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Acute lung injury: options to improve oxygenation

Ravi P Mahajan

Key points

Acute lung injury and acute respiratory distress syndrome often cause unresolving hypoxia.

Excessive transalveolar pressures should be avoided during mechanical ventilation.

Recommended approaches to ventilation include combination of optimal PEEP, small tidal volume, prolonged I:E ratio, and respiratory rate adjusted to minimize hypercapnia.

Nitric oxide and the prone position may provide temporary improvement in oxygenation.

Overall survival depends upon improvement in the function of other organs.

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Persistent hypoxia, despite adequate oxygen therapy, is common in patients suffering from acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Before attempting advanced support for ALI/ARDS, one must look for and treat relatively readily reversible conditions. These conditions include:

(i) pneumothorax,
(ii) pleural effusions,
(iii) mucus plugs and retained chest secretions,
(iv) major collapse of the lung tissue,
(v) bronchospasm,
(vi) cardiogenic pulmonary oedema,
(vii) hypotension and low cardiac output, and
(viii) equipment failure.

This brief review will address the aetiology, pathophysiology and management options of ALI/ARDS in intensive care.

Definitions

The American–European Consensus Conference on ARDS in 1994 defined ALI as 'a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiological, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension'. The criteria included the following:[1]

(i) hypoxia defined by $Pa_{O_2}/F_{I_{O_2}} < 300$ mm Hg,
(ii) bilateral infiltrates on chest x-ray, and
(iii) pulmonary capillary wedge pressure <18 mm Hg or no clinical evidence of increased left atrial pressure.

ARDS is considered to be a more severe form of ALI in which the same criteria apply except that hypoxia is more severe ($Pa_{O_2}/F_{I_{O_2}}$ <200 mm Hg regardless of PEEP).

ALI/ARDS

Aetiology

The clinical risk factors for ALI/ARDS are given in Table 1. The incidence of ARDS has been reported to be 43% in sepsis, 40% in emergency blood transfusions (>15 U/24 h), and 25% in multiple trauma.[2]

Table 1 Risk factors for ALI/ARDS

Direct lung injury	Indirect lung injury
Aspiration	Sepsis/SIRS syndrome
Toxic Inhalation	Pancreatitis
Infection	Massive blood transfusion
Near drowning	Multiple trauma
Trauma—lung contusion	Fat embolism

In ALI/ARDS, the pattern of pathological changes in the lungs may vary depending upon the nature of primary injury; consolidation of lungs predominates if the injury is 'direct', whereas interstitial oedema and alveolar collapse predominate if the injury is 'indirect' (Table 1).

Pathophysiology

ALI/ARDS develops after a major capillary leak in the lungs. Initially, during an *exudative* phase (24–48 h), lungs are infiltrated by activated cells of inflammation; these cells lead to endothelial injury, capillary disruption, and pulmonary oedema. Later, during the *proliferative* phase (2–7 days), fibroblasts infiltrate and begin to remodel the site of inflammation. Finally, in the *fibrotic* phase (after 7 days), alveolar wall thickens owing to fibrosis of the lung parenchyma. These changes are associated with impaired gas diffusion, decreased lung compliance, increased work of breathing, alveolar collapse and ventilation/perfusion (V/Q) mismatch leading to hypoxia and respiratory failure.

Options to improve oxygenation

Currently, two strategies improve oxygenation, i.e. ventilatory and pharmacological (Table 2).

Ventilatory support

In ARDS, different parts of lung parenchyma are differentially affected. Areas of collapsed (unventilated) alveoli may be scattered among

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Table 2 Options to improve oxygenation in ALI/ARDS

Ventilatory	Pharmacological
Non-invasive ventilation	Nitric oxide
Intermittent positive pressure ventilation using open lung approach	Surfactant replacement
Patient positioning	Enhanced resolution of alveolar oedema
High-frequency ventilation	Anti-inflammatory approach
Partial liquid ventilation	Antioxidants
Extracorporeal life support	Corticosteroids
	Anti-adhesion molecules
	Prostaglandin E1
	Ketoconazole
	Pentoxifylline

relatively normal lung areas. Thus, traditionally administered tidal volumes during positive pressure ventilation (10–15 ml kg^{-1}) can result in over-distension of the relatively normal (and more compliant) alveoli; this causes localized hyperventilation and inhibition of surfactant production. Also, excessive transalveolar pressures result in intense shearing forces at the junctions of the aerated lung units (mobile) and the consolidated lung units (immobile). A combination of these factors results in ventilator-induced lung injury, which may further worsen the pre-existing ALI/ARDS. To prevent it, transalveolar pressure should be kept <30 mm Hg.

Non-invasive ventilation

Clinically proven indications for non-invasive ventilation (using nasal/face mask) include acute exacerbations of chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary oedema. It avoids tracheal intubation and preserves spontaneous ventilatory effort. It increases FRC, reduces *V*/*Q* mismatch, optimizes mechanical efficiency and improves oxygenation. Because it minimizes the development of excessive transalveolar pressure, it has the theoretical advantage of minimizing the risk of iatrogenic lung injury. Therefore, it may have a role in preventing ALI in vulnerable patients; its role in established ALI/ARDS remains undefined.[3]

Open lung approach

The open lung approach is based on pressure-targeted ventilator strategies in combination with positive end-expiatory pressure (PEEP). PEEP is applied to recruit collapsed alveoli and maintain them 'open' throughout the respiratory cycle; in order to achieve this, PEEP is maintained at a level above the lower inflection point of the pressure-volume curve. The static peak pressures during inspiration are kept <40 cm H_2O to avoid excessive stretch on the alveolar wall. In addition, inverse ratio ventilation may also be used to keep recruited alveoli open for longer time. The immediate lung volume recruitment frequently improves oxygenation significantly. However, tidal volume varies with lung compliance and inevitably this remains <6 ml kg^{-1} with an associated increase in carbon dioxide (permissive hypercapnia).

The approach of permissive hypercapnia is controversial. Deleterious effects of increased carbon dioxide include increase intracranial pressure, hypertension and increased pulmonary vascular resistance; these limit its use in patients with neurological disease, coronary artery disease and heart failure.

In a recent ARDS Network trial, a 25% reduction in mortality has been shown in patients who were ventilated using a tidal volume of 6 ml kg^{-1} compared with 12 ml kg^{-1}. The ventilatory management was based on the following parameters:

(i) plateau inspiratory pressure ≤30 cm H_2O,
(ii) $F_{I_{O_2}}$/PEEP combinations varying between 0.3/5 mm Hg and 1.0/24 mm Hg to maintain $S_{p_{O_2}}$ >88%,
(iii) I:E ratios between 1:1 and 1:3,
(iv) respiratory rate of up to 35 bpm to minimize hypercapnia, and
(v) bicarbonate to maintain pH >7.3.

Further details on the protocol are available at www.ardsnet.org. This protocol combines the benefits of the 'open lung approach' with 'lung protection' offered by lower tidal volumes, while minimizing the harmful effects of respiratory acidosis. So far, this appears to be the most logical approach to support ventilation in patients who are either at the risk of developing ALI/ARDS or have already developed this disorder.[3–5]

Patient positioning

Changes to prone or steep lateral decubitus positions can improve oxygenation in ~50–70% of ARDS patients. This is attributable to the effect of gravity on increasing perfusion to the ventilated lung regions and thus minimizing *V*/*Q* mismatch. Other factors that improve oxygenation are:

(i) recruitment of alveoli in paravertebral areas,
(ii) increase in lung volume, and
(iii) redistribution of ventilation and perfusion minimizing the *V*/*Q* mismatch.

It is important to remember that any improvement in oxygenation lasts for a few hours only. Therefore, changing posture only buys time while other options are being considered; so far, there is no convincing evidence of improved overall outcome.[3]

The prone position can be complicated by difficulties in monitoring and nursing care, and a risk of accidental extubation during turning the patient.

High-frequency ventilation

This approach minimizes the development of large transalveolar pressure gradients. With the use of a specialized ventilator, small tidal volumes of 1–3 ml kg^{-1} are delivered at a high respiratory rate (>100 bpm for adults and >300 bpm for children). In this way, adequate gas exchange can be achieved without significant air trapping. Despite evidence of advantages in neonatal and paediatric patients, advantages of high-frequency ventilation over conventional ventilation in ARDS have not been established.

With new technology at hand, multicentre trials are now needed to determine the potential benefits of this approach.

Liquid ventilation

This technique uses a fluorocarbon liquid that is immiscible with water but can carry significant amounts of oxygen and carbon dioxide. Perflubron is most commonly used either for 'total' liquid ventilation or 'partial' liquid ventilation. In 'total' liquid ventilation, the lungs are filled entirely with the fluorocarbon liquid and ventilation is achieved through the liquid with a specialized ventilator. In 'partial' liquid ventilation, the lungs are filled only to functional residual capacity with fluorocarbon and are ventilated with a conventional gas ventilator. Fluorocarbon keeps the surfactant deficient alveoli open. It also optimizes the V/Q ratio by preferentially re-expanding gravity-dependent dorsal alveoli, and simultaneously redirecting blood flow towards the non-dependent lung. In addition, fluorocarbon can also remove intra-alveolar inflammatory mediators and cells.

Preliminary trials for partial liquid ventilation have shown improved gas exchange and decreased need for extracorporeal life support, but no difference in overall survival or ventilator-free days. A recent review has concluded that there is no evidence from randomized controlled trials to support or refute the use of partial-liquid ventilation in adults with ALI/ARDS.[6] Further trials with appropriate outcome measures are required.

Extracorporeal life support

Extracorporeal life support (ECLS) has been shown to improve outcome in neonatal respiratory distress syndrome. For adult ARDS patients, its use remains controversial. ECLS is a maximally invasive procedure that requires extensive health care resources. Its primary aim is to allow the lung complete rest in order to avoid any ventilator-induced injury. The options include extracorporeal membrane oxygenation (ECMO), extracorporeal carbon dioxide removal, and intravascular gas exchange (IVOX). Data supporting a significant benefit in adults are lacking at present, although enthusiasts are convinced that these methods have a significant role to play in those patients who do not respond to conventional mechanical ventilator strategies.[7]

This approach is likely to be of benefit in patients with isolated respiratory failure and when the cause for ALI/ARDS is reversible. Therefore, only a limited number of patients could potentially benefit as only 15% of patients with ALI/ARDS die from isolated respiratory failure; the remaining die from sepsis and associated multiple organ failure.

Pharmacological options

Most pharmacological approaches are at experimental stage. Some therapies may be more effective in early ARDS and some others may only be useful in its prevention. In general, pharmacological options have little or no effect once the disease progresses to the fibrotic phase.

Nitric oxide

Nitric oxide is delivered by inhalation to produce selective dilatation of pulmonary vessels in the aerated and ventilated parts of the lung; thus, it diverts blood flow from poorly ventilated parts and reduces shunt. It is used in doses of 5–80 p.p.m. The main advantage is lack of systemic effects. ARDS is often associated with increased pulmonary vascular resistance; inhaled nitric oxide reduces both intrapulmonary shunting as well as pulmonary vascular resistance, and thus improves oxygenation ($Pa_{O_2}/F_{I_{O_2}}$ ratio). However, despite significant short term improvements, recently published trials in ARDS have failed to show any difference in survival.[8]

Surfactant replacement

The role of surfactant replacement in neonatal respiratory distress syndrome is well recognized. In adults, its role is not yet established. Deficiency of surfactant in ARDS (due to increased breakdown and decreased production) is well known. Attempts have been made to replace it using either in-line nebulizer or by direct intrabronchial instillation using bronchoscopy. In the short term, it can improve lung compliance and oxygenation. However, no difference in 30 day survival, length of stay in intensive care unit, or duration of mechanical ventilation has been shown.[5] Some authors have suggested that surfactant replacement should be reserved for very early ARDS.

Enhanced resolution of alveolar oedema

In theory, stimulation of β_2 receptors in the alveolar epithelium can enhance fluid clearance from the alveoli. Initial studies with aerosolized salmeterol and terbutaline, or systemic administration of dobutamine have been encouraging.[5] However, the major limitation of this approach can be a well recognized down-regulation of β receptors in ARDS. Larger clinical trials of proving usefulness of this approach are lacking in literature.

Anti-inflammatory approach

A number of pharmacological agents have been proposed to suppress the process of inflammation and thus prevent long-term effects of ALI. It is clear that these agents can only be successful if they are given either to treat ALI in its very early stages, or to prevent it. They include: (i) antioxidants, (ii) corticosteroids, (iii) anti-adhesion molecule therapy, (iv) prostaglandin E1, (v) ketoconazole, and (vi) pentoxifylline.

In ALI/ARDS, activated inflammatory cells such as macrophages and neutrophils produce many reactive oxygen intermediates. In addition, lung and endothelial cells can also produce oxygen intermediates in the presence of high concentrations of oxygen. Investigations have shown increased oxidant activity in bronchoalveolar lavage fluid. Glutathione, a natural cellular antioxidant, is rapidly depleted in ALI. Its repletion can potentially improve the endogenous antioxidant defence. *N*-Acetylcysteine has been shown to improve glutathione production. It is

metabolized to cysteine which is the precursor of glutathione. Therefore, early intervention or prophylaxis with this therapy is a possibility. Investigations have shown that plasma levels of both vitamins E and C are diminished in patients with ALI. In theory, supplementation with these antioxidants can be effective. Despite these findings, there is a paucity of clinical data evaluating the effects of vitamin supplementation in ARDS.

In clinical trials for the treatment of early ARDS, a short course of steroids (<48 h) at high doses was shown to be of no benefit. In fact, it was shown to increase the incidence of complications related to infections. Recent studies indicate a potential for use of corticosteroids in the late, fibroproliferative stage of ARDS.[9] The involved mechanisms include modulation of macrophage and fibroblast activity. The potential risks of long-term steroid administration in this population are increased incidence of infections, impaired wound healing and glucose intolerance. Presently, large multi-centre trials are being conducted to determine the risks and benefits of this approach.

Anti-adhesion molecules prevent the interactions between the activated circulating inflammatory cells (neutrophils) and the endothelial cells. Many products have been developed; one such product is a monoclonal antibody to CD18. In animal models of haemorrhagic shock and resuscitation, this antibody has been shown to decrease the organ injury and improve survival. Preliminary data in patients with multiple trauma and haemorrhagic shock suggest some benefit of administration of the antibody within 6 h of injury. Results from larger trials are awaited.

Prostaglandin E1 prevents platelet aggregation and causes vasodilatation. In addition, it inhibits the activation of macrophages and neutrophils, and modulates the inflammatory response. Despite theoretical advantages, studies have shown contradictory results and no decisive improvements in mortality have been shown so far.

Ketoconazole, an imidazole antifungal agent, also has significant anti-inflammatory effects. It prevents the production of inflammatory mediators by the alveolar macrophages. A recent multicentre trial has shown no benefit in established ARDS, but its role in the prevention remains to be evaluated.

Pentoxifylline increases intracellular cyclic AMP by inhibiting enzyme phosphodiesterase. The anti-inflammatory actions include inhibitions of chemotaxis, release of tumour necrosis factor and platelet aggregation. Clinical usefulness is still not proven.[9]

Conclusions

To date, only low-tidal volume ventilation using the open lung approach has demonstrated a clear benefit in improving survival of patients with ALI/ARDS. The prone position and use of nitric oxide offer only a temporary improvement in oxygenation with little impact on outcome. The success of pharmacological options is likely to be influenced by the timing of treatment. The lack of efficacy of pharmacological interventions, despite theoretical advantages, can be attributed to a relative delay in instituting therapy. It is also becoming increasingly clear that a combination of interventions is more likely to succeed than just one intervention applied in isolation. Finally, ALI/ARDS is usually associated with multi-organ dysfunction and any improvement in lung function only will not translate into successful outcome unless other organ functions also improve.

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See multiple choice questions 40–42.