



Current Problems in Pulmonary Respiratory Distress Syndrome (Literature Review)

Namazova K*, Aslanov A, Hasanov F, Muradov N, Guliev K, Abbasova M, Musayeva N, Askerova G and Kerimov G

Academician M. Topchubashov Scientific Surgery Center, Azerbaijan

*Corresponding author: Namazova Kamala, Academician M. Topchubashov Scientific Surgery Center, Baku, Azerbaijan, Tel: +994515684747; Email: nkamala@mail.ru

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Abstract

Among critical illnesses with a mortality rate exceeding 50%, one of the prominent pathologies is acute respiratory distress syndrome (ARDS) of the lungs. The historical development of this pathology, its etiopathogenic characteristics, diagnostic criteria, and optimal modes of mechanical ventilation remain relevant topics. We decided to explore and illuminate modern perspectives on acute lung injury (ALI) and the progression to acute respiratory distress syndrome (ARDS) by reviewing local and international literature sources. Our study addresses the etiology, epidemiology, pathogenesis, diagnostic methods, prevention, and treatment of acute respiratory distress syndrome (ARDS). According to statistical data, the incidence of acute respiratory distress syndrome (ARDS) ranges from 1.5 to 88 cases per 100,000 people per year. Depending on etiology and diagnostic criteria, the global mortality rate from ARDS reaches 30-60%. Respiratory failure occurs in 3-15% of surgical patients, and in 25% of cases, sepsis is considered the cause of acute respiratory distress syndrome (ARDS). The measurement of the "Oxygenation or Carrico index" (PO_2/FiO_2) plays a significant diagnostic role in studying tissue hypoxia and choosing appropriate ventilation methods: when PO_2/FiO_2 is <300 mm Hg, it indicates acute lung injury; <200 mm Hg indicates ARDS; and <18 mm Hg suggests capillary blockage in the lungs.

Keywords: Acute Lung Injury; Acute Respiratory Distress Syndrome; Mechanical Ventilation; Respiratory Failure; Pulmonary Edema; ECMO; Prone Positioning

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; ALI: Acute Lung Injury; ASV: Requiring Artificial Ventilation.

Introduction

Acute Respiratory Distress Syndrome (ARDS) has become a focus of attention not only for clinicians but also for scientists of various specialties, including pathologists, pathophysiologists, morphologists, and those involved

in clinical and experimental medicine. The relevance of this problem has been increasingly discussed worldwide, especially since the COVID-19 pandemic [1,2].

ARDS is a severe complication of acute respiratory diseases. It is a non-specific response of the respiratory system triggered by various pro-inflammatory agents, resulting in hypoxemic respiratory failure in the absence of signs of cardiogenic pulmonary edema [1-3]. ARDS can develop due to both primary and secondary lung injuries. Its morphological manifestation is parenchymal edema caused

by systemic inflammatory response and increased capillary permeability in the pulmonary circulation [2].

ARDS was first identified in 1967 in a 12-year-old patient, and mortality was recorded in 7 out of 10 cases presenting with ARDS [3]. The syndrome develops rapidly; within 12–48 hours, the inflammatory process affects the lung parenchyma, requiring artificial ventilation (ASV). During the early hours, patients experience shortness of breath, cough, chest pain, and it is characterized by a high mortality rate.

Historical review of the literature reveals that during the Vietnam War, American doctors encountered respiratory failure in some injured patients 2–3 days after recovering

from severe traumatic shock. Since then, this clinical syndrome, accompanied by high mortality, has been a subject of research.

It was found that ARDS can develop not only after trauma but also as a result of sepsis, aspiration of gastric contents, massive blood transfusion, and other conditions. The syndrome has also been referred to as “shock lung” and “post-perfusion lung”. Starting in the 1960s and 1970s, authors from various countries provided information on acute respiratory failure syndrome and its clinical manifestations during critical conditions such as severe blood loss, mechanical trauma, sepsis, and cardiopulmonary resuscitation [3,4].

Parameter is evaluated	Indicator	Value	Score
Chest x-ray	Alveolar consolidation	No alveolar consolidation	0
		Alveolar consolidation in one quadrant of the lungs	1
		Alveolar consolidation in two squares of the lungs	2
		Alveolar consolidation in three quadrants of the lungs	3
		Alveolar consolidation in the four quadrants of the lungs	4
Hipoxemia	PaO ₂ /FiO ₂	≥ 300	0
		225-299	1
		175-224	2
		100-174	3
		< 100	4
Compliance of the respiratory system (ml/cm H ₂ O) (in mechanical ventilation)	Compliance	≥ 80	0
		60-79	1
		40-59	2
		20-39	3
		≤ 19	4
Positive expiratory pressure (cmH ₂ O) (in mechanical ventilation)	Positive expiratory pressure	≤ 5	0
		06-Aug	1
		09-Nov	2
		Dec-14	3
		≥ 15	4
Total points	The presence of lung damage	No lung damage	0
		Moderate lung damage	0.1-2.5
		Severe lung damage	>2.5

Table 1: The extent of lung damage.

In 1967, Ashbaugh DG, et al. [5] first described symptoms such as shortness of breath, diffuse alveolar infiltration, and edema as “stiff lung”; Hardaway RM and Norlander O referred to the pathological process as “shock lung”; Collins JA called it “septic lung”; and Shumer N along with Korolev BA and Shmerelson MB, termed it “post-perfusion lung syndrome” or “hypoventilation dyspnea.” According to statistical data, the incidence of ARDS varies from 1.5 to 88 cases per 100,000 population annually. In the United States, the prevalence is 78.9 cases per 100,000 population per year, with a high number of hospital bed-days attributed to these patients. Depending on etiology and diagnostics, global mortality from ARDS ranges from 30% to 60% [5]. Among patients treated in the Department of Anesthesiology and Intensive Care for various conditions, particularly surgical diseases, 3–15% develop respiratory failure, with ARDS being a primary cause. In 25% of cases, sepsis leads to ARDS [6-10].

In 1988, Murray JF and colleagues utilized expanded criteria for ARDS to assess the physiological severity of the lesion, distinguishing between the acute and chronic phases of the condition, and identifying the primary cause of lung injury, as outlined in Table 1. Based on etiopathogenetic factors, the American-European Consensus Conference (AECC) in 1992 proposed a unified perspective on ARDS. They defined it as an acute and persistent inflammatory process in the lungs, characterized by increased vascular permeability in the pulmonary circulation, leading to lung parenchymal damage and hypoxemia [11,12].

According to the AECC, ARDS is an acute condition marked by bilateral infiltration and severe hypoxemia in the absence of signs of cardiogenic pulmonary edema. Researchers noted that a $\text{PaO}_2/\text{FiO}_2$ ratio of <300 mmHg indicates acute lung injury, a ratio of <200 mmHg signifies ARDS, and <18 mmHg reflects capillary obstruction in the lungs.

Time interval	The onset of the syndrome (symptoms of lung damage) occurs one week after exposure to a known factor.		
Visualization of chest organs	Bilateral opacities occur that cannot be explained by effusion, atelectasis, or nodules.		
The mechanism of edema	Shortness of breath cannot be explained by heart failure or fluid overload. If there are no risk factors for heart failure, echocardiography should be done first.		
Hypoxemia	Light	Medium	Heavy
	$200 \text{ mm.Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300$ mm.Hg; CPAP ≥ 5 sm H_2O	$100 \text{ mm.Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200$ mm.Hg; CPAP ≥ 5 sm H_2O	$\text{PaO}_2/\text{FiO}_2 \leq 100$ mm.Hg CPAP ≥ 5 sm H_2O

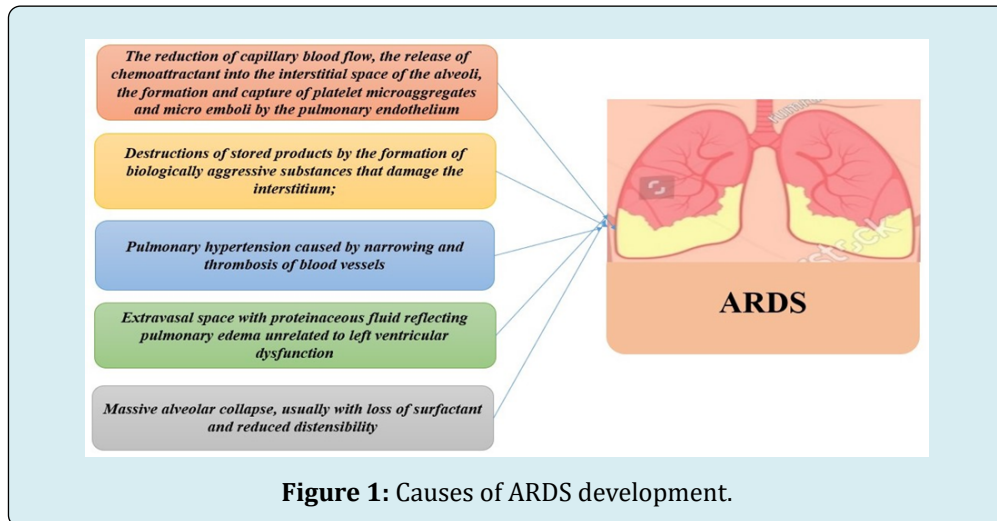
Table 2: Berlin criteria of ARDS.

Directly affecting the lungs (pulmonary origin)	Not directly affecting the lungs (extrapulmonary origin)
More common	
<ul style="list-style-type: none"> lung infection (non-aspiration pneumonia, cytomegalovirus infection) aspiration pneumonia caused by aspiration with liquids (gastric juice, liquid hydrocarbons). 	<ul style="list-style-type: none"> shock of any etiology infection (sepsis, peritonitis, etc.) severe injury massive blood transfusions
Less common	
<ul style="list-style-type: none"> inhalation with toxic substances (high concentration of oxygen, smoke, nitrogen dioxide, ammonium compounds, cadmium, chlorine, phosgene) pulmonary contusion fat embolism radiation pneumonitis pulmonary embolism suffocation reperfusion syndrome 	<ul style="list-style-type: none"> pancreatitis artificial blood circulation disseminated intravascular coagulation burns acute traumatic brain injury uremia carcinomatosis of the lymphatic system eclampsia condition after cardioversion intestinal infarction intrauterine death of the fetus hypothermic injury large-scale surgical interventions cardiopulmonary resuscitation

Table 3: Causes of acute lung injury and ARDS.

In 2012, a group of researchers from Berlin revised the definition of ARDS. The results of the ARDS Definition Task Force, which developed the new definition, were published on the JAMA website [13] (Table 2). The European Society of Intensive Care Medicine, the American Thoracic Society, and the Society of Critical Care Medicine adopted the Berlin criteria for ARDS. In 55% of cases, ARDS originates from

pulmonary causes, 20% from extrapulmonary causes, 21% from mixed causes, and in 4% of cases, the etiology remains unidentified (Table 3) [14]. Regardless of the cause, certain aspects of the pathogenesis of lung parenchymal lesions remain controversial, and the causes of ARDS development are illustrated in Figure 1.



One of the key factors in the etiopathogenesis of ARDS is the accumulation of neutrophils in the lungs, leading to leukocyte activation and the production of pro-inflammatory mediators from various cellular sources. This causes both local and systemic tissue damage, while anti-inflammatory cytokines contribute to the development of pulmonary fibrosis. Pro-inflammatory substances, along with factors involved in the secretion of mediators, cytokines, immunoglobulins, and chemokines, initiate the inflammatory process in the lungs in response to exogenous and endogenous stress factors affecting the epithelial cells of

the lower respiratory tract. Intracellular adhesion molecules (ICAM-1), which are normally present in small amounts in endothelial cells, play a critical role in the accumulation and activation of polymorphonuclear leukocytes in the lungs and their subsequent extravasation with the involvement of β_2 integrins. During ARDS, particularly in septic conditions, ICAM-1 concentrations increase. Proteases and oxidizing agents produced by activated leukocytes and macrophages play a significant role in the damage to the alveolar-capillary membrane (Figure 2).

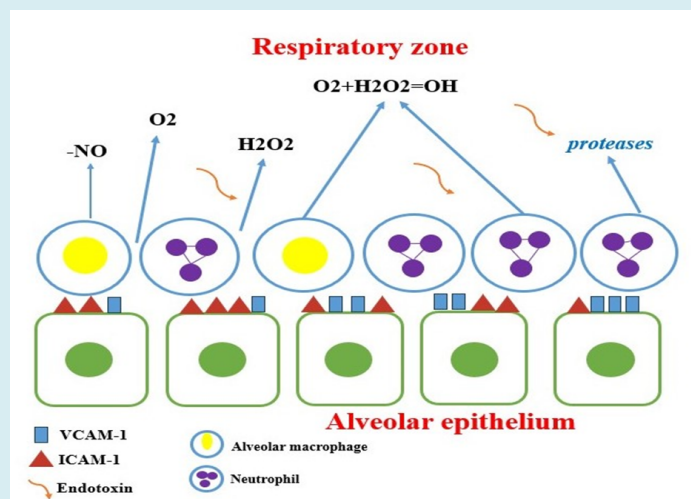


Figure 2: Scheme of the interaction of neutrophils, alveolar macrophages, endothelial cells from bacterial endotoxin.

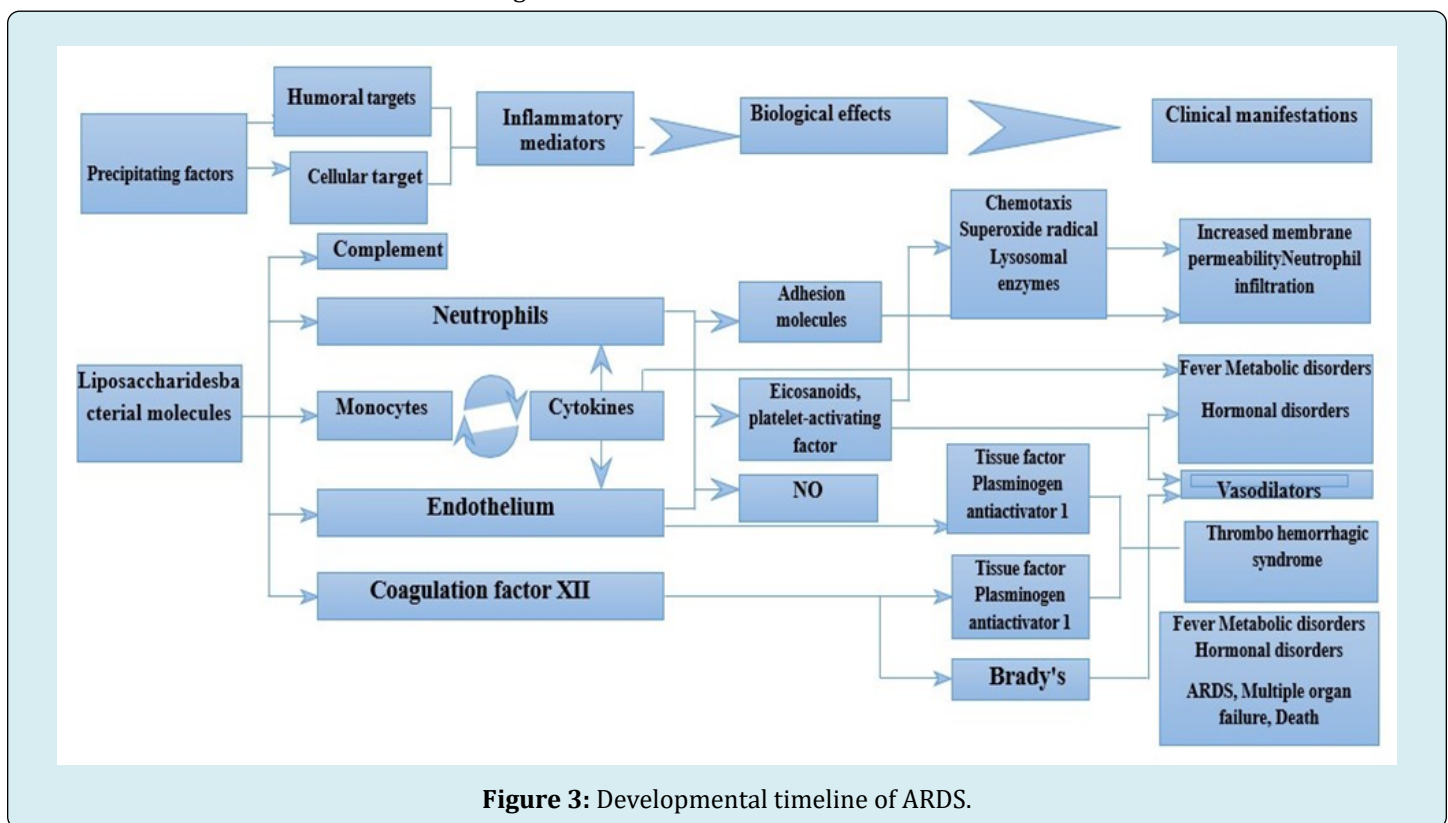
ARDS arises as either primary, associated with direct lung injury, or secondary, caused by indirect injury. It progresses through three stages:

- **Exudative Phase (onset of inflammation):** This phase is characterized by damage to the endothelial cells of the lungs and alveolar epithelial cells, leading to the formation of hyaline membranes and local thrombosis. These changes disrupt gas diffusion across the alveolar-capillary membrane, resulting in the development of hypoxemia.
- **Proliferative Phase:** Marked by hyperplasia of type II alveolar cells, fibroblasts, and myofibroblasts, this phase leads to the thickening of the alveolar septa and the transformation of alveolar hemorrhagic exudate into

cellular granulation tissue. A pathognomonic feature of this phase is the differentiation of type II alveolar cells into type I alveolar cells.

- **Fibrotic Phase:** This stage involves lung remodelling with the development of diffuse and focal fibrosis.

Results from experimental studies show that during the initial hours following the onset of injury, interstitial and alveolar edema and systemic inflammatory responses develop. According to A. Golubev and colleagues (2005), pulmonary edema and systemic inflammatory response form the pathogenetic basis of acute lung injury, as illustrated in Figure 3 [15,16].



Clinical Presentation of ARDS

ARDS can be divided into four clinical stages

Stage I (1-2 days): Depending on the clinical features, the primary cause, and severity, this is referred to as the “light interval” period, covering the time from the onset of the disease to the development of hypoxemia. Symptoms of ARDS begin approximately 12 hours after onset and are accompanied by respiratory failure, tachypnea, tachycardia, and hypertension.

Radiologically, deformation of the pulmonary pattern may be observed against a background of increased

pulmonary markings. Fine focal shadows can be noted in the peripheral regions (Figure 4).

Stage II (2-3 days): The patient’s condition progressively worsens. Depressed consciousness, up to drowsiness, and inspiratory dyspnea involving accessory respiratory muscles develop. Auscultation reveals harsh breathing and dry rales in the lungs. Oxygen inhalation helps manage hypoxemia. Radiologically, the deformation of the pulmonary pattern increases against a background of reduced pulmonary transparency (Figure 4).

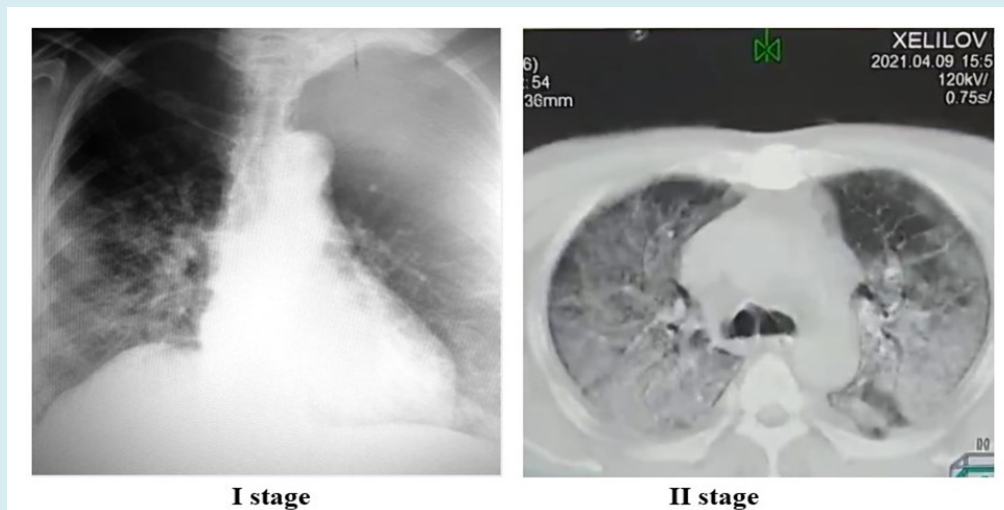


Figure 4: Radiological pattern of ARDS stage I and II.

Stage III (4-5 days): Symptoms of severe respiratory failure dominate at this stage, requiring respiratory support. Auscultation reveals wet rales, and hypoxemia develops. The $\text{PaO}_2/\text{FiO}_2$ ratio drops to <200 mmHg. Radiologically, reduced lung transparency with “lobe-shaped” opacities is

detected (Figure 5).

Stage IV: Consciousness is depressed to the level of coma, and multiple organ failure develops. The $\text{PaO}_2/\text{FiO}_2$ ratio falls to <100 mmHg. Radiologically, “snowstorm” opacities are observed (Figure 5).

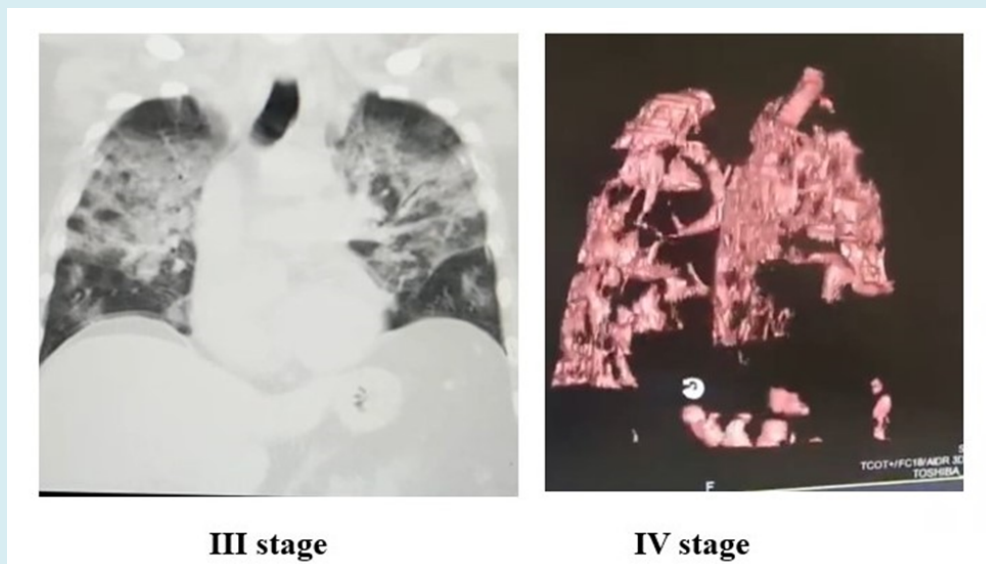


Figure 5: Radiological pattern in stage III and IV of ARDS

Approaches to ARDS Treatment

The primary goals in the treatment of ARDS are to support respiration, reduce hypoxemia, and suppress inflammatory processes. The cornerstone of ARDS intensive therapy is respiratory support. Additionally, infusion therapy, nutritional support, sedation, and muscle relaxation must be carefully managed. Treatment of comorbidities is also crucial

[17].

- **Mechanical Ventilation:** Low tidal volume ventilation strategies help prevent alveolar overdistension. This method is significant in reducing hypoxemia and hypercapnia.
- **Prone Positioning:** Prone positioning enhances oxygen delivery to larger lung areas, improving oxygenation.

- **Extracorporeal Membrane Oxygenation (ECMO):** Used in severe cases to support lung function.
- **Respiratory Support**
- The choice of oxygen therapy depends primarily on the presence of spontaneous ventilation and arterial oxygen concentration.
- **Non-invasive Ventilation:** For patients at high risk of developing hypoxemic respiratory failure but not requiring invasive ventilation, non-invasive methods such as CPAP or BiPAP are used via nasal cannula or face mask. These methods are most effective in the early stages of ARDS, with CPAP being preferred [18].
- **Invasive Mechanical Ventilation:** Tracheal intubation and invasive mechanical ventilation are required if ARDS progresses or respiratory failure becomes decompensated.
- Indications for Tracheal Intubation and Mechanical Ventilation

In cases of progressive or decompensated respiratory failure, invasive mechanical ventilation is the only effective method of respiratory support. Key parameters for safe mechanical ventilation include: peak airway pressure ≤ 35 cm H₂O; tidal volume 6-8 ml/kg; respiratory rate and minute ventilation to maintain PaCO₂ between 30-40 mmHg; peak inspiratory flow rate 40-90 L/min; Inspiration/expiration ratio of 1.5:1; minimum required FiO₂ to ensure adequate arterial oxygenation; optimal PEEP to maximize oxygen delivery to tissues while minimizing FiO₂ [19,20]. Prone positioning of patients in bed during ARDS management has been shown to improve the oxygenation index by 30-40%. However, studies suggest this method may lead to central hemodynamic disturbances, increased intracranial pressure, and tracheobronchial obstruction. While randomized studies indicate that kinetic therapy improves oxygenation, it does not enhance survival rates [21-23].

Conclusion

ARDS is associated with an inflammatory reaction that damages the alveolar-capillary membrane, leading to non-cardiogenic pulmonary edema, reduced lung compliance, increased shunting in the pulmonary circulation, and severe respiratory failure. Regardless of its etiology, the morphological changes in the lungs, clinical course, and treatment strategies are similar. Respiratory support remains the cornerstone of therapy, allowing the body to survive the acute phase of inflammation and facilitating the recovery of lung parenchyma with favourable outcomes. In recent years, protective ventilation with pressure-limited strategies has significantly improved the prognosis of ARDS patients. ARDS, characterized by a high mortality rate, is a complex and multifactorial syndrome requiring timely and effective treatment. Current treatment options are aimed at alleviating

symptoms but are limited in addressing underlying causes. Therefore, a deeper understanding of ARDS pathophysiology and the development of new therapeutic approaches are needed. While the literature provides extensive information on ARDS pathophysiology and treatment, further research could open new perspectives for more effective management and prevention of this syndrome.

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