

ACUTE LUNG INJURYBhabajyoti Bora¹, Nibedita Dev², Prathana Goswami³, Mihir Kumar Goswami⁴¹Surveillance Medical Officer (World Health Organization), Tezpur, Assam.²Associate Professor, DK Girls College, Mirza Guwahati, Assam.³Junior Research Fellow, Department of Pulmonary Medicine, Jorhat Medical College, Jorhat, Assam.⁴Professor and Head, Department of Pulmonary Medicine, Jorhat Medical College, Jorhat, Assam.**ABSTRACT****BACKGROUND**

Acute lung injury (ALI) and its most severe manifestation, acute respiratory distress syndrome (ARDS), are defined by physiological criteria i.e. ratio of PaO₂ to inspiratory oxygen fraction (FIO₂) ≤ 300 mmHg for ALI and ≤ 200 mmHg for ARDS, independent of positive end expiratory pressure (PEEP) and by bilateral pulmonary infiltrates as radiological criteria. The ARDS Definition Task Force proposes a new classification according to the severity of ARDS, i.e. mild: PaO₂/FIO₂ > 200 mmHg and ≤ 300 mmHg; moderate: PaO₂/FIO₂ >100 mmHg and ≤200 mmHg; and severe: PaO₂/FIO₂ ≤100 mmHg, because of its better predictive value for mortality. Principles of protective ventilator settings for patients with ALI/ARDS are low tidal volume (i.e. VT 6 mL per kg ideal body weight, plateau pressure <30 cm H₂O and peak pressure <35 cm H₂O). Permissive hypercapnia may be helpful to realize protective mechanical ventilation. Protection of the lungs may also be provided by the pump-driven veno-venous ECMO or pump less ILA. Cardiac failure must be excluded based either on pulmonary artery wedge pressure (<18 mmHg) or on clinical evaluation of left ventricular function, if the invasive measurement is unavailable, which is the ground reality of the unfortunate situation here in the medical colleges of Assam as well as in India.

KEYWORDS

Acute Lung Injury (ALI), Acute Respiratory Distress Syndrome (ARDS), Permissive Hypercapnia, Veno-Venous Extracorporeal Membrane Oxygenation (vv-ECMO), Tertiary Health Care Centers.

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BACKGROUND

Shock lung, Da Nang lung (from Vietnam War), adult respiratory distress syndrome, stiff lung syndrome, leaky capillary pulmonary oedema, and most recently name ARDS. In recent past, terms used acute lung injury (ALI) and ARDS are similar conditions of same spectra varying on different degree of hypoxemia.

- Acute lung injury: Ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO₂/FiO₂) less than 300 mmHg.
- Acute respiratory distress syndrome: PaO₂/FiO₂ less than 200 mmHg.

A distinct type of hypoxemic respiratory failure characterized by acute abnormality of both lungs was first recognized during the 1960s. Military clinicians working in surgical hospitals in Vietnam called it shock lung, while civilian clinicians referred to it as adult respiratory distress syndrome.¹ Subsequent recognition that individuals of any age could be afflicted led to the current term, acute respiratory distress syndrome (ARDS). These criteria should be re-evaluated, after 24 hours since their persistence is

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essential for the correct diagnosis of ALI/ARDS. Furthermore, timing may be of influence on the development of ALI/ARDS. Lung oedema may evaluated by CT or other established methods.

ALI/ARDS may be caused by various aetiologies like direct lung injury, e.g. pneumonia, aspiration, toxic inhalation, near drowning or lung contusion; or indirect lung injury, e.g. sepsis, burn, pancreatitis or massive blood transfusion. The two aetiologies may coexist.

Genetic Determinants

This is something that the researchers are trying to find out, as only a small proportion of patients who are exposed to typical insults actually develop ARDS. Studies that link mutations in the surfactant Proteins B (SP-B) gene to an increased risk of ARDS support this notion.

Drugs may precipitate ARDS in many cases. The names are-

1. Aspirin
2. Opioids
3. Phenothiazine
4. Tri cyclic antidepressant
5. Nitrofurantoin
6. Protamine
7. Radio contact media

Other causes of ARDS include Pancreatitis, obesity, thoracic surgery, cigarette smoking.

The exact incidence of ALI/ARDS is not known; its annual mortality rate has been estimated to be >30,000 patients per year in the USA. Despite recent advances in the

understanding of the pathophysiology of ARDS, improvements in supportive care, and multiple therapeutic efforts directed at modifying the course of the condition, mortality rates are persistently 35-40%.

The age-adjusted incidence of ARDS in a population-based study in USA was 86 per 100,000 person-years for individuals with an arterial oxygen tension to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) ratio ≤ 300 mmHg and 64 per 100,000 person-years for individuals with $\text{PaO}_2/\text{FiO}_2 \leq 200$ mmHg.²

In a recent large global study on ARDS in ICU population involving 29144 patients ARDS represented 10.4% (95% CI, 10.0%-10.7%) of total ICU admission and 23.4% (95% CI, 21.7%-25.2%) of all patients requiring mechanical ventilation and constituted 0.42 cases/ICU bed over 4 weeks; North America, 0.46; South America, 0.31; Asia, 0.27; Africa, 0.32; and Oceania, 0.57 cases/ICU bed per 4 weeks.³

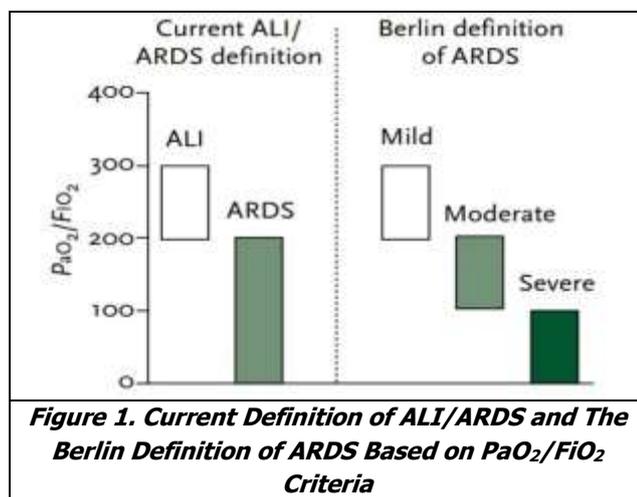


Figure 1. Current Definition of ALI/ARDS and The Berlin Definition of ARDS Based on $\text{PaO}_2/\text{FiO}_2$ Criteria

Review of Literature

Study of Ashbaugh DG et al (1967) shows that the respiratory-distress syndrome in 12 patients was manifested by acute onset of tachypnoea, hypoxaemia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy. The clinical and pathological features closely resembled those seen in infants with respiratory distress and to conditions in congestive atelectasis and post perfusion lung. Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxaemia. Corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia.

Neutrophils are an important component of the inflammatory response that characterizes acute lung injury (ALI). Abraham E (2003) reviewed the contribution of neutrophils to the development and progression of ALI and to highlight the major intracellular signalling pathways that are involved in neutrophil activation in the setting of ALI.

Study of Idell S. (2003) shows that disordered coagulation and fibrinolysis promote extravascular fibrin deposition in acute lung injury. It is this deposition that characterizes acute lung injury and repair. Expression of

uPA, uPAR, and PAI-1 by the lung epithelium, as well as the ability of uPA to induce other components of the fibrinolytic system, involves posttranscriptional regulation. These pathways may contribute to disordered fibrin turnover in the injured lung. The success of anticoagulant or fibrinolytic strategies designed to reverse the abnormalities of local fibrin turnover in acute lung injury supports the inference that abnormalities of coagulation, fibrinolysis, and fibrin deposition have a critical role in the pathogenesis of acute lung injury.

Rubinfeld GD et.al. (2005) articulate that acute lung injury is a critical illness syndrome consisting of acute hypoxemic respiratory failure with bilateral pulmonary infiltrates that are not attributed to left atrial hypertension.

Using a consensus process, a panel of experts convened in 2011 (an initiative of the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine) developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. A draft definition proposed 3 mutually exclusive categories of ARDS based on degree of hypoxemia: mild ($200 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mm Hg}$), moderate ($100 \text{ mm Hg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mm Hg}$), and severe ($\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mm Hg}$) and 4 ancillary variables for severe ARDS: radiographic severity, respiratory system compliance ($\leq 40 \text{ mL/cm H}_2\text{O}$), positive end-expiratory pressure ($\geq 10 \text{ cm H}_2\text{O}$), and corrected expired volume per minute ($\geq 10 \text{ L/min}$) which was mentioned in the ARDS Definition Task Force, Ranier VM et, al. (2012).

Mattay MA et al. (2012) reported that the acute respiratory distress syndrome (ARDS) is an important cause of acute respiratory failure that is often associated with multiple organ failure. Based on both experimental and clinical studies, progress has been made in understanding the mechanisms responsible for the pathogenesis and the resolution of lung injury, including the contribution of environmental and genetic factors. Improved survival has been achieved with the use of lung-protective ventilation.

Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be under recognized and undertreated and associated with a high mortality rate. These findings indicate the potential for improvement in the management of patients with ARDS which was evidently reported by Bellani G et.al (2016).

Key Components

- Acute, meaning onset over 1 week or less
- Bilateral opacities consistent with pulmonary oedema must be present and may be detected on CT or chest radiograph
- PF ratio < 300 mmHg with a minimum of 5 cm H_2O PEEP (or CPAP)
- "Must not be fully explained by cardiac failure or fluid overload", in the physician's best estimation using available information-an "objective assessment" (e.g. echocardiogram) should be performed in most cases if there is no clear cause such as trauma or sepsis.⁴

- ARDS is categorized as being mild, moderate, or severe: which of course can be staged differently from pathological point of view.

ARDS Severity	PaO ₂ /FiO ₂ *	Mortality**
Mild	200-300	27%
Moderate	100-200	32%
Severe	<100	45%
*on PEEP 5+; ** Observed in Cohort		
Table 1		

Pathogenesis

Main culprit in ARDS is activated circulating neutrophils⁵ which get sequestered in pulmonary microcirculations. They themselves attach with capillary endothelium and through the process of diapedesis move in to lung parenchyma. At this level, they degranulate themselves to release toxic oxidative radicals and proteolytic enzyme. Furthermore, subsequent damage to pulmonary capillary wall leads to exudation of erythrocytes, platelets, and proteins rich inflammatory fluid in the lung alveolus. These protein rich inflammatory exudates contain fibrin, which subsequently cause pulmonary fibrosis and long-lasting morbidity and mortality.

Tissue factor release from lung in response to ongoing inflammation is responsible for release of fibrin.⁶

The pathophysiology of ALI/ARDS is related to altered pulmonary capillary permeability and increased intrapulmonary shunt, which is associated with impaired gas exchange. ARDS has been divided into three stages, in which 1. Initial inflammatory phase (exudative) is followed by 2. Fibro-proliferation, which can lead to established interstitial and 3. Intra-alveolar fibrosis, the final phase.

Mechanical ventilation itself can seriously damage lung parenchyma (ventilator induced lung injury). ALI/ARDS often has systematic manifestations, triggering systemic inflammatory response syndrome (SIRS), or in extreme multiple organ dysfunction syndrome. (MODS)

Management

- Ventilatory management
- Non-ventilatory management.

Ventilatory Management

Pulmonary HTN occurs in up to 25% of patients cum ARDS who undergo ventilation. Causes include hypoxic vasoconstriction, vascular compression by positive air ways pressure, parenchymal destruction, air way collapse, hypercarbia and pulmonary vasoconstrictors.

Conventional ventilator support using high tidal volume O (10-13 ml/kg) causes ventilator induced lung injury is due to:

- Bio trauma: Here proinflammatory cytokines can appear in lung causing activation of neutrophils to initiates ARDS a kin pulmonary pathology and inflammatory injury in other organs.

- Atelectrauma: Due to decrease dispensability of alveolar and small airways, high velocity shear force created by mechanical conventional ventilation on collapsed airways epithelium may cause lung parenchymal injury.

So, here lung protective ventilation mode have been devised in three stages with optimal goals (mortality reduction >9%).

Stage 1

- First predicted body weight (PBW) of the patient is calculated as per formula:
- For male = 50 + (2.3 x (height in inches – 60)) kg
- For female = 45.5 + (2.3 x (height in inches – 60)) kg
- Set initial tidal volume (VT) 8 ml/kg PBW
- Set positive end- expiratory pressure (PEEP) of 5 cm H₂O- to decrease atelectrauma
- FiO₂: Selected to the lowest level to achieve peripheral capillary oxygen saturation (SPO₂) 88-95%
- Reduce VT by 1 ml/ kg PBW 2 hourly till it reaches 6 ml/kg of PBW.

Stage 2

When VT = 6 ml/kg, now plateau pressure (Ppi) is measured if greater than 30 cm H₂O, VT is decrease at the rate of 1 ml/kg PBW, until Ppi is less than 30 cm H₂O or VT is up to 4 ml/ kg of PBW.

Stage 3

Arterial blood gas monitoring:

- If acidity (ph) less than 7.15-7.30 increase respiratory rate (RR) until ph greater than 7.30 or RR = 35 beats/min
- If ph less than 7.15, achieve RR up to 35 beats/min, if ph is still less than 7.15 increase VT in 1 ml/kg till ph greater than 7.15.

Goals

VT = 6 ml/ kg, Ppi less than 30 cm H₂O
SPO₂ = 88-95%, ph 7.30-7.45

Note:

- Higher PEEP up to 15 cm H₂O may be recommended when PaO₂/FiO₂ less than 200 mmHg or SPO₂ less than 88 mmHg for short period
- Decrease VT- may cause hypercapnia and respiratory acidosis. Available data point that in protective ventilator support mode PaCO₂ 60-70 mmHg and ph 7.2-7.25 are safe for most of the patients.

In light of so many reports available for and against lung protective ventilation, this mode is most accepted as standard mode of ventilation in ARDS patients.

Principles of protective ventilator settings for patients with ALI/ARDS are-

- Tidal volume 6 ml.kg⁻¹ ideal body weight.
- Plateau pressure < 30 cm H₂O, peak pressure < 35 cm H₂O.

- This strategy of protective mechanical ventilation may be associated with permissive hypercapnia.

The 'optimal' setting of PEEP is not clear, since several methods have been proposed without any clear advantages over each other.

Higher PEEP (>15 cm H₂O) might be recommended in more severe ARDS patients. Prone position might be recommended in more severe ARDS patients, according to the expertise of the clinicians. Estimating the trans pulmonary pressure by means of oesophageal pressure measurement might help to find the ideal PEEP level. Alternative methods of ventilation include high-frequency ventilation and airway pressure release ventilation.

Protection of the lungs may also be provided by pump-driven veno-venous extracorporeal membrane oxygenation (vv-ECMO), which improves both oxygenation and carbon dioxide removal, and allows a highly protective low tidal volume ventilation. Recently, the CESAR trial provides the first evidence that vv-ECMO is superior to conventional treatment in the most severe forms of ARDS. Moreover, a pumpless extracorporeal lung assist was developed using arterio-venous bypass, in which a gas exchange membrane is integrated (interventional lung assist). Interventional lung assist provides effective carbon dioxide elimination and a moderate improvement in oxygenation, and therefore allows more protective mechanical ventilation.

Concerning pharmacological treatments of ALI/ARDS, inhaled nitric oxide has not been found to be particularly effective and there is no clear convincing data to support the widespread use of corticosteroids in both early and late phases of ALI/ARDS.

CONCLUSION

Severe ALI/ARDS is often associated with refractory hypoxemia and early identification and treatment are the need of the hour. This condition appears to be unrecognized, undertreated, and associated with high mortality rate. Supportive therapy includes neuromuscular blockade (with in 48 hours after onset of ARDS) and on adequate sedation strategy. The first principle of treatment is to identify potential underlying causes of ALI/ARDS. Furthermore, secondary lung injury, such as aspiration, barotraumas, nosocomial infections and oxygen toxicity, should be avoided. The main aims of supportive care are maintaining oxygen delivery to end organs by avoiding anaemia and optimizing cardiovascular function and body fluid balance; additionally, catabolism and nutritional support have to be balanced. Finally, based on experimental models a series of molecular mechanisms offer innovative opportunities for cell or gene therapy. These need to be elaborated in human studies, however. Concluding this article, I, as a respiratory physician would like to remark that a patient with acute respiratory distress is like a drowning victim in a sea, who sinks and appears on surface of sea with panting respiration-requesting for short breath for life. Acute respiratory distress syndrome is most devastating with high mortality and long-term morbidity out of all critically ill patients associated with pulmonary pathology.⁷

Further Reading

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