Review Article

Acute respiratory distress syndrome (ARDS)

M Ahmed Selim[1], Md. Monharul Islam Bhuiya[2]

Abstract: *Acute respiratory distress syndrome (ARDS) is a life threatening condition characterized by rapid onset of widespread inflammation in the lungs. Symptoms include shortness of breath, rapid breathing, and bluish skin coloration.[1] Among those who survive, a decreased quality of life is relatively common. Despite this, the recommended therapies to decrease mortality in ARDS remain limited and include low-tidal volume mechanical ventilation, prone ventilation This review article will summarize the key features of ARDS with a brief overview of the therapeutic options in the management of ARDS.*

Key words: *Acute respiratory distress, ARDS*

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Introduction

Acute respiratory distress syndrome (ARDS) is an acute life threatening inflammatory lung injury manifested by hypoxia and stiff lungs due to increased pulmonary vascular permeability and almost always requiring mechanical ventilation support.[1] ARDS represents an acute response to diverse provoking trigger factors and etiologies, resulting bilateral lung opacities on radiography and hypoxemia.

ARDS was first described by Ashbaugh *et al.* in 1967,[2,3] and since then there have been multiple studies addressing the various clinical aspects of the syndrome, its pathogenesis, risk factors, and treatment. However, despite the intense research, only few effective therapies for ARDS have been postulated, including the lung protection strategies.

1. * Associte Professor, Department of Medicine North East Medical College, Sylhet
2. Assistant Professor, Department of Medicine Sylhet Women's Medical College, Sylhet

Address of Corresponding author:
Dr. M Ahmed Selim
Associte Professor, Department of Medicine
North East Medical College, Sylhet
Email: dr_selim50@yahoo.com

In this review article, authors will summarize the key features of ARDS, a brief overview of the therapeutic options in the management of ARDS. In 1994, a new definition was recommended by the American-European Consensus Conference Committee[4,5] which recognized the variability in severity of pulmonary injury.[3]

The definition required the following criteria be met:

- acute onset, persistent4, dyspnea
- bilateral infiltrates on chest radiograph consistent with pulmonary edema
- hypoxemia, defined as PaO_2:FiO_2 < 200 mmHg (26.7 kPa)
- absence of left atrial (LA) hypertension
  - pulmonary artery wedge pressure < 18 mmHg (obtained by pulmonary artery catheterization)if no measured LA pressure available, there must be no other clinical evidence to suggest elevated left heart pressure.

If PaO_2:FiO_2 < 300 mmHg (40 kPa), then the definitions recommended a classification as "acute lung injury" (ALI). Note that according to these criteria, arterial blood gas analysis and chest X-ray were required for formal diagnosis.

Limitations of these definitions include lack of precise definition of acuity, nonspecific imaging criteria, lack of precise definition of hypoxemia with regards to minimum positive end expiratory pressure (affects arterial oxygen partial pressure), arbitrary PaO_2 thresholds without systematic data.[6,7,8]

According to the 2012 Berlin definition, ARDS is characterized by the following: [9,10]

- lung injury of acute onset, within 1 week of an apparent clinical insult and with progression of respiratory symptoms
- bilateral opacities on chest imaging (chest radiograph or CT) not explained by other lung pathology (e.g. effusion, lobar/lung collapse, or nodules)
- respiratory failure not explained by heart failure or volume overload
- decreased PaO_2/FiO_2 ratio (a decreased PaO_2/FiO_2 ratio indicates reduced arterial oxygenation from the available inhaled gas):
  - mild ARDS: 201 – 300 mmHg (≤ 39.9 kPa)
  - moderate ARDS: 101 – 200 mmHg (≤ 26.6 kPa)
  - severe ARDS: ≤ 100 mmHg (≤ 13.3 kPa)
  - Note that the Berlin definition requires a minimum positive end expiratory pressure (PEEP) of 5 cmH2O for consideration of the PaO2/FiO2 ratio. This degree of PEEP may be delivered noninvasively with CPAP to diagnose mild ARDS.

Note that the 2012 "Berlin criteria" are a modification of the prior 1994 consensus conference definitions

Causes may include sepsis, pancreatitis, trauma, pneumonia, and aspiration.[1] The underlying mechanism involves diffuse injury to cells which form the barrier of the microscopic air sacs of the lungs, surfactant dysfunction, activation of the immune system, and dysfunction of the body's regulation of blood clotting.[2] In effect, ARDS impairs the lungs' ability to exchange oxygen and carbon dioxide.[1] Diagnosis is based on a PaO_2/FiO_2 ratio of less than 300 mmHg despite a PEEP of more than 5 cm H_2O.[1] Heart related pulmonary edema, as the cause, must be excluded.[3]

Pathology

ARDS is a form of fluid accumulation in the lungs not explained by heart failure (noncardiogenic pulmonary edema). It is typically provoked by an acute injury to the lungs that results in flooding of the lungs' microscopic air sacs responsible for the exchange of gases such as oxygen and carbon dioxide with capillaries in the lungs.[11] Additional common findings in ARDS include partial collapse of the lungs (atelectasis) and low levels of oxygen in the blood (hypoxemia). The clinical syndrome is associated with pathological findings including pneumonia, eosinophilic pneumonia, cryptogenic organizing pneumonia, acute fibrinous organizing pneumonia, and diffuse alveolar damage (DAD). Of these, the pathology most commonly associated with ARDS is DAD, which is characterized by a diffuse inflammation of lung tissue. The triggering insult to the tissue usually results in an initial release of chemical signals and other inflammatory mediators secreted by local epithelial and endothelial cells.

Neutrophils and some T-lymphocytes quickly migrate into the inflamed lung tissue and contribute in the amplification of the phenomenon. Typical histological presentation involves diffuse alveolar damage and hyaline membrane formation in alveolar walls. Although the triggering mechanisms are not completely understood, recent research has examined the role of inflammation and mechanical stress. [12]

Diagnostic criteria for ARDS have changed over time as understanding of the pathophysiology has evolved. The international consensus criteria for ARDS were most recently updated in 2012 and are known as the "Berlin definition".[10,11] In addition to generally broadening the diagnostic thresholds, other notable changes from the prior 1994 consensus criteria[4] include discouraging the term "acute lung injury," and defining grades of ARDS severity according to degree of decrease in the oxygen content of the blood.

Medical imaging

Radiologic imaging has long been a criterion for diagnosis of ARDS. Original definitions of ARDS specified that correlative chest X-ray findings were required for diagnosis, the diagnostic criteria have been expanded over time to accept CT and ultrasound findings as equally contributory. Generally, radiographic findings of fluid accumulation (pulmonary edema) affecting both lungs and unrelated to increased cardiopulmonary vascular pressure (such as in heart failure) may be suggestive of ARDS. Ultrasound findings suggestive of ARDS include the following:

- Anterior subpleural consolidations
- Absence or reduction of lung sliding
- "Spared areas" of normal parenchyma
- Pleural line abnormalities (irregular thickened fragmented pleural line)
- Non homogeneous distribution of B-lines (a characteristic ultrasound finding suggestive of fluid accumulation in the lungs)[13]

Current therapies

Lung-protective ventilation

Various trials have demonstrated that mechanical ventilation with lower tidal volumes (LTV) and airway pressures (tidal volume of 4–6 ml/kg predicted body weight and maintenance of plateau pressure between 25 and 30 cm H_2O) reduces mortality in ALI and ARDS.[14] This lung-protective ventilation preserves barrier properties of the alveolar endothelium and alveolar epithelium by preventing alveolar over distension, which is one of the major causes of ventilator-induced lung injury.[15] The concept of open lung ventilation uses low tidal volume with high PEEP with the rationale that LTV will minimize the damage due to over distension while the high PEEP will minimize the cyclic atelectasis [6], has been shown to have a beneficial effect on the outcome of the patients. Lung-protective ventilation also down regulates mechanosensitive pro-inflammatory pathways, resulting in reduced neutrophil accumulation in the alveoli and lower plasma levels of IL-6, IL-8, and TNF.[7,12]

Prone position

The position of lung infiltrates in acute respiratory distress syndrome is non-uniform. Repositioning into the prone position (face down) might improve oxygenation by relieving atelectasis and improving perfusion. If this is done early in the treatment of severe ARDS, it confers a mortality benefit of 26% compared to supine ventilation.[16]

Fluid management

Several studies have shown that pulmonary function and outcome are better in people with ARDS who lost weight or whose pulmonary wedge pressure was lowered by diuresis or fluid restriction.[7]

Medications As of 2019, it is uncertain whether or not treatment with corticosteroids improves overall survival. Corticosteroids may increase the number of ventilator-free days during the first 28 days of hospitalization.[17]

Inhaled nitric oxide (NO) selectively widens the lung's arteries which allows for more blood flow to open alveoli for gas exchange. Despite evidence of increased oxygenation status, there is no evidence that inhaled nitric oxide decreases morbidity and mortality in people with ARDS.[20] Furthermore, nitric oxide may cause kidney damage and is not recommended as therapy for ARDS regardless of severity.[18]

Common risk factors for ARDS[4,5]

Direct	Indirect
Pneumonia	Non-pulmonary sepsis
Aspiration of gastric contents	Major trauma
Inhalation injury	Pancreatitis
Pulmonary contusion	Severe burns
Pulmonary vasculitis	Non-cardiogenic shock
Drowning	Drug overdose
	Multiple transfusions or transfusion associated acute lung injury (TRALI)

High-frequency oscillatory ventilation

High-frequency oscillatory ventilation (HFOV) is ideal for lung protection in ARDS, but the OSCAR study concluded with no 30-day survival benefit or cost benefit in patients in whom HFOV was used[20]. The meta-analysis of randomized control trials (RCT) by Gu *et al.* (2014) also concluded that with use of HFOV, there was no improvement in survival in ARDS patients, although it had no increase the risk of barotrauma or hypotension and also reduced the risk of oxygenation failure.[19,20]

Intravenous β-2 agonist in ARDS

The BALTI trial (2006) was a single center RCT, which showed the benefit of intravenous infusion of Salbutamol for 7 days in patients with ARDS, by causing significant reductions in extravascular lung water and plateau airway pressures[21].

Neuromuscular blockade

Neuromuscular blocking agents (NMBAs) are commonly used in ARDS, but their use remains controversial. In recent meta-analysis and review, the use of short term NMBAs in ARDS patients have shown a beneficial outcome mainly by decreasing the barotrauma and ventilator-induced lung injury.[22]

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) is mechanically applied prolonged cardiopulmonary support. There are two types of ECMO: Veno venous which provides respiratory support and venoarterial which provides respiratory and hemodynamic support. People with ARDS who do not require cardiac support typically undergo venovenous ECMO. Multiple studies have shown the effectiveness of ECMO in acute respiratory failure.[23,24] Specifically, the CESAR (Conventional ventilatory support versus Extracorporeal membrane oxygenation for Severe Acute Respiratory failure) trial[25] demonstrated that a group referred to an ECMO center demonstrated significantly increased survival compared to conventional management (63% to 47%).

Prognosis

The overall prognosis of ARDS is poor, with mortality rates of approximately 40%.[19]

Conclusion

There has been considerable research on ARDS in the past decade and better understanding of its pathogenesis. Despite this, the effective therapeutic measures to decrease mortality in ARDS seem to be low-tidal volume mechanical ventilation, prone ventilation for severe ARDS cases; and in life-threatening cases not responding to the conventional therapies, ECMO rescue technology serves as a bridge to recovery.

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