



Fluid management in acute respiratory distress syndrome

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Purpose of review

Fluid management is one of the most important measures shown to impact acute respiratory distress syndrome (ARDS) outcomes. This review summarizes the current strategies aimed at evaluating and modulating lung fluid balance.

Recent findings

Multiple recent studies have shown that a conservative fluid management in ARDS patients had beneficial effects on morbidity and mortality. These findings were replicated also in different patient populations assumed to have potential deleterious effects from this approach. So far, only one retrospective study raised the possibility of impaired cognitive function in ARDS patients managed with a conservative fluid strategy. Thermolulution methods and serum biomarkers can be used to monitor lung fluid balance and guide therapy. Recent evidence has indicated significant detrimental effects associated with beta-2 agonists use in ARDS, despite a putative beneficial role in the resolution of alveolar edema seen in preliminary studies.

Summary

Dynamic monitoring of lung fluid balance needs to be implemented to guide fluid therapy in ARDS patients. A conservative fluid strategy seems safe and yields overall good clinical outcomes, but its impact on cognitive function needs to be evaluated in further studies. The role of colloids and other pharmacological agents deserves further investigation.

Keywords

acute respiratory distress syndrome, conservative fluid management, extravascular lung water

INTRODUCTION

The acute respiratory distress syndrome (ARDS) affects around 200 000 people in the United States [1], with highly variable incidences reported world-wide.

Almost half a century after the initial description of ARDS [2], finding a cure for it remains an elusive goal. Since its initial description, great strides have been done in understanding the pathophysiology of ARDS. Interestingly, the mortality has been steadily decreasing over the last decades, most likely as a consequence of preventive measures, improved recognition with prompt management, and better ICU care overall [3]. Few milestones have marked the treatment of ARDS, the most important being the significant decrease in mortality after using a protective, low tidal volume ventilation [4]. Another important milestone was that a conservative fluid management improves the duration of mechanical ventilation in patients with ARDS without any other significant associated morbidity [5]. The aim of this review is to further dissect the effects of fluid management on ARDS outcome.

CURRENT ACUTE RESPIRATORY DISTRESS SYNDROME DEFINITION AND ITS IMPLICATIONS FOR CLINICAL MANAGEMENT AND RESEARCH

Over the years, multiple ARDS definitions tried to emphasize the basic clinical and pathological characteristics of this entity: acute onset after a specific cause, hypoxemia, radiologic infiltrates, increased permeability, proteinaceous pulmonary edema, and lack of hydrostatic pressure as cause. In 1994, the American–European Consensus Conference proposed a definition that was vastly adopted by clinicians and researchers worldwide [6]. However, almost like any other definition, it drew criticism for a variety of reasons. To eliminate

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KEY POINTS

- EVLW monitoring is a useful tool to guide fluid management in ARDS.
- Conservative fluid management is beneficial in ARDS patients without hemodynamic instability.
- Beta-2 agonists should not be routinely used in ARDS.
- A potential benefit from the use of colloids exists, but larger clinical studies are needed.

some of the ambiguities in the old definition, the European Society of Intensive Care Medicine, endorsed by the American Thoracic Society and the Society of Critical Care Medicine, convened a panel of international experts that proposed a new set of criteria that will most likely be known as the Berlin definition [7[¶]]. The Berlin definition of ARDS eliminated the term ‘acute lung injury’ (ALI) as a potential source of confusion for an entity having the same pathophysiologic mechanisms. More importantly, based on previous data it was agreed that high left atrial pressure and ARDS can coexist, but without hydrostatic edema being the sole explanation for the acute respiratory failure. This should allow the intensivists and researchers to diagnose more patients with ARDS and to use therapies aimed at both mechanisms of alveolar flooding. The same panel also emphasized the degree of hypoxemia severity as a prognostic indicator in ARDS patients. To eliminate any confusion, we will use the term ‘ARDS’ in this article for all studies involving either ALI or ARDS in the past.

LUNG FLUID HOMEOSTASIS AND PATHOPHYSIOLOGY

The hallmark alteration in ARDS is increased endothelial and epithelial permeability that leads to extravasation of fluid and other plasma constituents, albumin being the most important, in the interstitium and alveolar space, with multiple detrimental clinical consequences: hypoxemia, atelectasis and decreased lung compliance, and increased pulmonary artery pressures. These changes are triggered and maintained by a multitude of events, including increased lung inflammation and microvascular thrombosis.

Endothelial and epithelial barriers: structure and function

Lung endothelium is regarded as a continuous monolayer of cells that separates and at the same

time connects blood to the underlying lung tissue. In fact, its role is more extensive, acting almost as a veritable organ with multiple physiological, immunological, and synthetic functions [8]. At the pulmonary capillary level, the endothelial cells form a very tight barrier that restricts the movement of water, solutes, and other plasma constituents to interstitium and alveolar space. While fluid and solutes usually move passively between endothelial cells based on pressure gradients, albumin and other plasma macromolecules follow an active, energy-driven, transcellular pathway through a complicated system of vesicles [9]. The lung alveolar epithelial barrier comprises type I and II alveolar cells, interconnected by tight junctions. It is normally impermeable to protein, hence measuring the quantity of protein in the bronchoalveolar lavage in pathological conditions can be a good index of epithelial permeability [10]. The lung endothelial and alveolar epithelial cell monolayers together form the alveolar–capillary barrier.

Starling forces

Fluid movement in the lung is dictated by the alveolar–capillary barrier integrity, in combination with a fine balance between the hydrostatic and oncotic pressures on both sides of the capillary wall. For more than a century, researchers have relied on Starling’s law to explain and predict the direction of fluid movement in the lung from the capillary to the interstitium and alveoli. Figure 1 depicts the complex interplay between different forces at the alveolar–capillary barrier [11].

A recent review also created a modified Starling equation that accounts for the endothelial glycocalyx layer, the endothelial basement membrane, and the extracellular matrix, as new modulators of fluid filtration [12[¶]]. It is important to understand that along the lung capillaries, the events are more dynamic: the hydrostatic gradient favors the net ultrafiltration at the arteriolar end, whereas the oncotic gradient leads to partial fluid reabsorption at the venular end. At the same time, transudated fluid accumulates in the interstitium, where the lymphatics rapidly remove it [13]. However, increases in the left atrial pressure can impede this drainage and can also elevate the lung capillary hydrostatic pressure leading to cardiogenic pulmonary edema.

Alveolar fluid reabsorption

Immediate alveolar flooding from fluid accumulation in the interstitium is prevented by the tight junctions between the alveolar epithelial cells, and

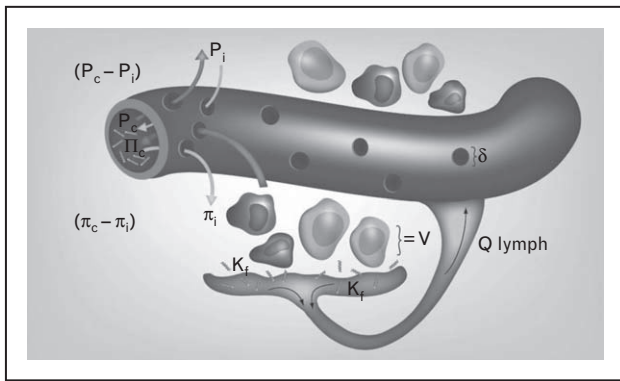


FIGURE 1. Graphic illustration of Starling's law as applied to the alveolar-capillary barrier. The Starling's equation is written as $Q_f = K_f[(P_c - P_{iF}) - \sigma(\pi_c - \pi_{iF})]$, where Q_f is flow or fluid flux across a membrane, K_f is the capillary filtration coefficient, P_c is the capillary hydrostatic pressure, P_{iF} is the interstitial hydrostatic pressure, σ is the oncotic reflection coefficient (usually 0.8 for nondamaged lung endothelium), π_c is the capillary colloid osmotic pressure, and π_{iF} is the interstitial colloid osmotic pressure. V represents the cellular component of filtered fluid; Q_{LYMPH} is the lymphatic flow. The driving forces that favor fluid filtration are P_c and π_{iF} , whereas P_{iF} and π_c oppose it. Reproduced and adapted with permission [11].

it is estimated that only perfusion pressures above 50 mmHg will lead to fluid leakage in the alveoli [13].

A large body of research has shown that the alveolar epithelium plays an important role in the resolution of ARDS. Fluid clearance from alveoli to the interstitium follows the direction of the active Na^+ transport across the type II alveolar cell [14]. The active Na^+/K^+ ATP-ase was identified as the facilitator of Na^+ transport out of the cell into the interstitium, with subsequent chloride secretion to maintain electrical neutrality. Water moves to follow Na^+ gradient, although the exact pathway is still a matter of controversy. Interestingly, alveolar fluid clearance is usually maximal or submaximal in a large majority of patients with hydrostatic pulmonary edema as compared to patients with ARDS, a finding that is correlated with better survival.

MEASUREMENT AND MONITORING OF LUNG FLUID BALANCE

Fluid therapy can be a lifesaving measure in many conditions, but lack of judicious use after the initial hemodynamic resuscitation can have detrimental consequences, pulmonary edema being a significant one. Hence, correct assessment and monitoring of fluid status seems imperative in ICU patients.

Fluid balance in ICU patients

The correct assessment of fluid status in ICU patients remains one of the greatest challenges for clinicians. This difficulty arises from misjudging common clinical parameters, missing or ignoring important data, or even misinterpreting obtained data. To illustrate this assumption, vascular pedicle width as measured by the chest radiograph was shown to have a limited role in assessing the fluid status in patients with ARDS and should not be used, unless other intravascular pressures are not available [15]. Early resuscitation with fluids seems imperative in patients with distributive shock to maintain a good intravascular volume, but an increased body of evidence suggests that unnecessary continuation of aggressive fluid resuscitation beyond the initial early goals is associated with poorer outcomes. ARDS is a frequent associated comorbidity in patients with severe sepsis or septic shock, and fluid management practices in this context can have a significant impact in ARDS outcomes [16].

Lung fluid balance assessment

One of the most important tools used to assess the lung fluid balance is extravascular lung water (EVLW). The reference method for EVLW measurement is wet-to-dry lung weight ratio, but obviously this cannot have any clinical applicability. Over the recent years, few other methods have been shown to provide good estimates of lung water. While radiologic methods like quantitative computed tomography scan, positron-emission tomography scan, and magnetic resonance imaging are usually static and of limited or no bedside availability, both double-indicator (thermo-dye) and single-indicator (thermal) dilution methods have shown a good correlation with the gravimetric analysis and can be available at bedside [17,18^{••}]. The principle behind the single transpulmonary thermodilution method is illustrated in Fig. 2.

In a recent observational cohort study [19], an EVLW over the predicted body weight index of 16 ml/kg or above was shown to have a sensitivity of 0.75 [confidence interval (CI) 0.47–0.91] and specificity of 0.78 (CI 0.61–0.89) for increased ICU mortality in patients with ARDS.

Other important parameters derived from thermodilution measurements are global end-diastolic volume and pulmonary vascular permeability indices. A retrospective study showed that a pulmonary vascular permeability index above 3 and a ratio of global end-diastolic volume index over EVLW index above 1.8×10^{-2} together had a sensitivity of 85% and a specificity of 100% in diagnosing ARDS [20].

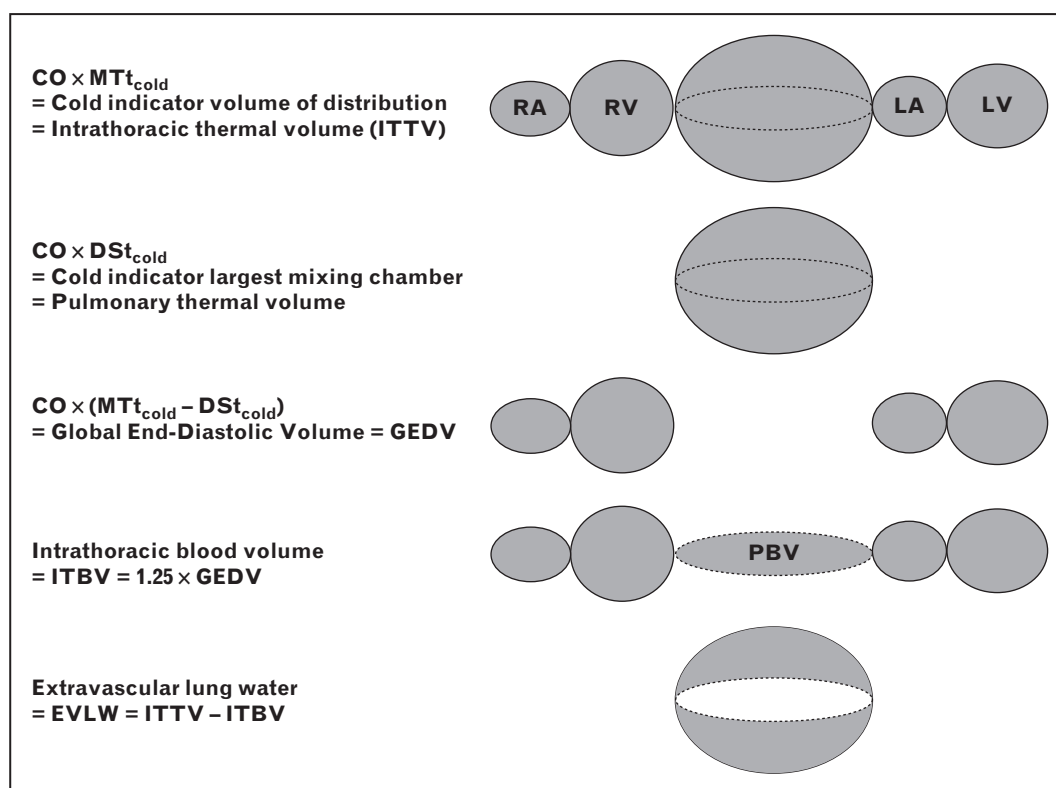


FIGURE 2. Principle behind EVLW measurement using the single thermodilution method. A thermal indicator, usually cold saline, is injected in one of the central veins, and the decay signal is detected by a thermistor in the distal aorta. The thermodilution curve will provide the mean transit time (MTt) and the down slope time (DSt). The intrathoracic blood volume (ITBV) is derived from the measurement of the global end-diastolic volume (GEDV) with the equation $ITBV = 1.25 \times GEDV$. The difference between the volume of distribution of the thermal indicator and ITBV yields EVLW. CO, cardiac output; EVLW, extravascular lung water; LA, left atrium; LV, left ventricle; PBV, pulmonary blood volume; RA, right atrium; RV, right ventricle. Reproduced and adapted with permission [17].

Special attention has also been given to evaluate the role of different biomarkers in diagnosing ARDS, establishing its severity, and monitoring the response to therapy. In one study, hypoalbuminemia (<17.5 g/l) and hypotransferrinemia (<0.98 g/l) were identified as markers of severe pulmonary vascular permeability of ARDS, irrespective of the underlying disease and fluid status [21]. Another interesting study identified that high plasma angiotensin-2 levels in noninfection-related ARDS were associated with increased mortality. A fluid conservative therapy also led to lower plasma angiotensin-2 levels, an observation explained by a possible decrease in endothelial inflammation in these patients [22*]. A recent pilot study also revealed that serum metabolic profiling using metabolomic analysis in ARDS patients receiving albumin can be a useful tool to monitor response to therapy [23].

Training the intensivists for the use of bedside chest ultrasound and echocardiography should lead to a more dynamic assessment of the extent of lung injury, cardiac function, and other conditions that

might interfere with rapid resolution of ARDS and its associated comorbidities. To illustrate this, bedside lung ultrasound was shown to be a powerful tool in experienced hands for the evaluation of lung injury and ARDS-associated conditions [24].

CURRENT MANAGEMENT STRATEGIES

On the basis of the known pathophysiologic mechanisms, we could safely postulate that limiting the forces that favor fluid filtration from the capillaries or augmenting those factors implicated in fluid reabsorption can limit fluid accumulation in the lung.

Conservative fluid management

More than two decades ago, a small retrospective study [25] that enrolled 40 patients showed that lowering the pulmonary capillary wedge pressure (PCWP) by more than 25% in patients with ARDS had a significant survival advantage as compared

with less than 25% reductions. Interestingly, all the patients included in this study had a PCWP less than 18 mmHg, were shock-free, and received diuretics, although at different doses. Shortly after, another randomized study done by a different group showed that fluid restriction guided by EVLW measurements led to significantly less ventilator and ICU days [26].

The Fluid and Catheter Treatment (FACT) trial [5] still represents the largest, multicenter study to evaluate the role of conservative fluid management in patients with ARDS. This study randomized 1000 patients to two different protocols: liberal versus conservative fluid management, based on targeted central venous pressure or PCWP. Although there was no significant 60-day mortality difference between the groups, patients in the conservative strategy group had significantly more days alive and free of mechanical ventilation, and free of the ICU. These important results did not occur at the expense of increased organ failures in these patients at 7 and 28 days. However, a recent analysis using a validated telephone-based neuropsychological test battery identified conservative fluid management as a potential risk factor for the development of long-term cognitive impairment [27[¶]]. This finding requires confirmation in further studies.

A possible assumption is that special patient populations at risk of developing ARDS or with ARDS might need a different approach to fluid management. A post hoc subgroup analysis of the surgical patients in the FACT trial replicated the findings of the initial study [28]. Until recently, only a limited number of pediatric studies analyzed the impact of different fluid strategies in children with ARDS. The latest post hoc analysis of a cohort of 313 children with ARDS revealed that increased fluid balance, in 10 ml/kg/day increments, was associated with increasing mortality (odds ratio 1.12, 95% CI 1.06–1.20, $P < 0.001$), only partially accounted for by the degree of hypoxemia at the onset of ARDS or the presence of nonpulmonary organ failures [29[¶]].

One of the limiting factors for a conservative fluid management, including diuretics administration, in ARDS patients is the possible precipitation of acute kidney injury (AKI). In an interesting analysis of the FACT trial, the presence of AKI after adjustment for fluid balance was increased in patients in the liberal arm, a finding associated also with decreased survival [30[¶]]. Another study reviewed 306 FACTT patients who developed AKI within the first 2 days of enrollment and found that positive fluid balance after the development of AKI was associated with increased mortality. Even more, higher diuretic dose after

AKI correlated with improved survival [31[¶]]. Another limiting factor is possible hemodynamic deterioration associated with fluid restriction. Hence, EVLW dynamic monitoring in conjunction with continuous cardiac output and stroke volume variation measurements seems essential to ensure perfusion of the vital organs while maximizing reductions in EVLW.

Colloids and other therapies

Hypoproteinemia was one of the first risk factors identified as leading to rapid development of ARDS in patients considered at risk [32]. Following this initial observation, two additional studies examined the benefits of albumin administration with or without the addition of furosemide in patients with ARDS [33,34]. Both studies showed improved physiological parameters in patients receiving at least albumin, but because of limited patient populations no hard clinical endpoints were demonstrated. The use of albumin or other colloids in the ICU has decreased because of prior meta-analyses and the Saline versus Albumin Fluid Evaluation study [35], which revealed no difference in mortality and other significant clinical endpoints for patients resuscitated with albumin, as compared to those resuscitated with normal saline. However, the patient population in this study was heterogeneous, making the need for large randomized studies of albumin use only in ARDS patients more imperative.

Multiple previous animal or small clinical studies had also documented the beneficial role of beta-agonists in the resolution of the alveolar edema, by potentiating alveolar fluid transport through cyclic AMP stimulation. Nevertheless, two recent clinical studies that used beta-2 agonists have produced disappointing results. One study that used inhaled beta-2 agonists was terminated early for futility [36[¶]], whereas the other study that used intravenous beta-2 agonists in ARDS patients showed significantly increased 28-day mortality in the intervention arm [37[¶]]. In consequence, routine and continuous use of beta-2 agonists, especially in the intravenous form, is not recommended.

CONCLUSION

Although the absence of a cardiac cause for pulmonary edema was eliminated from the current ARDS definition, we strongly believe that an early, correct, and dynamic lung fluid assessment is essential for a correct diagnosis and management of patients with ARDS. Fluid restriction seems to have an overall beneficial effect on ARDS-associated morbidity,

although recent data suggested a possible cognitive impairment in patients exposed to a conservative fluid management approach. Albumin or other colloids seem to have a potential benefit in patients with ARDS, but larger, prospective studies with hard clinical endpoints are needed before it becomes the standard of care.

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Conflicts of interest

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