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**REVIEW**

# Acute Lung Injury – From Pathophysiology to Treatment

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**Summary**

Acute lung injury is characterized by acute respiratory insufficiency with tachypnea, cyanosis refractory to oxygen, decreased lung compliance, and diffuse alveolar infiltrates on chest X-ray. The 1994 American-European Consensus Conference defined "acute respiratory distress syndrome, ARDS" by acute onset after a known trigger, severe hypoxemia defined by $PaO_2/FiO_2 \leq 200$ mm Hg, bilateral infiltrates on chest X-ray, and absence of cardiogenic edema. Milder form of the syndrome with $PaO_2/FiO_2$ between 200-300 mm Hg was named „acute lung injury, ALI". Berlin Classification in 2012 defined three categories of ARDS according to hypoxemia (mild, moderate, and severe), and the term "acute lung injury" was assigned for general description or for animal models. ALI/ARDS can originate from direct lung triggers such as pneumonia or aspiration, or from extrapulmonary reasons such as sepsis or trauma. Despite growing understanding the ARDS pathophysiology, efficacy of standard treatments, such as lung protective ventilation, prone positioning, and neuromuscular blockers, is often limited. However, there is an increasing evidence that direct and indirect forms of ARDS may differ not only in the manifestations of alterations, but also in the response to treatment. Thus, individualized treatment according to ARDS subtypes may enhance the efficacy of given treatment and improve the survival of patients.

**Key words**

Acute lung injury • Acute respiratory distress syndrome • Pathophysiology • Therapy • ARDS subtypes

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## Introduction

Acute respiratory distress characterized by tachypnea, cyanosis refractory to oxygen delivery, decreased lung compliance, and diffuse alveolar infiltrates evident on chest X-ray was firstly described in 1967. Within the following decades, definitions of the acute respiratory distress syndrome (ARDS) have several times changed. Regarding improved definitions and more precise diagnostic methods, it has been expected that the prognosis should also improve. However, despite use of lung protective ventilation, neuromuscular blockers, and prone positioning, mortality of this syndrome still remains around 40 %.

Nevertheless, there is an increasing evidence that direct (pulmonary) and indirect (extrapulmonary) forms of ARDS may differ not only in the manifestations of lung alterations, but also in the response to treatment. Thus, individualized treatment according to ARDS subtypes may enhance the efficacy of given treatment and improve the survival of patients.

This article provides a review of current knowledge on pathophysiology of ARDS, biomarkers of ARDS as well as on novel treatment approaches which may be of benefit.

## Definitions of ARDS

ARDS was firstly described in 1967 by Ashbaugh and co-workers, who noticed similar



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respiratory symptoms in 12 pacients with acute respiratory failure, which were caused by various triggering factors. Syndrome was resistant to the used treatment and symptoms were similar to symptoms of respiratory distress syndrome (RDS) in premature neonates, suggesting the relation to dysfunction of pulmonary surfactant (Ashbaugh *et al.* 1967).

Later, the definition and classification criteria of ARDS have changed. In addition, the name of the syndrome has changed from "adult" to "acute" to emphasize that this syndrome may occur in children, as well. In 1994, American-European Consensus Conference postulated the following criteria: a) acute onset of symptoms after a known risk factor with maximum within a week; b) severe hypoxemia resistant to oxygen therapy, with more severe form of respiratory insufficiency defined by a ratio between arterial partial pressure of oxygen and fraction of inspired oxygen ($PaO_2/FiO_2$)≤200 mm Hg (26.7 kPa) named „ARDS", and a milder form of this syndrome with $PaO_2/FiO_2$ 200-300 mm Hg (40 kPa) named „acute lung injury (ALI)"; c) diffuse bilateral infiltrates on chest X-ray; d) absence of cardiogenic pulmonary edema verified by wedge pressure in the pulmonary artery ≤18 mm Hg or absence of clinical symptoms of hypertension of the left ventricle (Bernard *et al.* 1994).

In 2012 in attempt to improve the validity and reliability of the definition, so-called Berlin Classification defined three categories of ARDS according to hypoxemia at a level of positive end-expiratory pressure (PEEP) of ≥5 cm $H_2O$ (0.5 kPa): a) mild ARDS with $PaO_2/FiO_2$ between 200-300 mmHg, b) moderate ARDS with $PaO_2/FiO_2$ between 100-200 mm Hg, and c) severe ARDS with $PaO_2/FiO_2$≤100 mm Hg. The category "acute lung injury", which in the previous definition expressed the milder form of ARDS, was omitted from the Berlin definition and this term has been assigned for general description of the situation or for animal models where the clinical definition criteria cannot be fulfilled (ARDS Definition Task Force 2012, Fioretto and de Carvalho 2013).

## Epidemiology of ARDS

Data on incidence of ARDS may largely vary due to several factors including geographical differences and regional genetical variability, differences in health care systems, as well as differences in diagnostic criteria for ARDS (Seeley 2013). For instance, study by Rubenfeld *et al.* (2005) found an incidence of mild ARDS of 79/100000 and moderate/severe ARDS of 59/100000 with a total mortality about 40 %. However, newer study has shown a declining trend of ARDS incidence in the USA, from incidence of 81/100,000 in 2001 to 38/100,000 in 2008 (Li *et al.* 2010). In recent multicenter prospective study carried out in 459 ICUs in 50 countries in 5 continents, ARDS represented 10.4 % of total admission to intensive care unit (ICU) and 23.4 % of all patients requiring mechanical ventilation. The prevalence was 30.0 % for mild ARDS, 46.6 % for moderate ARDS, and 23.4 % for severe ARDS, and overall, unadjusted ICU and hospital mortality was 35.3 and 40.0 %, respectively and both augmented with increased ARDS severity (Bellani *et al.* 2016).

Except of mortality, long-term consequences in pacients who had survived ARDS in terms of substantial reduction in health-related quality of life and physical and mental dysfunction of a various extent should be taken into account, as well. While most patients may return to normal or near-normal lung physiology, they may exhibit marked and persistent muscle weakness with reduced determinants of functional status (reduced distance walked in 6 min etc.), higher occurrence of polyneuropathy, myopathy, tracheal stenosis, contractures, sensorineural hearing loss, but also higher occurance of depression, anxiety and post-traumatic stress disorder, and significant cognitive impairment in executive function, memory, and attention, social isolation etc. (Herridge *et al.* 2016, Bein *et al.* 2018).

## Etiology of ARDS

ARDS has been defined by exposure to a known direct (pulmonary) or indirect (extrapulmonary) insult or worsening of respiratory symptoms within 7 days. The most common cause of direct ARDS is pneumonia and of indirect ARDS sepsis. However, other factors may also contribute to the pathogenesis of ARDS. Very important seem to be genetic factors with more than 40 candidate genes associated with ARDS (Liu and Li 2014), among which the angiotensin-converting enzyme (ACE) gene-2 protein contributing to regulation of pulmonary vascular permeability was identified as the cell entry receptor for coronavirus that recently caused severe acute respiratory distress syndrome (SARS-CoV) (Kuba *et al.* 2005). In the context of actual COVID-19 pandemic, expression of ACE2 receptors and treatment with ACE2-increasing drugs in relation to the risks and prognosis of

SARS-CoV-2 infection have been intensively studied (Fang *et al.* 2020, Milne *et al.* 2020, Aronson and Ferner 2020).

Additional factors increasing the risk of ARDS are e.g. virulence factors, race differences, environmental factors (chronic alcohol abuse, cigarette smoke exposure), older age (>65 years), chronic lung disease, concomittant diseases etc. (Matthay *et al.* 2012, Spadaro *et al.* 2019). Development and worsening of ARDS can be potentiated by inappropriate mechanical ventilation where the ventilator-induced lung injury can be caused by excessive lung stretch (volutrauma) or pressure (barotrauma), repetitive alveolar opening and closing, leading to shearing injury (atelectrauma), and potential oxygen toxicity. These changes also trigger systemic inflammation, potentially inducing extra-pulmonary organ failure (biotrauma) (Sweeney and McAuley 2016).

**Table 1.** The most frequent risk factors of ARDS (Ware and Matthay 2000, Mortelliti and Manning 2002, Saharan *et al.* 2010).

| Risk factors of ARDS | |
|---|---|
| **Direct lung injury** | **Indirect lung injury** |
| Pneumonia | Sepsis |
| Aspiration of gastric content | Severe trauma with shock |
| Lung contusion | Repetitive blood transfusion |
| Fat embolism | Acute pancreatitis |
| Near-drowning | Drug abuse |
| Inhalation injury (smoke, gases) | Burns |
| Reperfusion edema after lung transplantation or lung embolectomy | Disseminated intravascular coagulation (DIC) |

## Pathogenesis of ARDS

Acute, exudative phase (0-7 days) is characterized by rapid onset of respiratory dysfunction. Tachypnoea, tachycardia and respiratory alkalosis, which may precede a finding of diffuse bilateral infiltrates on X-ray, may occur within first 12-24 h after initiating insult. These findings are associated with diffuse alveolar damage with destruction of epithelial-endothelial barrier, allowing excessive leak of protein-rich fluid and blood cells into the interstitium and alveoli (Ware and Matthay 2000, Matthay *et al.* 2012). Tissue injury triggers transmigration of neutrophils which are activated and together with alveolar macrophages, platelets and other inflammatory and fixed lung cells produce a wide variety of substances which exacerbate inflammation but can also serve as biomarkers of acute phase (see further).

Damage of surfactant-producing alveolar type II cells and inactivation of surfactant layer in the alveoli by edematous plasma proteins and pro-inflammatory cytokines lead to alveolar atelectasis and decreased lung compliance. The loss of function of epithelial ion channels impairs the generation of osmotic forces necessary to return edema fluid from alveoli to the interstitium. These changes together with development of hyaline membranes from leaking plasma proteins, alveolar hemorrhage, and decreased pulmonary compliance result in worsening of the gas exchange. Besides contribution to increased permeability, alveolar vascular damage is associated with altered vasomotor tone (both vasoconstriction and vasodilation) and formation of microthrombi. Increasing right ventricular afterload results into pulmonary hypertension. The right ventricular dysfunction can be further exacerbated by inappropriate mechanical ventilation and fluid overload. Combined epithelial and endothelial damage finally end up in worsening ventilation-perfusion mismatch and refractory hypoxia (Mortelliti and Manning 2002, Sweeney and McAuley 2016). Nevertheless, the mechanisms by which the microvascular endothelium and alveolar epithelium are injured can be more complex and may vary depending on the triggering pulmonary or extrapulmonary event (Spadaro *et al.* 2019).

Within 5-7 days from the insult, the exudative phase fluently converts to the proliferative phase, which is characterized by proliferation and fenotypic changes of fibroblasts and alveolar cells type II, differentiating into type I alveolar cells. Regeneration of epithelial layer

permits the clearance of edematous liquid from the lung, and the remaining intraalveolar debris is also cleared by inflammatory cells, particularly by macrophages. As reparation continues, restoration of vasomotor tone reduces the shunts, and gradually decreasing pulmonary hypertension leads to improved oxygenation that is followed by recovering lung compliance. In some patients the proliferative phase may progress into the fibrotic phase, which is associated with diffuse fibrotic changes of the lung tissue due to failure of removal of alveolar collagen (Ware and Matthay 2000, Matthay *et al.* 2012, Bhargava and Wendt 2012). However, fibroproliferative changes may develop sooner, as indicated by evidence of collagen synthesis as early as 24 h of the course of ARDS, thus, may be initiated simultaneously with inflammatory changes (Marshall *et al.* 2000, Spadaro *et al.* 2019).

## Clinically relevant biomarkers of ARDS

In relation to the above-mentioned changes, various biologically active substances are produced or released from damaged cells in high concentrations. Many of them may serve as biomarkers providing information for identification of patients at risk for ARDS, progression of the lung injury, response to treatment, or prognosis. Several biomarkers for exudative and proliferative (or fibroproliferative) phases of ARDS have been investigated in the blood, pulmonary edema fluid or bronchoalveolar lavage fluid (BALF), and exhaled air. However, while none of them is reliable enough if considered alone, combinations of biomarkers are recommended. Lists of the most important biomarkers of exudative and fibroproliferative phases of ARDS are provided in Table 2 and Table 3.

**Table 2.** Biomarkers of acute (exudative) phase of ARDS (Bhargava and Wendt 2012, Fujishima 2014, Hussain *et al.* 2018).

| | Marker | Biological source of biomarker | Change in ARDS |
|---|---|---|---|
| *Alveolar cells type I* | sRAGE | Plasma, BALF | ↑ |
| *Alveolar cells type II* | SP-A, SP-B, SP-D | Plasma, BALF | ↓ BALF, ↑ plasma |
| | KL-6 | Plasma, BALF | ↑ |
| *Non-ciliary bronchial cells* | CC16 | Plasma, BALF | ↑ |
| *Extracellular matrix* | Laminin | Plasma, BALF | ↑ |
| | Elastin/Desmosin | Urine | ↑ |
| | MMPs | Plasma, BALF | ↑ |
| *Endothelial cells* | Angiopoietin-2 | Plasma | ↑ |
| | sP-selectin | Plasma | ↑ |
| | sICAM-1 | Plasma | ↑ |
| | vWF | Plasma | ↑ |
| | Thrombomodulin | Plasma | ↑ |
| *Coagulation* | PAI-1 | Plasma | ↑ |
| | protein C | Plasma | ↓ |
| | vWF | Plasma | ↑ |
| *Inflammation* | IL-1β, IL-6, IL-8, | Plasma, BALF | ↑ |
| | IL-10 | Plasma, BALF | ↑ |
| | TNFα | Plasma, BALF | ↑ |
| | CRP | Plasma | ↑ |

BALF: bronchoalveolar lavage fluid; CC16: Club cell protein; CRP: C-reactive protein; IL: interleukin; KL: *Krebs von den Lungen* protein; PAI: plasminogen activator inhibitor; sICAM: soluble intercellular adhesion molecule; SP: specific surfactant protein; sRAGE: soluble receptor for advanced glycation end products; vWF: von Willebrand factor; TNF: tumor necrosis factor; MMPs: matrix metalloproteinases; sP-selectin: soluble P-selectin.

**Table 3.** Biomarkers of late (fibroproliferative) phase of ARDS (Bhargava and Wendt 2012, Fujishima 2014, Hussain *et al.* 2018).

| | Marker | Biological source of biomarker | Change in ARDS |
|---|---|---|---|
| *Proliferation of epithelium* | KGF | BALF | ↑ |
| | HGF | BALF | ↑ |
| *Proliferation of endothelium* | VEGF | Plasma, BALF | ↑ plasma, ↓ BALF |
| | Angiopoietin-2 | Plasma | ↑ |
| *Apoptosis of epithelial cells* | Fas/FasL | BALF | ↑ |
| *Proliferation of fibroblasts* | N-PCP-III | BALF | ↑ |

BALF: bronchoalveolar lavage fluid, KGF: keratinocyte growth factor; HGF: hepatocyte growth factor; VEGF: vascular endothelial growth factor; N-PCP-III: N-terminal procollagen peptide-III.

## ARDS subphenotypes

*Direct vs. indirect lung injury groups*

According to molecular phenotyping, direct and indirect ARDS phenotypes have been described (Calfee *et al.* 2015). In direct lung injury, noxious stimulus hits primarily the lung structures. Activation of innate immune response by binding of bacterial products or cell-injury associated endogenous molecules (danger-associated molecular patterns, DAMPs) to pattern recognition receptors (e.g. Toll-like receptors) on the lung epithelium and alveolar macrophages initiates the acute inflammatory response (Matthay *et al.* 2012). In addition, neutrophil extracellular traps (NETs), extracellular histones, and granular proteins (e.g. neutrophil elastase and myeloperoxidase) released from dying neutrophils also act as DAMPs and induce epithelial and endothelial cell death. When enter the circulation, histones stimulate platelet aggregation, enhance recruitment of neutrophils, and aggravate inflammation (Xu *et al.* 2015, Lv *et al.* 2017). Extensive activation of leukocytes can progress to systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), and multiple organ failure (Bhatia and Moochhala 2004).

If the primary cause of ARDS is located in extrapulmonary tissues, the lung inflammation and edema generation may be triggered by high concentrations of histones to which is the lung highly susceptible (Abrams *et al.* 2013, Xu *et al.* 2015). However, other substances including pro-inflammatory cytokines TNFα and IL-1β, high-mobility group box (HMGB)-1 protein, or mitochondrial deoxyribonucleic acid (DNA) can also act as DAMPs and induce lung inflammation and ARDS (Fujishima 2014).

Nevertheless, there are additional differences between the direct and indirect ARDS, as well. In the direct form of ARDS, the injury is more localized to alveolar epithelial cells, with alveolar collapse, accumulation of neutrophils, fibrin deposition, and formation of hyaline membranes and alveolar wall edema. In the indirect ARDS, diffuse injury to endothelial cells is prominent, with typical finding of interstitial edema and less obvious lung accumulation of neutrophils than in the direct form.

The substances released from injured lung cells or produced by activated cells spill over into the blood and thereby can serve as valuable biomarkers of ARDS reflecting damage to specific cells and dynamics of the process (Bhargava and Wendt 2012, Mokra and Kosutova 2014). In the direct ARDS, concentrations of TNFα, IL-1β, IL-6, and IL-8 elevate mainly in the bronchoalveolar lavage fluid (BALF) or lung tissue. Because of primary injury to epithelial cells, surfactant protein (SP)-D as a valuable marker of type II alveolar cells injury and receptor for advanced glycation end products (RAGE) as a marker of type I alveolar cells injury have been identified. In the indirect ARDS, increased pro-inflammatory cytokines are detected predominantly in the plasma indicating that the lung injury is caused by the action of mediators released from extrapulmonary foci into the systemic circulation (Pelosi *et al.* 2003, Shaver and Bastarache 2014). Damage of endothelial cells and prominent systemic inflammation can be confirmed by elevated plasma levels of von Willebrand factor (vWF), IL-6, IL-8, and angiopoietin-2 (Bhargava and Wendt 2012, Calfee *et al.* 2015).

It has been shown that the differences in the pathomechanisms of ARDS of pulmonary and

extrapulmonary origins may influence the efficacy of the used therapeutic strategies, as well (Pelosi *et al.* 2003, Rocco and Pelosi 2008). In animal models, methylprednisolone more effectively attenuated the inflammatory changes, lung mechanics and morphometrics in a model of direct ARDS (Leite-Junior *et al.* 2008), while response to recruitment maneuvers and PEEP on oxygenation and lung mechanics was better in a model of indirect ARDS (Kloot *et al.* 2000). The first clinical data indicate that the epithelium could be a treatment target with keratinocyte growth factor (KGF) for direct ARDS, whereas the endothelium could be targeted in indirect ARDS using statins and recombinant angiopoietin 1 (Calfee *et al.* 2015). Thus, the above-mentioned specific combinations of biomarkers not only help to distinguish patients with direct ARDS from those with an indirect ARDS, but may also help in the diagnosis and identification of patients who may benefit from different therapeutic strategies (Spadaro *et al.* 2019).

*Hyperinflammatory vs. hypoinflammatory groups*

According to their clinical and biological characteristics and response to treatment, hyperinflammatory and hypoinflammatory subphenotypes have been described (Calfee *et al.* 2014, Reilly *et al.* 2014, Calfee *et al.* 2015). The hyperinflammatory phenotype, covering about one third of ARDS patients, is associated with higher plasma levels of IL-6, IL-8, soluble tumor necrosis factor receptor (sTNFR)-1, and plasminogen activator inhibitor (PAI)-1 and lower protein C, worse metabolic acidosis with lower serum bicarbonate, higher vasopressor requirements, higher prevalence of sepsis, fewer ventilator-free and organ failure-free days, and increased mortality. Among the biomarkers, IL-6, interferon gamma (IFN-γ), angiopoietin 1/2 and PAI-1 have been identified to cluster ARDS into two biological phenotypes with different mortality rates (Bos *et al.* 2017), and different responses to PEEP (Calfee *et al.* 2014) and fluid management strategies (Famous *et al.* 2017).

## Other promising biomarkers

*Metabolomics*

There is an increasing number of publications demonstrating that the analysis of lower molecular weight cell metabolites (metabolomics), which is generally performed using nuclear magnetic resonance (NMR) and mass spectrometry (MS), may bring additional information for diagnosis and treatment of ARDS and/or sepsis (Stringer *et al.* 2016, Eckerle *et al.* 2017). Investigation of metabolic changes may be useful for detection of physiological changes in real time allowing monitoring of potential insults, disease progression and drug responses, while these changes occur in relation to alterations in the gene and protein activity, which are associated with the disease (Stringer *et al.* 2016). Metabolomics studies performed in experimental models as well as in patients with ARDS analysed a variety of samples from exhaled breath, serum, BALF and lung tissue and found that the lung injury results in a perturbation of energy and oxidative stress metabolism (Evans *et al.* 2014, Stringer *et al.* 2016, Viswan *et al.* 2017, Bos 2018, Viswan *et al.* 2019).

*MicroRNA (MiRNA)*

MiRNA, non-coding RNA molecules which regulate gene expression at the post-transcriptional level, play an important role in inflammation and/or apoptosis in ARDS (Ferruelo *et al.* 2018). They can serve as useful biomarkers because of their easy identification in various body fluids, resistance to environmental conditions, and changes of expression in various disease states (Cardinal-Fernández *et al.* 2016). Recently, many circulating miRNAs (miR-25, miR-133a, miR-146, miR-150, miR-223 etc.) were found to be associated with various pathological conditions, such as inflammation, infection, and sepsis, while some of them correlated well with the disease stage, and patients' short and long term prognosis (Benz *et al.* 2016).

In ARDS patients, three whole blood miRNA markers (miR-181a, miR92a and miR-424) were significantly associated with ARDS, with miR-181a and miR-92a as risk biomarkers for ARDS and miR-424 as a protective biomarker (Zhu *et al.* 2017).

## Treatment of ARDS

Despite understanding the pathophysiology of ALI/ARDS has greatly improved within the last decades, mortality remains high and efficacy of standard therapeutic approaches is limited.

*Non-pharmacological interventions*

The currently used therapy is based on so-called ***lung-protective mechanical ventilation***. The ventilation protecting the lung from additional „ventilator-induced lung injury (VILI)“ should: 1) use low tidal volumes

(<6 ml/kg of the predicted body weight) combined with limited inspiratory plateau pressures (<30 cm $H_2O$) to prevent a lung overdistension ("barotrauma/volutrauma"); 2) use sufficiently high levels of PEEP to prevent a repetitive opening and closing of the terminal lung units ("atelectrauma") (Haberthür and Seeberger 2016, Umbrello *et al.* 2017).

For re-inflation of the collapsed lung regions, different types of recruitment maneuvers, such as sustained inflation, intermittent sighs and stepwise increase in inspiratory pressure could be of benefit, however, their use is discussed (Chiumello *et al.* 2016).

Some improvement may bring the high-frequency oscillatory ventilation (HFOV) which uses very small tidal volumes (2 ml per kg of predicted body weight) at high frequencies of up to 900 breaths per min, *via* several atypical mechanisms of gas transfer (Sweeney and McAuley 2016). However, two large randomised controlled trials failed to show any benefit from this mode of ventilation in adults with ARDS (Ferguson *et al.* 2013, Young *et al.* 2013).

When mechanical ventilation is unable to provide an adequate gas exchange because a critical volume of alveolar units has failed, extracorporeal membrane oxygenation (ECMO) can be used as a life-saving respiratory support. ECMO replaces endogenous alveolar gaseous exchange, allows reduction in ventilatory settings, and reduces the risk of VILI (Sweeney and McAuley 2016). Use of ECMO in refractory hypoxemia (Peek *et al.* 2009) may improve survival, however, is limited to the specialized centers.

Other approach with favorable results is prone positioning which should be reserved to patients with severe ARDS, especially in the acute phase (Lichtenstein and Mezière 2008, Umbrello *et al.* 2017). Because of ability to recruit lung parenchyma this approach enables better ventilation/perfusion matching with a consequent improvement in clearance of carbon dioxide, more homogenous distribution of ventilation with a reduction of VILI and recruitment of dorsal lung regions through the redistribution of lung densities (Gattinoni *et al.* 2013, Guérin and Mancebo 2015).

In 2017, guidelines on the above-mentioned interventions were summarized in the International Clinical Practice Guideline for mechanical ventilation on adults with ARDS (Fan *et al.* 2017).

Conservative fluid management is an essential aspect of therapy since pulmonary edema is a main feature of ARDS. Fluid excess is linked to hemodynamic instability, decreased oxygenation and worsening lung injury scores. On the other hand, the conservative fluid management enhanced lung function and shortened the duration of mechanical ventilation and intensive care (Wiedemann *et al.* 2006), and may also decrease mortality (Semler *et al.* 2016).

*Pharmacotherapy*

Within the last decades, several groups of medicaments have been used for pharmacotherapy of ARDS, however, a positive response to some of them has been shown just in specific subgroups of patients (Boyle *et al.* 2013, Standiford and Ward 2016).

Among the pharmacological interventions, use of neuromuscular blocking agents (NMBAs) seems to be the most promising. As spontaneous breathing in the patients with severe ARDS might generate high transpulmonary pressure, use of NMBAs enables amelioration of patient-ventilator synchrony in reduced oxygen consumption leading to improved survival (Neto *et al.* 2012, Hraiech *et al.* 2015). However, data from recent meta-analyses bring inconsistent information on the lung function or mortality (Hua *et al.* 2020, Zheng *et al.* 2020).

Because of their potent anti-inflammatory and antiedematous actions, corticosteroids have been tested in experimental models of acute lung injury (Mokra *et al.* 2013, Mokra *et al.* 2016, Kosutova *et al.* 2016, Mikolka *et al.* 2019) where they significantly reduced inflammation, edema formation, and oxidative stress. Promising is also combination of corticosteroids with exogenous surfactant (Mikolka *et al.* 2013, Mikolka *et al.* 2016). In patients with ARDS, some improvements in duration of mechanical ventilation, duration of hospitalization or oxygenation have been observed for low-to-moderate dose of corticosteroids, if administered early (<14 days from insult) (Tongyoo *et al.* 2016, Meduri *et al.* 2018). However, if steroids are started 14 days or more after the diagnosis of ARDS, they can be even harmful (Steinberg *et al.* 2006, Mokra *et al.* 2019). The combination of inhaled $\beta_2$-agonists and corticosteroid (formoterol/budesonide) administered early in patients at risk of ARDS has prevented development of ARDS and improved oxygenation (Festic *et al.* 2017).

Beneficial could be phosphodiesterase (PDE) inhibitors exerting a wide spectrum of actions including anti-inflammatory, antioxidant and antiedematous effects. In experimental models of ARDS, treatment with both non-selective and selective PDE-3, PDE-4 or PDE-5

inhibitors led to significant improvement of lung functions and to reduced inflammation (Fakioglu *et al.* 2004, Mokra *et al.* 2008, Mokra *et al.* 2012, Schick *et al.* 2012, Kosutova *et al.* 2018a, Kosutova *et al.* 2018b). However, there are only few clinical studies on the use of PDE inhibitors, with questionable results (Salari *et al.* 2005, Cornet *et al.* 2010).

Pre-treatment with aspirin decreased the incidence of ARDS (Boyle *et al.* 2015), however, the recent data are inconsistent (Wang *et al.* 2018, Du *et al.* 2018). Inhaled nitric oxide (NO) transiently improved oxygenation and long-term lung function in ARDS survivors, but without effect on mortality, and because of risk of renal impairment, this treatment is not recommended (Gebistorf *et al.* 2016). Similarly, many other treatments (statins, beta-agonists, non-steroidal anti-inflammatory drugs, antioxidants, exogenous surfactant, neutrophil elastase inhibitors, anticoagulants, anti-TNF biologics etc.) with favorable pre-clinical results failed in the clinical trials (Spadaro *et al.* 2019). With respect to the lung regeneration, cell therapies and intravenous mesenchymal stem cell therapy have been under intensive research in ARDS (Wilson *et al.* 2015, Silva *et al.* 2019, Abraham and Krasnodembskaya 2020).

Nowadays, there is a significant trend to use anti-inflammatory therapies according to ARDS subtyping defined by blood biomarker levels, where the anti-inflammatory agents are expected to be more efficient in patients with hyperinflammatory phenotype of ARDS (Thompson *et al.* 2017, Meyer and Calfee 2017).

## Conclusions

ARDS is a life-threatening syndrome with extreme heterogeneity. Despite intensive investigation in this field, there is no specific pharmacotherapy for ARDS up to now with significant and uniform effect on the disease development and mortality, although the pre-clinical trials have demonstrated promising results. Due to complexity of the pathomechanisms involved in ARDS, targeting a single pathogenetic pathway is not an effective way. Nevertheless, subphenotyping of ARDS patients according to blood biomarkers and clinical features may help clinicians to select patients who may benefit from specific therapeutic strategies and ultimately tailor the treatment for individual patients.

## Conflict of Interest

There is no conflict of interest.

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