REVIEW ARTICLE

Acute Respiratory Distress Syndrome: A Literature Review and Current Updates

Ata Mahmoodpoor[1]*, Atabak Najafi[2], Mohammad Reza Afhami[3], Mohammad Taghi Mortazavi[4], Sarvin Sanaie[5], Afshin Iranpour[6], Vahid Fattahi[7]

Acute respiratory distress syndrome (ARDS) is a complex disorder of heterogeneous etiologies characterized by a consistent, recognizable pattern of lung injury and a potentially devastating form of acute inflammatory lung injury with a high short-term mortality rate and significant long-term consequences among survivors. Recently, the new definition of ARDS has been published, and this definition suggested severity-oriented respiratory treatment by introducing three levels of severity according to PaO2/FiO2 and positive end-expiratory pressure. Supportive care, principally with mechanical ventilation, remains the cornerstone of therapy from maintaining normal physiological parameters to avoiding ventilator-induced lung injury while providing adequate gas exchange. Basic elements of this strategy consist of avoiding lung overdistension by limiting tidal volumes and airway pressures, use of PEEP with or without lung recruitment maneuvers in patients with severe ARDS. This review focuses on changes in ARDS definition, epidemiology, clinical and basic research, and current and future directions in treatment.

Keywords: acute respiratory distress syndrome; Berlin definition; pathophysiology

Acute respiratory distress syndrome (ARDS) is arapidly progressive form of acute respiratory failure characterized by severe hypoxemia and nonhydrostatic pulmonary edema. The syndrome represents a recognizable common pattern of acute alveolar capillary injury which is triggered by a wide range of primary disease processes with almost unknown etiologies. Epidemiologic studies showed that impact of this clinical syndrome is significant at ~200,000 cases per year in the US, leading to high patient morbidity and health care burden [1]. Cellular damage in ARDS is characterized by inflammation, apoptosis, necrosis and increased alveolar-capillary permeability, which lead to development of alveolar edema [2]. Since its first description in 1967 [3], there have been a large number of studies addressing various clinical aspects of the syndrome (risk factors, epidemiology, treatment) as well as studies addressing its pathogenesis (underlying mechanisms, biomarkers, genetic predisposition). Despite numerous randomized clinical trials aimed at regulating the lung inflammatory response, the only proven therapy to consistently reduce mortality is a protective ventilation strategy [4]. The risk of linking multiple etiologies as a single common pathway is an enhanced notice on the syndrome and its clinical management, with a declined view of the importance of the underlying risk factors. Specific treatments, when applied to a non-specific condition, could be expected to show variable efficacy. This might explain the relative lack of specific therapeutic interventions in ARDS to date.

Berlin Definition of ARDS

Ashbough and colleagues established ARDS as a clinical syndrome [3] that is unresponsive to usual methods of respiratory therapies and was based upon five key clinical features: (1) the presence of a defined risk factor; (2) severe hypoxemia despite administration of supplemental oxygen; (3) bilateral pulmonary infiltrates; (4) reduced lung compliance; and (5) the absence of congestive heart failure. Murray and colleagues in 1988 expanded the definition of ARDS to incorporate the risk factor, the relative acuteness of the disease process, and measures of severity like lung injury score(LIS) [5]. In 1994, a joint American-European Consensus Conference (AECC) refined the definition of ARDS to standardize clinical research trials for the disease. Despite the apparent simplicity of this definition, a number of clinical limitations are recognized [6]. Over the past 19 years of practice, the diagnostic accuracy of the ARDS definition by AECC has been questioned [7]. The reliability of the chest radiographic criteria of ARDS has been demonstrated to be moderate, with substantial interobserver variability [8-9]. In addition, the hypoxemia criterion (i.e.

From the [1]Fellowship of Critical Care Medicine, Cardiovascular Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Anesthesiology and Critical Care Department, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
[3]Anesthesiology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[4]Anesthesiology Department, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[5]Lung and Tuberculosis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
[6]Department of Anesthesiology and Intensive Care, UAE.
[7]Anesthesiology Department, Faculty of Medicine, Tabriz, Iran.
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*Corresponding author: Ata Mahmoodpoor, MD. General ICU, Shohada Hospital, El-Goli street, Tabriz, Iran. E-mail: amahmoodpoor@yahoo.com

PaO2/FiO2 <200 mmHg) can be markedly affected by the patient's ventilator settings, especially the PEEP level used [10]. Finally, the wedge pressure can be difficult to interpret and if a patient with ARDS develops a high wedge pressure that should not exclude the ARDS diagnosis in that patient. Based on these problems, the European Society of Intensive Care Medicine, American Thoracic Society and the Society of Critical Care Medicine assembled an international expert panel to revise the ARDS definition [11]; the panel met in 2011 in Berlin, and hence the new definition was coined as the Berlin definition. The aim of developing the new definition was to try and improve feasibility, reliability and predictive validity [11]. The Berlin definition was developed to achieve a more reliable definition that will facilitate case recognition and better match treatment options and clinical outcomes to severity of illness categories. Important incremental advances in this ARDS definition include: the focus on feasibility, reliability, and validity during definition development; the incorporation of an empiric evaluation process in refining the definition; and the creation of explicit examples to aid in application of the radiographic and origin of edema criteria [12]. Berlin criteria are shown in (Table 1).

Risk Factors for ARDS

There are many common etiologic risk factors for ARDS, which the AECC definition classified into direct and indirect lung injury categories as pneumonia, non-pulmonary sepsis, aspiration of gastric contents, major trauma, pulmonary contusion, pancreatitis, inhalational injury, severe burn, drug overdose, multiple transfusions or TRALI, drowning. Identification of the risk factor leading to ARDS in an individual patient, regardless of its direct or indirect nature, rather serves to guide therapy for the underlying disease leading to ARDS. Over the past decade there have been considerable trials to analyze the contribution of genetic factors that might increase the ARDS risk or associated with worst outcome. Trials showed that almost more than 30 genes have been associated with increased risk of ARDS which can regulate coagulation, inflammation, generation of reactive oxygen species, endothelial cell permeability and apoptosis [13-15]. After correcting for multiple comparisons, it was shown that the genotype of the I/D polymorphism in ACE may be a predictor of ALI/ARDS mortality in Asian populations [16]. The potential importance of environmental factors in the development of ALI/ARDS has been tested for two major factors: chronic alcohol abuse and more recently cigarette smoke exposure. Chronic alcohol abuse, increase the risk of ARDS and also multi organ failure [17]. Calfee et al showed that both active and passive cigarette smoke exposure are independently associated with the development of ALI after severe blunt trauma [18-19]. It is clear that platelets can contribute with neutrophils to the development of acute lung injury, and since cigarette smoke can alter platelet function, there may be an important link in this regard.

Table 1- Berlin definition for ARDS

	ARDS		
	Mild	**Moderate**	**Severe**
Timing	Acute onset within 1 week of a known respiratory Clinical insult or new / worsening respiratory symptoms		
Hypoxemia	200 <PaO2/FiO2 ≤ 300 with PEEP or CPAP ≥ 5 cmH2O	100<PaO2/FiO2 ≤ 200 with PEEP ≥5 cmH2O	PaO2/FiO2 <100 with PEEP ≥ 5 cmH2O
Origin of edema	Respiratory failure associated to known risk factors and not fully explained by cardiac failure or fluid overload. Need objective assessment of cardiac failure or fluid overload if no risk factor are present		
Radiologic Abnormalities	Bilateral Opacities	Bilateral Opacities	Opacities involving at least 3 quadrants
Additional Physiological Derangement	N/A	N/A	VE Corr > 10 L/min CRS < 40 ml /cmH2O

Outcome predictors

Hypoxemia and impaired excretion of carbon dioxide are the primary physiologic abnormalities in patients with ARDS which are due to V/Q mismatch and right to left shunting. Age, Acute Physiology and Chronic Health Evaluation II (APACHEII), cirrhosis, compliance and arterial PH are also considered as outcome predictors in previous studies. Trials have showed that oxygenation index ([mean airway pressure × FiO2 × 100] / PaO2) may be a superior predictor as it integrates both airway pressure and oxygenation [20-21].

Therapeutic interventions

Mechanical ventilation

Tidal volume

Correction of hypoxemia and hypercapnia are essential in ARDS management and the majority of patients with ARDS require mechanical ventilatory support. Mechanical ventilation can lead to inflammatory response to cyclic tidal alveolar hyperinflation and recruiting/derecruitting injury [22]. The cyclic overdistention produced by excessive transpulmonary pressure has been identified as one of the major determinants of ventilator induced lung injury (VILI).

Following numerous studies, the landmark ARDS Network study showed clear evidence of large mortality benefit when patients with ARDS were ventilated with a lung-protective strategy aimed at avoidance of alveolar overdistension using tidal volumes of 6 ml/kg predicted body weight with plateau pressures ≤30 cmH2O [23]. As a result of these investigations, clinical researchers began to focus on the importance of "volutrauma" as an important clinical parameter to avoid in ARDS ventilatory management. Tidal volumes in patients with ARDS should therefore be in the order of 6 ml/kg predicted body weight with plateau pressures (Pplat) <30 cmH2O, accepting pH as low as 7.15 to achieve these targets. The clinical data supporting the importance of tidal volume and Plat control in ARDS is supported by assessment of lung metabolic activity. By combining CT and PET imaging, investigators have determined that ARDS lung metabolic activity is increased in aerated regions in proportion to the tidal volume and Pplat. Pplat> 26-27 cm H20 correlate with greater lung inflammation in these well ventilated regions consistent with an injury signal. These imaging data provide further support for a lung origin to changing systemic inflammatory mediators in response to tidal volume change [24]. There are different modes for ventilator support for ARDS patients. Physicians should choose between spontaneous breathing modes with partial support or controlled modes; either a pressure controlled mode or a volume controlled one. Spontaneous breathing allows for better patient ventilator synchrony, lower sedation requirement, and better reservation of diaphragmatic function with shorter duration for mechanical ventilation [25-27]. The main disadvantage of this mode is generation of high transpulmonary pressure and tidal volumes which requires muscle relaxants for suppression. Balancing the risks between increasing sedation in order to provide lung protection and allowing spontaneous ventilation in a more awake patient is often a difficult clinical problem with limited applicable evidence. Pressure controlled ventilation allows for better patient-ventilator synchrony in that the decelerating flow pattern allows better distribution of inspired gases and lower transpulmonary pressure. On the other hand volume-controlled ventilation allows safe tidal volume [28]. Pressure regulated volume control ventilation combines the advantages of both approaches, but may be problematic when patients are making variable or intermittent inspiratory efforts. Various less conventional modes like proportional assist ventilation, neurally adjusted ventilator assist have not demonstrated to offer significant benefits over conventional modes of ventilation in ARDS [29].

PEEP

In selecting a PEEP level, physicians should consider both the target level (low, moderate, high) and the method for determining the actual numeric value of PEEP.ARMA trial investigators did not issue the role of PEEP during the study so the impact of PEEP on minimizing VILI could not be assessed. Despite the heterogenous nature of the ARDS which complicates the interaction of PEEP with injured lung, previous studies showed that higher levels of PEEP could prevent VILI independent of PEEP associated benefits to oxygenation [30]. Results of ALVEOLI trial, a follow up trial of ARMA showed that higher levels of PEEP didn't improve outcome compared to original ARMA PEEP management [31]. The Lung Open Ventilation Study (LOV), used PEEP based upon an oxygenation scale conceptually similar to the ALVEOLI trial. Contrary to the lack of a significant mortality benefit, this strategy resulted in a significant improvement in secondary outcomes of reduced refractory hypoxemia and reduced requirement for rescue therapy [32]. The Expiratory Pressure Study Group (EXPRESS) trial did not show any significant effect on mortality with using high PEEP recruitment strategy in the randomized population. The recruitment strategy did result in better oxygenation, more ventilator free days, more organ failure free days, and a reduced requirement for rescue therapy [33]. Results of recent meta analysis showed that higher PEEP strategy is associated with improved survival in subset of patients with ARDS, but patients with mild ARDS may not benefit or may experience harm from higher PEEP levels. The higher PEEP strategy is associated with no evidence of serious adverse effects although a slight increase in pneumothorax was noted [34]. A second meta-analysis showed similar results without the mortality benefit [35]. For determination of the exact level of PEEP several methods have been shown like using a PEEP/Fio2 table in which PEEP is titrated to meet acceptable oxygenation. Other methods include titrating PEEP to a maximal acceptable plateau pressure while maintaining a safe tidal volume [36-37]. The analysis of pressure volume relationships has been proposed to titrated PEEP using a variety of methods. Both the lower inflection point of maximum curvature on the pressure volume curve and the stress index have been employed with variable results [38-39]. Another approach is setting of PEEP guided by esophageal pressures as a surrogate for pleural pressure. The use of transpulmonary pressure measurements to titrate PEEP demonstrated improved oxygenation and lung compliance. Other experimental methods of setting PEEP include titration to the minimum dead space fraction, optimal cardiac output, or transcutaneous oxygen tension, although none of these methods appears widely used in current clinical practice. Titration of PEEP based upon oxygenation indices alone does not reveal a therapeutic benefit to higher PEEP levels. This may replicate a weak relation between oxygenation indices and alveolar stability. Radiographic and physiologic techniques have been shown to better manage PEEP for minimal VILI [40]. These techniques require validation in large populations for showing any mortality effect. The elusive PEEP strategy for ARDS management may be dependent on measurement of "recruitment" rather than oxygenation as the characteristic that determines PEEP's value in the management of the ARDS patients. Recruitment maneuvers increase transpulmonary pressure which result in opening previous atelectatic alveoli, increase the size of ARDS lung and allows distribution of inspired gas among lung units leading to less VILI [40]. Common methods for recruitment maneuvers are sustained inflation breath or a stepwise increase in PEEP accompanied by low levels of pressure controlled ventilation [41]. Common complications of recruitment maneuvers are desaturation, transient hypotension, barotraumas and overdistension. Recruitment maneuvers are associated with an immediate improvement in oxygenation with variable sustainability, but have not been shown to improve clinically important outcomes [42]. They may be more useful as a rescue therapy in refractory hypoxaemia or following deterioration in oxygenation attributable to worsening atelectasis.

Prone positioning

Prone positioning because of pathophysiological basis has been used for many years in the management of ARDS. Prone positioning has been recognized to improve oxygenation due to increase in end expiratory lung volume, improved ventilation perfusion matching, more uniform distribution of lung stress and strain with tidal cycling and regional improvement in lung and chest wall mechanics. The potential risks for prone positioning are tube dislodgement with turning maneuvers and pressure related injury. To overcome the issue of sample size for the most severe ARDS populations, meta-analysis has been employed to study results. These analyses have suggested that prone positioning can be beneficial when restricted to patients with severe ARDS. So, the results suggest prone positioning as a "rescue" regimen for patients with intractable hypoxemia [43-44].

Hemodynamic monitoring and Fluid balance

Many studies showed that more than fifty percent of patients with ARDS have evidence for cardiovascular dysfunction on presentation. So optimal hemodynamic monitoring and need for pulmonary artery catheter are considered as important challenges. Based on results of the Fluid and Catheter Treatment Trial (FACTT) and another trial, current clinical guidelines have moved away from advocating the use of PAC in ARDS management [45-46]. Current data highlights the interaction between right ventricular function and ventilation strategy in ARDS patients. Physician should recognize the cardiovascular pulmonary interaction and evaluate both physiologic benefits of ventilation strategies on pulmonary indices and the harmful effect on right heart function and tissue oxygenation. The routine use of bedside echocardiography brings this information more readily and allows informed clinical decision in critically ill patients [47]. Because of increase in vascular and epithelial permeability in patients with ARDS, fluid management is one of the most difficult treatments to manage in septic shock patients with ARDS. ARDS is typically associated with a systemic inflammatory response leading to an increased preload dependence of the ventricle for ideal performance. Yet, elevation in pulmonary capillary occlusion pressure to reach better preload response, is associated with more lung water in the setting of injury to the alveolar/capillary membrane, so there is a controversy in treatment aims of hemodynamic management [47]. A conservative fluid management strategy with a relatively low central venous pressure is associated with the need for fewer days of mechanical ventilation compared with a liberal fluid management strategy in ARDS [48]. Conservative fluid management is highly recommended after hemodynamic stabilization in ARDS patients. In hemodynamically unstable patients, dynamic monitoring of lung fluid balance needs to be implemented to guide the administration of fluids in ARDS patients [49]. The dry intervention strategy was implemented after the early aggressive resuscitation period had passed. These studies remind the clinician that ARDS is a dynamic disease process both clinically and pathologically so timing of the intervention is critically important in the design and analysis of clinical trials.

Neuromuscular blockade

Neuromuscular blocking drugs (NMBDs) are commonly used in ARDS, but the benefits and risks of using these agents are controversial. NMBD, facilitate patient-ventilator synchrony and improve poor oxygenation when traditional sedation is not adequate, but considering frequent critical illness myopathy with these drugs risk/benefit profile of these medications in ARDS patients are questionable. Short term paralysis may facilitate patient ventilator synchrony during mechanical ventilation, would eliminate patient triggering, active expiratory muscle activity and overventilation, lower metabolism and overall ventilator demand so limit volutrauma and atelectrauma. The role of NMBD in the management of ARDS requires further exploration in additional clinical trials. Whether the therapeutic benefit is related to specific drug (Cisatracurium) or specific class remains undefined [50-51].

Inhaled vasodilators

Pulmonary hypertension, right heart failure and severe hypoxemia have prompted intensivists to use inhaled vasodilators for ARDS patients. The two most frequently investigated agents are inhaled nitric oxide and inhaled prostacyclin. Inhaled NO is a potent but extremely short acting pulmonary vasodilator which reduces intrapulmonary shunt and improves perfusion to well-ventilated alveoli. The use of nitrous oxide is not associated with any significant decrease in mortality, despite improvements in oxygenation [52]. A recent meta analysis showed that inhaled NO has a small beneficial effect on oxygenation but no significant effect on pulmonary artery pressure, ventilator free days or mortality. The results showed an increase in renal failure during the studies. Because the NO dose response appear to vary with time in ARDS patients the fix dose intervention approach could have revealed adverse effects associated with long term administration [53]. Inhaled prostacyclin has similar theoretical benefits to nitric oxide in terms of selective pulmonary vasodilatation. Prostacyclin is considerably less expensive and does not require the same commercial delivery system as nitric oxide, but the nebulizer requires continual observation during prostacyclin delivery, and the technique remains an unproven rescue therapy for life-threatening hypoxaemia. However, this drug lacks the experience in randomized clinical trials characteristic of NO [54-55]. Based upon the published trials to date, the use of inhaled vasodilators must be considered a rescue therapy for patients with intractable hypoxemia and/or pulmonary hypertension where other interventions such as high PEEP titration, prone positioning, and High frequency oscillatory ventilation (HFOV) have been unsuccessful [55].

Bronchodilators

Beta agonists activates beta 2 receptors on alveolar type I and type II cells which increases intracellular cAMP leading mainly to increase alveolar fluid clearance. Despite a putative beneficial role in the resolution of alveolar edema seen in preliminary studies, recent trials showed evidence for increase in mortality with routine use of beta-2 agonist in ARDS patients [56].

HFOV

HFOV seems ideal for lung protection in ARDS. HFOV was effective in improving oxygenation in adults with ARDS particularly when instituted early. In adults with moderate to severe ARDS early application of HFOV

compared with an employment of a ventilation strategy low tidal volume and high PEEP dose not decrease in-hospital mortality [57-58]. HFOV is best considered a rescue regimen for patients with intractable hypoxemia [58]. Ongoing clinical trials hope to address more specifically the role of this therapy in patients with ARDS.

ECMO

If lung protective strategy is critical to the support of ARDS patients, ECMO could provide the most optimal method for to lung rest. The potential benefit of ECMO is offset by an incremental bleeding risk of anticoagulation use and infection risk due to catheter usage [59]. The role of ECMO in ARDS is controversial and its availability currently is limited to specialized centers. Some recent evidence support the use of extracorporeal lung support in patients with H1N1 influenza [60-61]. Transfer to an ECMO centre should be considered in patients with reversible disease in whom lung-protective ventilation cannot provide acceptable gas exchange when other rescue measures have failed, and should be utilized early in the course of disease, before irreversible lung injury has occurred. Further research is needed regarding the timing of the initiation of ECMO, the standardization of therapy and monitoring, and understanding as to which type of ECMO reduces morbidity and mortality rates in patients with ARDS.

Future non-ventilatory therapeutic options

Gene therapy

Impaired alveolar fluid clearance is the main determinant of ventilation perfusion mismatch and subsequent hypoxia in ARDS patients. This concept is the basic of gene therapy for reestablish alveolar fluid clearance and keeps the lung dry. The driving force of fluid reabsroption is based on the active transport of Na ion from the alveolar space to epithelial space. Based on negative results of beta agonist therapy in ARDS, gene therapy approaches to restore and potentiate the Na movement across the alveolar epithelial barrier overcome the problem of systemic side effects of beta 2 agonists. Transfer of alfa 2 subunit or beta 1 subunit of Na/K ATPase has been shown to increase the expression of Na/K ATPase on alveolar epithelial cells and to improve alveolar fluid clearance [62-65]. Lung injury in ARDS is characterized by a pro-inflammatory increase in vascular permeability and neutrophil infiltration, which sustain alveolar edema and damage to alveolar barrier. Several studies have focused on the role of gene therapy in modulating the pro-inflammatory response in the lung. Anti-inflammatory effects have been found with the delivery of genes encoding anti-inflammatory cytokines such as interferon protein 10 (IP-10), IL 12 and transforming growth factor beta-1 (TGF-β1) [66-68]. Inducible Heme oxygenase isoform HO-1 is an important molecule with anti-inflammatory, anti-apoptotic and anti-viral properties which has been used in different genetic approaches to alleviate acute lung injury [69-70]. Gene transfer of HO-1 could be considered as a lung protective strategy against hyperoxia, influenza virus pneumonia and endotoxin mediated lung injury [70].

Mesenchymal stem cell

MSCs have several properties that make them promising as a therapeutic approach in ARDS. MSCs differentiating into several cell types have regenerative properties and may repair damaged tissues. MSCs seem to be potent immunomodulators; they may interact with circulating and tissue monocytes and macrophages and reprogram them to enhance an anti-inflammatory response [71-73].

Prognosis and quality of life of survivors from ARDS

Along with high mortality risks, survivors suffer significant decrements in their quality of life. In survivors of acute lung injury, there was no difference in physical function, survival, or multiple secondary outcomes at 6 and 12 months follow-up after initial trophic or full enteral feeding.

Contrary to the limited success of interventional randomized clinical trials, clinical data suggests that prognosis from ALI/ARDS is improving. Notwithstanding the intensity of support needed to correct gas exchange deficits during the acute process, the respiratory system recovery appears to be relatively short-term and complete. In this regard, the accountability for long-term survivors of ARDS is focused on psychological and neuromuscular dysfunction. Results of recent ARDS cohort study showed almost normal lung function recovery at both 1-year and 5-year intervals. Despite this improvement, assessment of physical function in these survivors shows a plateau at year 2 with incomplete recovery to normal. Six minute walking distance remains declined compared to normal persons at 5-year follow-up. The majority of the surviving patients were able to return to work at 1 year (78%) and 5 years (94%) [74]. These data have provided a new therapeutic window for non-ventilatory management of the ARDS patient to reduce immobility and prevent neuromuscular weakness during the period of acute support.

Summary

ARDS is a heterogeneous syndrome with common clinical and pathophysiologic components. ARDS still represents a deadly form of respiratory failure with long term consequences in patient survivors and indeed, their families. Adoption of the new definition may be useful to better classify patients according to severity and prognosis. Absence of effective therapeutic interventions depends on the complex pathogenesis of the syndrome characterized by different overlapping signaling pathways. Gene therapy and mesenchymal stem cells might be encouraging novel therapeutic strategies targeted on modulation of key pathophysiologic mechanisms of ARDS.

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