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The Acute Respiratory Distress Syndrome: Mechanisms and Perspective Therapeutic Approaches

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Abstract

Acute Respiratory Distress Syndrome (ARDS) is a severe lung inflammatory disorder with a 30–50% mortality. Sepsis and pneumonia are the leading causes of ARDS. On the cellular level there is pulmonary capillary endothelial cell permeability and fluid leakage into the pulmonary parenchyma, followed by neutrophils, cytokines and an acute inflammatory response. When fluid increases in the interstitium then the outward movement continues and protein rich fluid floods the alveolar spaces through the tight junctions of the epithelial cells. Neutrophils play an important role in the development of pulmonary edema associated with acute lung injury or ARDS. Animal studies have shown that endothelial injury appears within minutes to hours after Acute Lung Injury (ALI) initiation with resulting intercellular gaps of the endothelial cells. The Endothelial Cell (EC) gaps allow for permeability of fluid, neutrophils and cytokines into the pulmonary parenchymal space. The neutrophils that infiltrate the lungs and migrate into the airways express pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and contribute to both the endothelial and epithelial integrity disruption of the barriers.

Pharmacological treatments have been ineffective. The ARDS Network trial identified low tidal volume mechanical ventilation, positive end expiratory pressure and fluid management guidelines that have improved outcomes for patients with ARDS. Extracorporeal membrane oxygenation is used in specialized centers for severe cases. Prone positioning has recently proven to have significantly decreased ventilator days and days in the intensive care unit.

Current investigation includes administration of mesenchymal stem cell therapy, partial fluid ventilation, TIP peptide nebulized administration and the continued examination of pharmacologic drugs.

Keywords

Acute lung injury; Acute respiratory distress syndrome; ARDS biomarkers; ARDS pathology; Heparin; Adenosine

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Introduction

Acute Respiratory Distress Syndrome (ARDS) is a severe lung inflammatory disorder with a 30–50% mortality [1,2]. Sepsis and pneumonia are the leading causes of ARDS. On the cellular level there is pulmonary capillary endothelial cell permeability and fluid leakage into the pulmonary parenchyma, followed by neutrophils, cytokines and an acute inflammatory response [3]. When fluid increases in the interstitium then the outward movement continues and protein rich fluid floods the alveolar spaces through the tight junctions of the epithelial cells. ARDS was initially described in the 1960s' by Petty and Ashbaugh [4]. In 1994 a large clinical network was established through the National Heart, Lung and Blood Institute (NHLBI) with the goal of efficiently testing promising agents, devices or management strategies to improve the care of patients with ARDS (NHLBI ARDS Network website). The ARDS Network trial identified low tidal volume mechanical ventilation, Positive End Expiratory Pressure (PEEP) and fluid management guidelines that have improved outcomes for patients with ARDS. Other management modalities have been tested including steroids, antifungals, beta agonist and nitric oxide. The pharmacologic trials have not yielded a therapeutically effective strategy. Treatment modalities include Extracorporeal Membrane Oxygenation (ECMO), ventilator bundles and persistent evaluation of pharmacological entities such as heparin [5]. Current research is primarily focused on the role of biological biomarkers in early therapeutics or preventative approaches for ARDS [6] and mesenchymal stem cell treatment [7].

Pathophysiology

ARDS is a Non-Cardiogenic Pulmonary Edema (NCPE). The NCPE in ARDS is ultimately a result of capillary permeability secondary to cellular damage, inflammatory cascades, and over inflation by mechanical ventilation resulting in endothelial permeability. The endothelial cell barrier is a single layer of continuous endothelium lining the pulmonary capillaries and forms a single layer between blood and the pulmonary interstitium. The pulmonary capillaries have extremely thin walls to allow rapid exchange of respiratory gases across them [8]. In ARDS disturbances of pulmonary capillary fluid balance and pulmonary permeability occur as a direct result of bacterial infection, endotoxins and subsequent inflammation that cause disruption in the capillary EC barrier with barrier disruption and subsequent pulmonary venous congestion. As the fluid overload initially enters the pulmonary interstitium it is taken up by the lymphatic system to be returned to the vascular system. The hydrostatic forces are then altered as a direct result of injury to the capillary endothelium. The interstitial space can increase its volume by as much as 40% without resulting in pulmonary edema [9]. However persistent fluid accumulation overwhelms the lymphatic drainage and tissue edema results. Finally, when the fluid overwhelms the hydrostatic forces and the excess fluid flows into the alveoli. The edema that is caused by the increasing fluid and vascular permeability is a hallmark of inflammation and tissue injury [10]. The edema formation can have severe consequences because the fluid and protein components in the edematous tissues and alveoli increase the diffusion barrier for oxygen and carbon dioxide with subsequent disruption of gas exchange thus precipitating hypoxia and respiratory failure. The ensuing pulmonary edema in patients with ARDS has been shown to be a high protein pulmonary edema. In fact, the fluid/ plasma ratio may be

used to differentiate the etiology of pulmonary edema in ARDS and cardiogenic pulmonary edema. The fluid/plasma ratio is a measurement of the alveolar fluid obtained by Bronchial Alveolar Lavage (BAL), to the serum plasma during acute pulmonary edema and has been shown sensitive enough to differentiate a low protein fluid that results from cardiac pulmonary edema compared to a high protein ratio that occurs with illness such as ARDS [11,12]. The protein concentration in the pulmonary interstitium of ARDS exceeds 60% of the plasma value whereas the protein concentration in non ARDS causes is less than 45% [13,14]. The result is a high permeability of the EC barrier and a high protein in the interstitial space with the protein content similar to blood. The acute rate of volume accumulation is another factor in the subsequent hypoxic respiratory failure and pulmonary edema. Pulmonary alveoli, the primary sites of gas exchange with the blood, are composed of a thin alveolar epithelium that covers 99% of the surface area in the lung and contains thin, squamous type I cells and cuboidal type II cell. Type I cells cover 95% of the alveolar surface. The epithelial lined alveolar spaces facilitate gas exchange and form a tight barrier to fluid and protein movement from the interstitial and vascular spaces maintaining relatively dry alveoli. Tight junctions connect adjacent epithelial cells near the apical surfaces and maintain apical and basal-lateral cell polarity. The tight junctions are important elements of the permeability barrier necessary to maintain normal gas exchange. The alveolar type II cell that secretes surfactant contributes to the vectorial transport of sodium. Active transport of sodium provides a major driving force for fluid removal from the alveolar space. Amiloride sensitive sodium channels on the apical surface, mainly the Epithelial Sodium Channel (ENaC) are involved in fluid transport with the driving force represented by the sodium/potassium adenosine triphosphatase (Na^+/K^+-ATPase) on the basolateral surface [15]. Injury of the alveolo-capillary barrier alters active Na^+ transport, leading to impaired edema fluid clearance from the alveolar spaces. The primary force driving fluid reabsorption from the alveolar space into the interstitium and the pulmonary circulation is active Na^+ transport. Sodium is taken up on the apical surface of the alveolar epithelium by Amiloride-sensitive and insensitive Na^+ channels and is subsequently pumped out of the cell by Na^+/K^+-ATPase on the basal-lateral side (Gene Therapy in Critical Care Medicine http://dx.doi.org/10.5772/52701, by Moreno-Gonzalez and Zarain-Herzberg, 2013). Pulmonary edema is caused by a dysregulated function of the ion channels in type II alveolar epithelial cells [15].

The Role of Neutrophils ALI/ARDS

Neutrophils play an important role in the development of pulmonary edema associated with ALI/ARDS [16]. Initially pulmonary macrophages are activated and recruit neutrophils to the injured capillaries where they are found leaking into the pulmonary parenchymal interstitium. Here they sequester and initiate an important component of the inflammatory response in endotoxin induced ALI/ARDS. This activation and migration of neutrophils is a characteristic event in the progression of ALI and ARDS. Animal studies have shown that endothelial injury appears within minutes to hours after ALI initiation with resulting intercellular gaps of the EC. The EC gaps allow for permeability of fluid, neutrophils and cytokines into the pulmonary parenchymal space [17]. The neutrophils that infiltrate the lungs and migrate into the airways express pro-inflammatory cytokines such as TNF-α,

IL-1β, and contribute to both the endothelial and epithelial integrity disruption of the barriers [16,18]. It has also been well documented that the percentage of neutrophils correlates directly with the alveolar-arterial partial pressure of oxygen (PO_2) difference in ALI/ARDS pulmonary edema [19]. Neutrophil sequestration is aided by chemotactic factors and by the adhesion molecules on both the neutrophils and capillary endothelial cells [20,21].The activated neutrophils expressing IL-1β produce other pro-inflammatory cytokines after endotoxin administration. In fact the removal of neutrophils after endotoxin administration almost entirely prevents an increase of IL-1β expression and attenuates endotoxin induced TNF-α. Neutrophils are the major source of IL-1β in murine models of the lung in ALI [18]. Another feature of the neutrophils that accumulate in the lung of murine models is increased activation of the transcriptional regulatory nuclear factor cappa B(NF-κB). NF-κB is a protein complex that controls transcription of DNA and is involved in cellular responses to stimuli such as pulmonary edema due to ALI/ARDS. It is key in regulating the endotoxin induced immune response in neutrophils and produces increased amounts of pro-inflammatory cytokines whose transcription is dependent on NF-κB [22]. Neutrophils also become an increasing liability in the edematous pulmonary interstitium as they release free radicals

The Molecular Mechanisms of the Pulmonary Barrier Injury in ALI/ARDS

The thin alveolar-capillary barrier allows oxygen-carbon dioxide (CO_2) exchange for normal respiration. The major consequence of pulmonary edema is impaired gas exchange that interrupts the normal fluid exchange balance. The alveoli epithelium removes fluid by molecular mechanisms of sodium transport however the capillary endothelial barrier function has only incompletely defined pathways affecting the concurrent barrier disruption. Permeability of the EC in the capillaries with concurrent alveolar-capillary membrane damage and with leakage of fluid, neutrophils, proteases, cytokines and free radicals that all contribute to the ensuing pulmonary edema is a prominent feature of permeability edema and ALI/ARDS [23]. The alveolar liquid clearance from the alveolus into the interstitium is based on active sodium transport largely through the highly regulated apical Amiloride sensitive Epithelial Sodium Channel Complex (ENaC) with concomitant passive water transport and the Na^+, K^+ ATPase exchange [24,25]. The Na^+, K^+ ATPase exchange transports the alveolar liquid into the interstitium and ultimately into the lymphatic and blood vessels [26,27]. However these transport processes are often impaired in ALI or ARDS. It is likely that the induction of increased permeability of the pulmonary capillary bed is directly linked to reversible physical modifications of the pulmonary capillary endothelium [28]. The capillary endothelial regulation of endothelial permeability involves various pathways such as those involving (ROS), Rho Guanosine Triphosphate Enzymes (GTPases), and tyrosine phosphorylation of junctional proteins that all converge to regulate junctional permeability. They either affect the stability of junctional proteins or modulate their interactions [27]. The regulation of permeability at the junctions is mediated by active communication between the proteins of the adherens junctions and the Actin cytoskeleton. Actin mediated endothelial cell contraction is the result of Myosin Light Chain (MLC) phosphorylation by MLC kinase (MLCK) in a Ca^{2+}/calmodulin- dependent manner. RhoA also potentiates MLC phosphorylation by inhibiting MLC phosphatase activity through its

downstream effector Rho kinase (ROCK). As the Actin/myosin driven contraction generates a contractile force it pulls Vascular Endothelial (VE)-cadherin inward. This contraction will force VE-cadherin to dissociate from its adjacent partner causing endothelial gaps the basic pathology in permeability pulmonary edema [27]. It is increasingly recognized that the injured lung cells release inflammatory mediators into the systemic circulation contributing to the deleterious effect on other organs. One study showed that, in the septic patient with ARDS, human epithelial pulmonary cells stimulated with bacterial Lipopolysaccharide (LPS) release inflammatory mediators that are able to induce a translational clinically relevant and harmful response in brain cells [1].

Biomarkers

One of the challenges in ARDS is to identify patients at risk of developing ARDS or to predict mortality once the disease is established. The ARDS net Clinical trial network looked at the biologic index of biomarkers combined with clinical risk factors. This clinical trial looked at markers that had been shown to be increased in ARDS. The result showed significant changes in inflammatory cytokines interleukins (IL-6 and IL-8), coagulation proteins Plasminogen Activator Inhibitor-1(PAI-1), protein C, epithelial proteins, a serologic biomarker for interstitial lung disease (KL-6), Surfactant Protein (SP-D), Receptor For Advanced Glycation End Products (RAGE) and Endothelial Proteins Angiopoietin-2 (ANG-2), Intercellular Adhesion Molecule 1 (ICAM-1), von Willebrand Factor (vWF) [6,29]. They found the two best performing biomarkers were IL-8, a potent Neutrophil chemo-attractant and SP-D, produced by type 2 alveolar epithelial cells [29]. Endocan, an endothelial cell specific molecule-1 secreted from pulmonary and kidney vascular endothelial cells has recently been shown to be significantly increased in moderate or severe ARDS non-survivors. Endocan levels predicted the mortality of patients with ARDS. Procalcitonin (PCT) was also significantly increased in the same study in ARDS [6]. Clara Cell Protein (CC16) performed well as a potential biological marker for ARDS in patients with ventilator associated pneumonia and ARDS [30]. It is likely that no one biomarker will be able to predict with complete accuracy the risk of development, diagnosis and prognostic course of ARDS in patients. Rather it is projected that there will be a panel of the best potential markers to select these patients.

Management

Current management of ARDS is unchanged since the ARDSnet trials revealed the only strategy that improved survival is Mechanical Ventilation (MV) with low tidal volumes of 6mg/kg ideal body weight. Other trials revealed that days on the ventilator and in the intensive care unit are shortened by a conservative fluid strategy and that restricting fluid intake and promoting fluid excretion is more effective that a liberal fluid strategy in patients with ARDS [31]. There are clear guidelines for the treatment of the two most common underlying causes of ARDS. The standard for pneumonia classification with the severity CURB-65 score (confusion, uremia, respiratory rate, blood pressure, age greater than 65) or the Pneumonia Severity Index (PORT) scores to admit the appropriate patients to the hospital ward or intensive care unit based on the models that have been shown to predict mortality. Sepsis bundles with early goal directed therapy for patient with sepsis of any

source have improved the outcomes for patients with sepsis and also likely reduced cases of ARDS. These criteria for common causes of ARDS have likely decreased the development of ARDS in some cases by improved care of these underlying causes. However the incidence, prevalence and mortality are too high and there is an intensive search for a healing therapy. Alternative ventilation modes of ventilation are utilized when conventional low tidal volume MV is unsuccessful. Airway Pressure Release Ventilation (APRV) and High Frequency Oscillatory Ventilation (HFOV) are modes designed to prevent or minimize Ventilator Induced Lung Injury (VILI). The goal of both of these modes is to use an open lung strategy to improve oxygenation while keeping the lungs uniformly open. APRV, a high continuous positive airway pressure is delivered for a long duration and then falls to a lower pressure for a shorter duration. Alveolar recruitment is maximized by the high continuous positive airway pressure. There is no proof that APRV improves mortality, however, there are ongoing studies that may reveal further information about this mode of ventilation [32,33]. HFOV uses an oscillatory pump to deliver a respiratory rate of 3 to 15 Hertz (up to 900 breaths per minute) through the endotracheal tube. The constant mean airway pressure maintains alveolar recruitment, avoids low end-expiratory pressures and avoids high peak pressures. Although HFOV is initially associated with improved oxygenation it has not been associated with improved survival [34]. Another MV mode that has been utilized is Partial Liquid Ventilation (PLV) is a technique of MV in which the lungs are insufflated with oxygenated Perfluorochemical (PFC) liquid rather than oxygen-containing gas mixture. The lungs are slowly filled with a volume of PFC close to the functional residual capacity during gas ventilation. The PFC in the lungs is oxygenated and carbon dioxide is removed by means of gas breaths cycling in the lungs with traditional MV [35]. In ARDS some studies have shown that PLV can improve gas exchange in ARDS by recruitment of the atelectatic, consolidated dependent regions of the lungs that contribute to physiologic shunt during gas ventilation Pulmonary blood flow is also redistributed to less severely injured and/or atelectatic regions of the lung thus improving ventilation perfusion matching [36]. The most recent Cochrane Database Systematic Review update shows that in spite of trials and persistent research with two new trials there is not enough evidence that supports the use of PLV in ARDS and some evidence suggests an increased risk of adverse events associated with its use [37]. A non-pharmacologic application for treatment of severe ARDS that is not being effectively treated by the current clinical types of mechanical ventilation is Extracorporeal Membrane Oxygenation (ECMO). ECMO is a form of partial cardiopulmonary bypass that can be employed in longer term support of respiratory and/or cardiac function [38]. ECMO offers artificial temporary and respiratory support that is maintained until the patient recovers from severe respiratory failure [39]. ECMO use for respiratory failure was first described in 1972, however the technology was primitive and knowledge about acute lung injury was limited with the terminology of “shock lung” used in the articles description [40]. Despite initial problems ECMO use continued in some centers and there was renewed interest as a treatment for ARDS when ECMO was proposed as a rescue therapy in the 2009 H1N1 pandemic, and had good outcomes [39]. The main indication for the use of ECMO is in refractory hypoxemia and the risk of mortality is 80% or greater. The Extracorporeal Life Support Organization (ELSO) has published guidelines that address personnel, training, resources, use of ECMO and quality assurance. According to the ELSO guidelines for ARDS the criteria for consideration are as follows: (A) a 50%

mortality risk that is associated with a PaO2/FiO2 < 150 on FiO2 > 90% and/or Murray score 2–3 and(B) an 80% mortality risk that is associated with a PaO2/FiO2 < 100 on FiO2> 90% and/or Murray score 3–4 despite optimal care for 6 hours or more and CO_2 retention on mechanical ventilation despite high Pplat (>30cm H2O) and severe air leak syndromes (ELSO guidelines http://www.elsonet.org/index.php?option=com_phocadownload). There are no absolute contraindications of ECMO however there are some conditions that may be relative contraindications. The main adverse outcome is bleeding including CNS hemorrhage. Prone positioning in ARDS has recently been evaluated in a multicenter, prospective, randomized, controlled trial with 466 patients with severe ARDS with a PaO2/FIO2 ratio of < 150 mm Hg, FIO2 of > 0.6 and a PEEP of > 5 cm H2O. The patients who underwent prone-positioning were left in sessions of at least 16 hours or the controls were left in supine position throughout their ICU stay. Survival after severe ARDS was significantly higher (32.8%) in the prone group than in the supine group (16%) despite the fact that the mortality in the supine group was lower than anticipated (P<0.001) [41]. Prior Meta analysis suggested that survival was improved with prone positioning compared with supine positioning however with the most recent results in a well conducted trial prone positioning may be integrated into the standard of care for the severe ARDS patient.

New Treatment Strategies

Mesenchymal Stem Cells (MSCs) are a potential new approach for treatment of ARDS. MSCs are multipotent, self-renewing cells initially isolated from bone marrow that can differentiate into a variety of cell types. The interest in a cell based therapy has been piqued since the ineffectiveness of specific pharmacologic therapies has evolved. Numerous studies have demonstrated that the soluble factors or products derived from human MSCs generate a local immunosuppressive microenvironment by secreting cytokines [42,43]. As a result there is intense study focusing on the paracrine properties of MSCs [7]. It also appears that MSCs do not generate allo-responsiveness and this makes MSCs an attractive treatment [43]. It has been found that Bone Marrow Derived (BMD) MSC markers are negative for cluster of differentiation 45 and 11b (CD45 and CD11b) and are capable of differentiating into a variety of cell types, including endothelial, epithelial and neuronal cells. When BMDMSCs are infused into mice they can be found with the phenotypic characteristics of cells in the organ where they reside. In the lung, BMDMSCs have been detected as type I and type II alveolar epithelial cells, endothelial cells, fibroblasts and bronchial epithelial cells. It seems certain that these cells have the capacity to localize into injured lung and differentiate into specific cell types [44]. In a study with bleomycin-induced lung injury in mice it was found that transplanted MSCs localized to the injured lung and assumed parenchymal cell phenotypes. In this model of lung injury MSCs transplant prevented increased lung expression of immune related inflammatory cytokines interleukin (IL)-1β, interferon (IFN)-γ, IL-2, IL-4 that may provide an environment beneficial to lung repair. MSCs were also shown to induce production of anti-inflammatory prostaglandins and IL-10 and this may be the mechanism of the suppressive inflammatory effect. In addition to MSCs suppression of the local microenvironment [44]. The administration of MSCs in an endotoxin model of acute lung injury via administration of MSC directly into the airspaces of the lung 4 h after the intrapulmonary administration of lipopolysaccharide significantly

decreased lung water, a measure of pulmonary edema and bronchoalveolar lavage protein, a measure of endothelial and alveolar epithelial permeability and increased survival compared with phosphate buffered saline-treated mice. The protection was shown to be mediated by a shift from a proinflammatory to an anti-inflammatory response to endotoxin that includes enhanced production of IL-10 [45]. Based on in vitro and in vivo studies multiple studies suggesting MSC benefits in various clinical disorders including acute lung injury there has been a randomized, placebo-controlled pilot study with the objective to examine the possible adverse events after systemic administration of allogeneic adipose-derived MSCs in ARDS patients and to determine potential efficacy of MSCs on ARDS. Twelve adult patients with ARDS with a partial pressure of arterial oxygen to fraction inspired oxygen (PaO2/FiO2) ratio of < 200 were randomized to receive allogeneic MSCs or placebo. There were no infusion toxicities or serious adverse events between the two groups. The conclusion was that administration of allogeneic MSCs appeared to be safe in the treatment of ARDS. However there were no significant differences in the levels of inflammatory cytokines with the dose of MSCs that was used. Further optimization of the strategy will be required to reach the goal of reduced lung injury in ARDS [46]. A Phase 1, open label, dose escalation, multi-center trial of allogeneic bone marrow-derived human MSCs to treat ARDS is recruiting patients (http://clinicaltrials.gov/ct2/show/NCT01775774). Tumor necrosis factor is a potent pro-inflammatory cytokine produced by many cell types. It is involved in systemic inflammation and is a member of a group of cytokines that stimulate the acute phase reaction. It is principally produced by activated macrophages although it can be produced by other cell types. TNF is also able to reduce lung edema in different inflammatory processes such as non-cardiogenic pulmonary edema. The lectin-like domain of TNF, mimicked by a circular seventeen amino acid peptide, TIP peptide, is responsible for the reduction in lung edema clearance in murine models of non-cardiogenic pulmonary edema [24,47,15,48]. Studies of lung injury induced in 16 pigs by BAL lavage followed by injurious ventilation received either nebulized TIP or water. The Extravascular Lung Water Index (EVLWI), the PaO2/FIO2 ratio and the pulmonary shunt fraction were assessed. The inhalation of TIP induced an amelioration of clinical surrogate parameters of the lung function in a porcine lung injury model demonstrating the TIP peptide as an innovative approach as supportive therapy in ARDS [48]. Based on these findings the TIP peptide is now in clinical trials in Europe with the findings yet to be published. Pharmacologic therapies continue to be investigated although most are still in the early development stage. Some of these include adenosine [49], heparin and low anticoagulant heparins [50–51], growth hormones [52], Heat Shock Protein 90 inhibitors [53]. Effective pharmacotherapy for ARDS remains extremely limited [54].

Conclusion

The most common causes of adults with severe ARDS are sepsis and pneumonia and mortality rates continue to be high. The underlying pathology includes local and systemic inflammation. Biomarkers are identified however the emergence of a single biomarker has not surfaced and will likely have a panel of biomarkers to predict the severity and course of ARDS. The use of lung protective MV, alternative modes of ventilation, ECMO and prone positioning can improve mortality. Active research includes mesenchymal cells installation,

TIP peptide and persistent evaluation for a pharmacologic therapy to benefit patients in severe ARDS.

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Abbreviations

ARDS	Acute Respiratory Distress Syndrome
ALI	Acute Lung Injury
EC	Endothelial Cell
TNF-α	Tumor Necrosis Factor-Alpha
IL 1β	Interleukin 1 Beta
PEEP	Positive End Expiratory Pressure
ECMO	Extracorporeal Membrane Oxygenation
NHLBI	National Heart, Lung, Blood Institute
NCPE	Non-Cardiogenic Pulmonary Edema
BAL	Bronchial Alveolar Lavage
ENaC	Epithelial Sodium Channel
Na^+/K^+-ATPase	Sodium/Potassium Adenosine Triphosphatase
PO_2	Partial Pressure Of Oxygen
NF-Kb	Nuclear Factor-Kappa B
DNA	Deoxyribonucleic Acid
CO_2	Carbon Dioxide
ROS	Reactive Oxygen Species
GTPases	Guanosine Triphosphate Enzymes
MLC	Myosin Light Chain
MLCK	Myosin Light Chain Kinase
ROCK	Rho Kinase
VE	Vascular Endothelial
LPS	Lipopolysaccharide
IL	Interleukin
PAI-1	Plasminogen Activator Inhibitor-1, a serological biomarker for interstitial lung disease (KL-6)

SP-D	Surfactant Protein-D
RAGE	Receptor For Advanced Glycation End Products
ANG-2	Angiopoietin-2
ICAM-1	Intercellular Adhesion Molecule1
vWF	Von Willebrand Factor
PCT	Procalcitonin
CC16	Clara Cell Protein 16
CURB-65	Confusion, Blood Urea Nitrogen, Respiratory Rate, Blood Pressure, Age 65
PORT	Pneumonia Severity Index Score
APRV	Airway Pressure Release Ventilation
HFOV	High Frequency Oscillatory Ventilation
VILI	Ventilator Induced Lung Injury
MV	Mechanical Ventilation
PLV	Partial Liquid Ventilation
PFC	Perfluorochemical
ELSO	Extracorporeal Life Support Organization
PaO_2/FIO_2	Partial Pressure Of Arterial Oxygen To Fraction Inspired Oxygen
Pplat	Plateau Pressure
CNS	Central Nervous System
Hg	Mercury
cm	Centimeters
H_2O	Water
ICU	Intensive Care Unit
MSCs	Mesenchymal Stem Cells
BMD	Bone Marrow Derived
CD 45 or CD 11b	Cluster Of Differentiation
IFN-γ	Interferon Gamma
TNF	Tumor Necrosis Factor

References

1. Rodriguez-Gonzalez R, Ramos-Nuez A, Martin-Barrasa JL, Lopez-Aguilar J, Baluja A, Alvarez J, et al. Endotoxin-induced lung alveolar cell injury causes brain cell damage. Exp Biol Med Maywood NJ. 2014

2. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000; 342:1334–1349. [PubMed: 10793167]

3. Ware LB, Matthay MA. Clinical practice. Acute pulmonary edema. N Engl J Med. 2005; 353:2788–2796. [PubMed: 16382065]

4. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967; 2:319–323. [PubMed: 4143721]

5. Dixon B, Schultz MJ, Hofstra JJ, Campbell DJ, Santamaria JD. Nebulized heparin reduces levels of pulmonary coagulation activation in acute lung injury. Crit Care Lond Engl. 2010; 14:445.

6. Tang L, Zhao Y, Wang D, Deng W, Li C, Li Q, et al. Endocan levels in peripheral blood predict outcomes of acute respiratory distress syndrome. Mediators Inflamm. 2014; 2014:625180. [PubMed: 25132734]

7. Matthay MA, Goolaerts A, Howard JP, Lee JW. Mesenchymal stem cells for acute lung injury: preclinical evidence. Crit Care Med. 2010; 38:S569–S573. [PubMed: 21164399]

8. Costello ML, Mathieu-Costello O, West JB. Stress failure of alveolar epithelial cells studied by scanning electron microscopy. Am Rev Respir Dis. 1992; 145:1446–1455. [PubMed: 1596017]

9. Sartori C, Rimoldi SF, Scherrer U. Lung fluid movements in hypoxia. Prog Cardiovasc Dis. 2010; 52:493–499. [PubMed: 20417342]

10. Zimmerman GA, McIntyre TM. PAF, ceramide and pulmonary edema: alveolar flooding and a flood of questions. Trends Mol Med. 2004; 10:245–248. [PubMed: 15177186]

11. Fremont RD, Kallet RH, Matthay MA, Ware LB. Postobstructive pulmonary edema: a case for hydrostatic mechanisms. Chest. 2007; 131:1742–1746. [PubMed: 17413051]

12. Ware LB, Fremont RD, Bastarache JA, Calfee CS, Matthay MA. Determining the aetiology of pulmonary oedema by the oedema fluid-to-plasma protein ratio. Eur Respir J. 2010; 35:331–337. [PubMed: 19741024]

13. Fein A, Grossman RF, Jones JG, Overland E, Pitts L, Murray JF, et al. The value of edema fluid protein measurement in patients with pulmonary edema. Am J Med. 1979; 67:32–38. [PubMed: 463915]

14. Staub NC, Nagano H, Pearce ML. Pulmonary edema in dogs, especially the sequence of fluid accumulation in lungs. J Appl Physiol. 1967; 22:227–240. [PubMed: 6017888]

15. Yang G, Hamacher J, Gorshkov B, White R, Sridhar S, Verin A, et al. The Dual Role of TNF in Pulmonary Edema. J Cardiovasc Dis Res. 2010; 1:29–36. [PubMed: 21188088]

16. Bdeir K, Higazi AA, Kulikovskaya I, Christofidou-Solomidou M, Vinogradov SA, Allen TC, et al. Neutrophil alpha-defensins cause lung injury by disrupting the capillary-epithelial barrier. Am J Respir Crit Care Med. 2010; 181:935–946. [PubMed: 20093642]

17. Grommes J, Soehnlein O. Contribution of neutrophils to acute lung injury. Mol Med Camb Mass. 2011:293–307. [PubMed: 21046059]

18. Abraham E. Neutrophils and acute lung injury. Crit Care Med. 2003; 31:S195–S199. [PubMed: 12682440]

19. Weiland JE, Davis WB, Holter JF, Mohammed JR, Dorinsky PM, Gadek JE. Lung neutrophils in the adult respiratory distress syndrome. Clinical and pathophysiologic significance. Am Rev Respir Dis. 1986; 133:218–225. [PubMed: 3004270]

20. Haskó G, Xu D-Z, Lu Q, Németh ZH, Jabush J, Berezina TL, et al. Adenosine A2A receptor activation reduces lung injury in trauma/hemorrhagic shock. Crit Care Med. 2006; 34:1119–1125. [PubMed: 16484904]

21. Geerts L, Jorens PG, Willems J, De Ley M, Slegers H. Natural inhibitors of neutrophil function in acute respiratory distress syndrome. Crit Care Med. 2001; 29:1920–1924. [PubMed: 11588452]

22. Blackwell TS, Blackwell TR, Holden EP, Christman BW, Christman JW. In vivo antioxidant treatment suppresses nuclear factor-kappa B activation and neutrophilic lung inflammation. J Immunol Baltim Md 1950. 1996; 157:1630–1637.

23. Holter JF, Weiland JE, Pacht ER, Gadek JE, Davis WB. Protein permeability in the adult respiratory distress syndrome. Loss of size selectivity of the alveolar epithelium. J Clin Invest. 1986; 78:1513–1522. [PubMed: 2431002]

24. Elia N, Tapponnier M, Matthay MA, Hamacher J, Pache J-C, Brundler M-A, et al. Functional identification of the alveolar edema reabsorption activity of murine tumor necrosis factor-alpha. Am J Respir Crit Care Med. 2003; 168:1043–1050. [PubMed: 12842853]
25. Folkesson HG, Matthay MA. Alveolar epithelial ion and fluid transport: recent progress. Am J Respir Cell Mol Biol. 2006; 35:10–19. [PubMed: 16514116]
26. Hamacher J, Stammberger U, Roux J, Kumar S, Yang G, Xiong C, et al. The lectin-like domain of tumor necrosis factor improves lung function after rat lung transplantation--potential role for a reduction in reactive oxygen species generation. Crit Care Med. 2010; 38:871–878. [PubMed: 20081530]
27. Lucas R, Verin AD, Black SM, Catravas JD. Regulators of endothelial and epithelial barrier integrity and function in acute lung injury. Biochem Pharmacol. 2009; 77:1763–1772. [PubMed: 19428331]
28. Kaner RJ, Ladetto JV, Singh R, Fukuda N, Matthay MA, Crystal RG. Lung overexpression of the vascular endothelial growth factor gene induces pulmonary edema. Am J Respir Cell Mol Biol. 2000; 22:657–664. [PubMed: 10837361]
29. Ware LB, Koyama T, Billheimer DD, Wu W, Bernard GR, Thompson BT, et al. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. Chest. 2010; 137:288–296. [PubMed: 19858233]
30. Determann RM, Millo JL, Waddy S, Lutter R, Garrard CS, Schultz MJ. Plasma CC16 levels are associated with development of ALI/ARDS in patients with ventilator-associated pneumonia: a retrospective observational study. BMC Pulm Med. 2009; 9:49. [PubMed: 19958527]
31. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, et al. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006; 354:2564– 2575. [PubMed: 16714767]
32. Daoud EG, Farag HL, Chatburn RL. Airway pressure release ventilation: what do we know? Respir Care. 2012; 57:282–292. [PubMed: 21762559]
33. Downs JB, Stock MC. Airway pressure release ventilation: a new concept in ventilatory support. Crit Care Med. 1987; 15:459–461. [PubMed: 3568710]
34. Gu XL, Wu GN, Yao YW, Shi DH, Song Y. Is high-frequency oscillatory ventilation more effective and safer than conventional protective ventilation in adult acute respiratory distress syndrome patients? A meta-analysis of randomized controlled trials. Crit Care Lond Engl. 2014; 18:R111.
35. Cox CA, Wolfson MR, Shaffer TH. Liquid ventilation: a comprehensive overview. Neonatal Netw NN. 1996; 15:31–43. [PubMed: 8715647]
36. Hirschl RB, Parent A, Tooley R, McCracken M, Johnson K, Shaffer TH, et al. Liquid ventilation improves pulmonary function, gas exchange, and lung injury in a model of respiratory failure. Ann Surg. 1995; 221:79–88. [PubMed: 7826165]
37. Galvin IM, Steel A, Pinto R, Ferguson ND, Davies MW. Partial liquid ventilation for preventing death and morbidity in adults with acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev. 2013; 7:CD003707. [PubMed: 23881653]
38. Tulman DB, Stawicki SPA, Whitson BA, Gupta SC, Tripathi RS, Firstenberg MS, et al. Veno-venous ECMO: a synopsis of nine key potential challenges, considerations, and controversies. BMC Anesthesiol. 2014; 14:65. [PubMed: 25110462]
39. Rozé H, Repusseau B, Ouattara A. Extracorporeal membrane oxygenation in adults for severe acute respiratory failure. Ann Fr Anesthèsie Rèanimation. 2014; 33:492–494.
40. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome). Use of the Bramson membrane lung. N Engl J Med. 1972; 286:629–634. [PubMed: 5060491]
41. Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013; 368:2159–2168. [PubMed: 23688302]
42. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm Lond Engl. 2005; 2:8.

43. Ryan JM, Barry F, Murphy JM, Mahon BP. Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. Clin Exp Immunol. 2007; 149:353–363. [PubMed: 17521318]
44. Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, et al. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. Am J Respir Cell Mol Biol. 2005; 33:145–152. [PubMed: 15891110]
45. Gupta N, Su X, Popov B, Lee JW, Serikov V, Matthay MA. Intrapulmonary delivery of bone marrow-derived mesenchymal stem cells improves survival and attenuates endotoxin-induced acute lung injury in mice. J Immunol Baltim Md 1950. 2007; 179:1855–1863.
46. Zheng G, Huang L, Tong H, Shu Q, Hu Y, Ge M, et al. Treatment of acute respiratory distress syndrome with allogeneic adipose-derived mesenchymal stem cells: a randomized, placebo-controlled pilot study. Respir Res. 2014; 15:39. [PubMed: 24708472]
47. Czikora I, Alli A, Bao H-F, Kaftan D, Sridhar S, Apell H-J, et al. A novel tumor necrosis factor-mediated mechanism of direct epithelial sodium channel activation. Am J Respir Crit Care Med. 2014; 190:522–532. [PubMed: 25029038]
48. Hartmann EK, Boehme S, Duenges B, Bentley A, Klein KU, Kwiecien R, et al. An inhaled tumor necrosis factor-alpha-derived TIP peptide improves the pulmonary function in experimental lung injury. Acta Anaesthesiol Scand. 2013; 57:334–341. [PubMed: 23216436]
49. Gonzales JN, Gorshkov B, Varn MN, Zemskova MA, Zemskov EA, Sridhar S, et al. Protective effect of adenosine receptors against lipopolysaccharide-induced acute lung injury. Am J Physiol Lung Cell Mol Physiol. 2014; 306:L497–L507. [PubMed: 24414256]
50. Gonzales JN, Kim KM, Zemskova MA, Rafikov R, Heeke B, Varn MN, et al. Low anticoagulant heparin blocks thrombin-induced endothelial permeability in a PAR-dependent manner. Vascul Pharmacol. 2014; 62:63–71. [PubMed: 24469066]
51. Tuinman PR, Dixon B, Levi M, Juffermans NP, Schultz MJ. Nebulized anticoagulants for acute lung injury - a systematic review of preclinical and clinical investigations. Crit Care Lond Engl. 2012; 16:R70.
52. Czikora I, Sridhar S, Gorshkov B, Alieva IB, Kasa A, Gonzales J, et al. Protective effect of Growth Hormone-Releasing Hormone agonist in bacterial toxin-induced pulmonary barrier dysfunction. Front Physiol. 2014; 5:259. [PubMed: 25076911]
53. Antonov A, Snead C, Gorshkov B, Antonova GN, Verin AD, Catravas JD. Heat shock protein 90 inhibitors protect and restore pulmonary endothelial barrier function. Am J Respir Cell Mol Biol. 2008; 39:551–519. [PubMed: 18474672]
54. Duggal A, Ganapathy A, Mohana Ratnapalan M, Adhikari NK. Pharmacological treatments for acute respiratory distress syndrome: systematic review. Minerva Anestesiol. 2015; 81:567–588. [PubMed: 24937499]