 90-day mortality was seen between the two groups, but more patients in the HES needed renal-replacement therapy. In a meta-analysis of critically ill patients requiring volume resuscitation, hydroxyethyl starch was associated with a significant increased risk of mortality and acute kidney injury [92]. Therefore, its use is not recommended due to serious safety concerns.

In another open-label trial, patients with severe sepsis were randomized to receive either 20% albumin and crystalloid solution or crystalloid solution alone [93]. Even though the protocol did not specify the proportion of patients with ARDS, the majority (around 80%) required mechanical ventilation at baseline. Patients in the albumin group had a higher mean arterial pressure and a lower net fluid balance, but the 28- and 90-day mortalities were similar. In an earlier double-blind trial, 4% albumin was compared with normal saline for intravascular-fluid resuscitation in a heterogeneous group of ICU patients [94]. Similar outcomes (including mortality) were seen at 28 days. In addition, no mortality difference was seen in the pre-specified subgroup of patients with ARDS (RR 0.93, 0.61–1.41). Finally, a large meta-analysis found no evidence that colloids reduce the risk of death compared with crystalloids in patients with trauma, burns, or following surgery [95].

Based on these data, albumin does not appear to be superior to crystalloid and HES should be avoided when administering fluid to ARDS patients.

Blood transfusion aiming at increasing oxygen delivery was studied. Patients with septic shock were randomized to receive transfusion when the hemoglobin level was 7 g per deciliter or less or 9 g per deciliter or less [96]. Approximately 70% of the patients were mechanically ventilated at baseline, but no specific data were given on ARDS. Mortality at 90 days was similar between the two groups, suggesting that a conservative transfusion strategy may be appropriate in patients with ARDS, at least in those with underlying septic shock. Another study found that in critically ill patients, a restrictive transfusion strategy is at least as effective as a liberal one (possibly superior), with the potential exception of acute myocardial infarction and unstable angina [97]. Based on this, a conservative transfusion strategy appears to be the appropriate one in the ARDS population.

Prognosis and outcome

The outcome of patients with ARDS depends primarily on the underlying cause of lung injury. Survival to home discharge appears to be lower in patients with sepsis and highest in patients with ARDS secondary to trauma [98]. Other predictors of death include age, severity of hypoxemia, and APACHE score.

Historically, the mortality ranged from 40% to 60%, with the majority of deaths being related to sepsis and non-respiratory organ dysfunction [13]. More recent reports suggest that the mortality may be decreasing [23, 30, 31, 99]. Reasons for this improvement are not entirely clear, but they are likely related to the use of low tidal volume, better supportive care, and better management of sepsis.

CONCLUSION

ARDS continues to be a major challenge facing the 21st century critical care clinician. Major advances have been achieved in the last few years in understanding the pathophysiology of the syndrome, but translating this knowledge into improved outcomes has been more difficult. The use of low tidal volume, and prone position in severe cases, are the only interventions known to be unequivocally effective in reducing mortality. Fluid management of these patients remains an area of great uncertainty. Frequent competing priorities (e.g., hypoxia and hypotension) co-exist, making this management very difficult and risky. In general, a conservative fluid strategy appears to be beneficial, without major side effects. Therefore, unless aggressive resuscitation is needed to restore a depleted intravascular volume, we recommend keeping these patients on the dry side. If fluids are to be given, one has to closely monitor the patient’s hemodynamics, gas exchange, and respiratory mechanics, both for benefits and potential side effects. In experienced hands, lung ultrasound can provide evidence of worsening edema. Pressors may be used if fluids cannot be administered, particularly when gas exchange is limited. The optimal type of fluids is not well established, but it appears that the use of hydroxyethyl starch should be discouraged owing to the risk of renal failure. Crystalloids may be considered the first choice fluid for resuscitation, unless there is a specific indication for the use of colloids. Finally, since no single method is independently good enough to guide the fluid/pressor management, the clinician has to combine several clinical, laboratory, and radiographic parameters to do so.

It is very encouraging that the quality of clinical trials in ARDS has improved over the last 2 decades. However, further studies are still needed to improve our understanding of this syndrome, especially in the
arena of fluid and hemodynamic management, to translate that into better outcome.

**CONTRIBUTION**

All authors have contributed to this review. All authors take responsibility for the integrity of the work as a whole, from inception to published article.

**DISCLOSURE**

None of the authors has a relationship to any organization with a direct financial interest in the subject of this manuscript. None of the authors has any conflict of interest to disclose.

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