Acute respiratory distress syndrome

M.H. Rao, A. Muralidhar, A. Krishna Simha Reddy
Department of Anaesthesiology and Critical Care, Sri Venkateswara Institute of Medical Sciences, Tirupati

ABSTRACT

Acute respiratory distress syndrome (ARDS) is characterized by non-cardiogenic pulmonary oedema and respiratory failure. In 1994, ARDS was defined by the American – European Consensus Conference (AECC) and since then issues regarding the reliability and validity of this definition have emerged. The Berlin definition was developed by a panel of experts in a convention in 2011 with an initiative of European Society of Intensive Care Medicine endorsed by American Thoracic Society, mainly focusing on feasibility, reliability and validity and objective evaluation of performance. The definition proposed three exclusive categories of ARDS based on degree of hypoxaemia, namely, mild, moderate and severe. The updated and revised Berlin definition of ARDS may serve as model to create a more accurate, evidence based critical illness syndrome and to improve clinical care, research, health services planning and resource management. The article describes clinical, aetiological and physiological basis of ARDS and summarizes how its molecular pathogenesis leads to physiologic alterations of respiratory failure. It provides a physiologic basis for understanding and implementing modern strategies for the respiratory management of patients with ARDS.

Key words: Berlin definition, Respiratory failure, Non-cardiogenic pulmonary oedema, Hypoxemia, Positive end-expiratory pressure


INTRODUCTION

During World War I, many soldiers who sustained thoracic and non-thoracic injuries developed diffuse lung infiltrates, respiratory failure, which progressed into non-cardiogenic pulmonary oedema, severe hypoxaemia and majority of the patients died. Sometimes pancreatitis, massive blood transfusion, sepsis and other conditions also may be the causative factors for respiratory distress syndrome (RDS). Ashbaugh et al described 12 such patients in 1967, and used the term “adult respiratory distress syndrome” to describe this condition because there existed another entity called “infant respiratory distress syndrome” (IRDS”). Subsequently, a committee of leading investigators in the field met in 1994 to develop a consensus between the American Thoracic Society (ATS) and the European Society of Intensive Care Medicine (ESICM). The AECC changed the term from “adult respiratory distress syndrome” to “acute respiratory distress syndrome (ARDS)” because the syndrome occurred in both adults and children.

The AECC2 defined ARDS as acute onset of respiratory symptoms, bilateral infiltrates on the frontal chest radiograph, pulmonary capillary wedge pressure (PCWP) less than 18 mm Hg when measured or no evidence of left atrial hypertension, ratio of arterial, oxygen: tension (PaO₂) to fraction of inspired oxygen (FIO₂) less than 200.

The AECC definition2 was widely adopted by clinical researchers and clinicians and has advanced the knowledge of ARDS by allowing the acquisition of clinical and epidemiological data. However, after 18 years of applied research, a number of issues regarding various

Corresponding author: Dr M. Hanumantha Rao, Professor and Head, Department of Anaesthesiology and Critical Care, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. e-mail: drmhrao@yahoo.com

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criteria of the AECC definition have emerged, including a lack of explicit criteria for defining acute, sensitivity of PaO$_2$/FiO$_2$ to different ventilator settings, poor reliability of the chest radiograph criteria, and difficulties distinguishing hydrostatic oedema. This led to the genesis of Berlin definition.\(^3\)

**EPIDEMOLOGY**

The incidence of ARDS varies widely. Estimates from prospective US cohort studies using the AECC definition\(^2\) range from 64.2\(^4\) to 78.9\(^5\) cases/100,000 person-years. Other estimates were as follows: Northern Europe (17 cases/100,000),\(^6\) Spain (7.2 cases/100,000),\(^7\) and Australia/New Zealand (34 cases/100,000).\(^8\) Reasons for the large variation in ARDS incidence are unclear, and may include major differences in demographics and healthcare delivery systems.\(^7\)

The known causes and risk factors for the development of ARDS (Table 1),\(^9\)-\(^11\) can be categorized as insults ensuing from either direct or indirect injury to the lung. It is now well established that sepsis is currently the most commonly identified cause of ARDS, and is associated with the worst outcome overall.\(^5\),\(^11\),\(^12\) Trauma-related ARDS has been typically associated with significantly lower mortality than other causes of ARDS.\(^5\)

**ARDS in the tropics**

Rare, but important treatable causes of ARDS in the tropics include infections, such as, malaria, tuberculosis, enteric fever, leptospirosis, scrub typhus, heart stroke, paraquat poisoning, among others.

Malaria is an important treatable cause of ARDS in the tropics including India and in the returning traveler in the non-endemic areas. ARDS is an important complication in severe, complicated falciparum malaria and has been described in *Plasmodium vivax* and *Plasmodium ovale* malaria also.\(^13\),\(^14\) Malarial ARDS is more common in adults than in children. Pregnant women and non-immune individuals are more prone to develop this condition. Increased alveolar capillary permeability resulting in intravascular fluid loss into the lungs appears to be the key pathophysiologic mechanism. In malaria, ARDS can develop either at initial presentation or after initiation of treatment when the parasitaemia is falling and the patient is improving.\(^13\)

**Mortality**

Approximately 25% to 40% of ARDS cases are fatal, which is an improvement from the ARDS, mortality rate of 50% to 70% 20 years ago.\(^16\)-\(^18\)

Death usually results from multisystem organ failure rather than respiratory failure alone. According to Berlin definition\(^3\) increasing severity of ARDS was associated with increasing mortality (27%, 32%, and 45%).

**PATHOGENESIS**

Aspiration, trauma or sepsis can lead to the insult or injury to the alveolar epithelium and

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ARDS = acute respiratory distress syndrome.
capillary endothelium. Injury is generally detected in both the endothelium and epithelium at the time of diagnosis.\textsuperscript{19,20} This injury invariably leads to a leakage of plasma proteins through the interstitial compartment and into the alveolar space. Many of these plasma proteins in turn activate procoagulant and proinflammatory pathways that lead to the fibrinous and purulent exudates. There is increased release of proinflammatory cytokines, and a profound acute inflammatory response is generated. This is heralded by epithelial cell apoptosis and necrosis,\textsuperscript{21} further activation of other inflammatory cascades, and a robust recruitment of neutrophils.\textsuperscript{22} The release of various growth and profibrotic factors can ultimately lead to healing and/or remodelling. The increased expression of tissue factor and other procoagulant factors ultimately leads to coagulation within the microvasculature and airspaces, accompanied by a suppression of fibrinolysis that helps perpetuate the microthrombi and fibrinous exudates that are pathognomonic of ARDS.

Injury to the alveolar epithelium plays a critical role in the pathogenesis of ARDS. The loss of tight junctions and barrier function leads to seepage of plasma proteins and oedema fluid into the alveolar space, leading to increased shunt fraction, higher alveolar surface tension, and a greater propensity for alveolar collapse. The resorption of protein from the alveolar space is believed to occur more slowly, and is differentially regulated depending on the burden of protein present. Removal of larger insoluble proteins, such as fibrin-rich hyaline membranes requires degradation, and can take much longer.\textsuperscript{23}

The damaged and injured endothelium is also play an important role in the pathogenesis of ARDS through increased endothelial permeability, release of inflammatory molecules, expression of cell adhesion molecules, and an up-regulation of procoagulant pathways. Endothelial cells can be stimulated to release preformed von Willebrand factor (vWF)\textsuperscript{24} as well as potent neutrophil (PMN) activating factors.\textsuperscript{25}

Endothelial activation in ARDS is highlighted by the finding that elevated plasma vWF levels have been shown to predict the development of ARDS in patients at risk\textsuperscript{26} and predict poorer outcomes in patients in whom ARDS has already developed. Higher vWF levels are also associated with fewer organ failure-free days in patients with ARDS.\textsuperscript{27} Activated leucocytes and endothelial cells can also contribute to another recognized pathologic manifestation of ARDS, namely dysregulated intravascular and extravascular fibrin accumulation.\textsuperscript{28,29} Impaired fibrinolysis and increased procoagulant activity within the alveolar lining fluid have long been recognized in patients with ARDS. Numerous additional pathways have been implicated in the pathogenesis of ARDS. Endotoxin (lipopolysaccharide) is considered to be the initiator of ARDS in the settings of sepsis and pneumonia.\textsuperscript{30} Oxidant-mediated injury through the generation of oxidant species such as superoxide and hydrogen peroxide, is also a well-recognized pathway for injury in ARDS. Dysregulation of cell death and apoptosis through the release and accumulation of soluble Fas ligand is also thought to contribute to injury and may also become a potential future target for therapeutic intervention.\textsuperscript{21,31} The role of mechanical ventilation in contributing to the development and exacerbation of ARDS is now widely recognized, its mechanisms extensively researched,\textsuperscript{32,33} and its appreciation has led to the most significant contribution to date in the management of this condition: the use of lower tidal volumes.

Inflammatory response leading to organ dysfunction and failure continues to be the major problem after injury in many clinical conditions such as sepsis, severe burns, acute
pancreatitis, hemorrhagic shock, and trauma. In general terms, systemic inflammatory response syndrome (SIRS) is an entirely normal response to injury. Systemic leucocyte activation, however, is a direct consequence of a SIRS and if excessive, can lead to distant organ damage and multiple organ dysfunction syndrome (MODS). When SIRS leads to MODS and organ failure, the mortality becomes high and can be more than 50%. Acute lung injury that clinically manifests as ARDS is a major component of MODS of various etiologies. Inflammatory mediators play a key role in the pathogenesis of ARDS, which is the primary cause of death in these conditions. Recent studies that demonstrate the critical role played by inflammatory mediators such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-1beta, interleukin-6 (IL-6), platelet activating factor (PAF), interleukin-10 (IL-10), granulocyte macrophage-colony stimulating factor (GM-CSF), C5a, intercellular adhesion molecule (ICAM)-1, substance P, chemokines, vascular endothelial growth factor (VEGF), insulin like growth factor-I (IGF-I), keratinocyte growth factor (KGF), reactive oxygen species (ROS), and reactive nitrogen species (RNS) in the pathogenesis of ARDS.

These mechanisms are summarized in (Figure 1)

**PATHOPHYSIOLOGY**

Due to accumulation of extravascular lung water (i.e., pulmonary oedema), the physiological derangements of ARDS invariably manifest as refractory hypoxaemia, decreased respiratory compliance, and a propensity for alveolar closure. As alveolar oedema fluid and protein accumulate within the alveoli, physiologic shunt develops as blood flows through capillary units perfusing alveoli that are either filled with fluid, or have collapsed from the resulting increase in surface tension. Hypoxic vasoconstriction, the normal autoregulatory reflex severely impaired within the diseased regions of the lung. Hence, the physiologic shunt in ARDS is accentuated by increasing of flow to the poorly ventilated regions of the lung. In addition, increased vasoconstriction within well-ventilated regions and thrombi that arise within the microvasculature can both contribute to the development of physiologic dead space or wasted ventilation as blood fails to perfuse the better aerated regions of the lung. The combined effects of these derangements result in refractory hypoxemia and increased minute ventilation needs, helping to explain the often challenging demands of managing these patients in the ICU.

Pulmonary vascular resistance is commonly elevated in patients with ARDS. This results in oxygen shunting and increased pulmonary capillary permeability. The increased microvascular permeability may also contribute to the development of adult respiratory distress syndrome (ARDS), a severe form of lung injury characterized by hypoxemia and diffuse alveolar damage. The etiology of ARDS is diverse, including sepsis, trauma, critical illness, and other conditions associated with systemic inflammation. The pathogenesis of ARDS involves a complex interplay of inflammatory mediators and cellular dysfunction, leading to widespread tissue injury and organ failure.

**Figure 1:** Pathogenesis of ARDS

PMN = polymorphonuclear neutrophils; PAF = platelet-activating factor; IL = interleukin; GM-CSF = Granulocyte-macrophage colony-stimulating factor; C5a = complement component 5a; SIRS = Systemic inflammatory response syndrome
from a hypoxia-induced reduction in the luminal diameter of the vascular bed, and thrombotic obstruction of the microvasculature.\textsuperscript{39,40} This in turn leads to the common finding of pulmonary hypertension in these patients, which can alter right ventricular loading and function. The decrease in respiratory compliance is primarily due to an increase in lung elastance, particularly in the more direct forms of ARDS such as pneumonia. The increased elastic properties of the aerated lung result from increased tissue stiffness due to interstitial oedema and increased alveolar surface tension, but the contribution from interstitial oedema is thought to be negligible relative to that from alveolar oedema.\textsuperscript{41} The increase in alveolar surface tension is thought to develop from the increased surface forces generated by a greater abundance of alveolar lining fluid and a decrease in surfactant activity.\textsuperscript{42} The lower resting lung volumes in ARDS result from persistently fluid-filled or collapsed alveoli, leading to what has been colloquially referred to as baby lung.\textsuperscript{43} Unfortunately, the affected regions of the lungs are often so diseased that they may remain fluid-filled or completely collapsed throughout each tidal inflation\textsuperscript{44} and hence contribute negligibly to compliance. The unaffected healthy lung areas are over distended and volutrauma can occur, this can lead to ventilator associated lung injury (VALI).\textsuperscript{32}

The predominant histopathologic findings of ARDS are fundamentally uniform, and it is diffuse alveolar damage\textsuperscript{19}. It can be further subdivided into exudative, proliferative, and fibrotic phases.\textsuperscript{19,45} Exudative phase typically occupies the first week and is characterized by epithelial and endothelial cell necrosis, neutrophil sequestration, platelet-fibrin thrombi, interstitial oedema, and exudates within the air spaces that consist primarily of fluid, fibrin, and red blood cells.\textsuperscript{19} These exudates compact into dense, protein-rich hyaline membranes that stain strongly with eosin and line the alveoli and alveolar ducts. The proliferative phase starts from second week to fourth week; it is characterized by organization of the intra alveolar exudates and proliferation of type II alveolar cells, fibroblasts, and myofibroblasts. During this phase, the alveolar ducts are occluded by metaplastic squamous cells and granulation tissue.\textsuperscript{46} The fibrotic phase is seen in patients who survive past 3 or 4 weeks.\textsuperscript{19} On histologic examination, alveolar septa are expanded and airspaces filled with sparsely cellular connective tissue, and remodeling can progress to the point of complete air space obliteration and honey combing.\textsuperscript{46}

**Clinical features**

The signs and symptoms of ARDS can vary in intensity, depending on its cause and severity. They include severe shortness of breath, labored and unusually rapid breathing, low blood pressure, confusion and extreme tiredness. The symptoms of ARDS come on suddenly, usually within hours or days of the event that initially caused injury to the lung. Other symptoms can occur, depending on the event that caused the ARDS. For example, if pneumonia is causing the ARDS, symptoms may also include chest pain and fever.

Frontal chest radiograph shows extensive bilateral infiltrates. These infiltrates initially appear as bilateral heterogeneous opacities, but later become more homogenous over hours to days.\textsuperscript{45} Computed tomography (CT) has demonstrated the distribution of ARDS to often be heterogeneous and patchy, with mixed ground-glass opacities and consolidation, often concentrated in the more gravitationally dependent regions of the lung.\textsuperscript{48}
Magnetic resonance imaging (MRI) has also been used in the experimental setting to differentiate between hydrostatic and permeability oedema, but this method has also not been widely implemented clinically.

**DIAGNOSIS**

**Berlin definition**

A convention in 2011 with 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 Berlins definition, mainly focusing on feasibility, reliability, validity, and objective evaluation of its performance. The definition proposed three mutually exclusive categories of ARDS based on degree of hypoxaemia: mild (200 mm Hg < PaO₂/FIO₂ ≤ 300 mm Hg), moderate (100 mm Hg < PaO₂/FIO₂ ≤ 200 mm Hg), and severe (PaO₂/FIO₂ ≤ 100 mm Hg) and four ancillary variables for severe ARDS: radiographic severity, respiratory system compliance (≤ 40 mL/cm H₂O), positive end-expiratory pressure (≥ 10 cm H₂O), and corrected expired volume per minute (≥ 10 L/min). The four ancillary variables did not contribute to the predictive validity of severe ARDS for mortality and were removed from the definition, after it was empirically evaluated using meta-analysis of 4188 patients with ARDS from 4 multi-centre clinical data sets and 269 patients with ARDS from 3 single-center data sets containing physiologic information. The Berlin definition stages of mild, moderate, and severe ARDS were associated with increasing mortality (27%, 32%, and 45% respectively) and increasing median duration of mechanical ventilation in survivors (5 days, 7 days and 9 days respectively). The final Berlin definition had better predictive validity for mortality compared to AECC definition with an area under the receiver-operating characteristic curve of 0.577 vs 0.536. The updated and revised Berlin definition for ARDS addresses a number of limitations of the AECC definition. The approach of combining consensus discussions with empirical evaluation may serve as a model to create more accurate, evidence-based, critical illness syndrome definitions and to improve clinical care, research, health service and resource planning.

**Differential diagnosis**

Because the presenting symptoms of ARDS are non-specific, other respiratory, cardiac, infectious, and toxic aetiologies must be considered in the differential diagnosis. Patient history (e.g., comorbidities, exposures, medications) in conjunction with a physical examination focusing on the respiratory and cardiovascular systems can help narrow the differential diagnosis and determine the optimal course of treatment.

Often, ARDS must be differentiated from congestive heart failure and pneumonia. Congestive heart failure is characterized by fluid overload, whereas patients diagnosed with ARDS, do not show signs of left atrial hypertension or overt volume overload. Patients with congestive heart failure may have oedema, jugular venous distension, third heart sound, an elevated brain natriuretic peptide level, and a salutary response to diuretics. Patients with ARDS would not be expected to have these findings.

Because pneumonia is a leading cause of ARDS, distinguishing patients with uncomplicated pneumonia from those who have pneumonia complicated by ARDS presents a greater diagnostic challenge. In general, a patient with uncomplicated pneumonia may have signs of systemic and pulmonary inflammation (i.e., fever, chills, fatigue, sputum production, pleuritic chest pain,
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and localized or multifocal infiltrates); accompanying hypoxia should respond to oxygen administration. If hypoxia does not correct with oxygen administration, ARDS should be suspected. In those with combined pneumonia and ARDS, treatment entails antibiotics and ventilator management.

**TREATMENT**

Treatment of ARDS includes definitive treatment aimed at the underlying aetiological cause, other supportive measures, mechanical ventilation, prevention of stress ulcers and venous thromboembolism, and nutritional support.

Pharmacologic options for the treatment of ARDS are limited. Although surfactant therapy may be helpful in children with ARDS, a Cochrane review did not find it to be beneficial in adults. The use of corticosteroids is controversial. Randomized controlled trials and cohort studies tend to support early use of corticosteroids (with dosages of methylprednisolone ranging from 1 to 120 mg per kg per day) for decreasing the number of days on a ventilator; however, no consistent mortality benefit has been shown with this therapy.

In addition to ventilatory measures, patients with ARDS should receive low-molecular-weight heparin (40 mg of enoxaparin or 5,000 units of dalteparin subcutaneously per day) or low-dose, unfractionated heparin (5,000 units subcutaneously twice daily) to prevent venous thromboembolism, unless contraindicated. Patients should also be on stress ulcer prophylaxis with an agent such as sucralfate (1 g via nasogastric tube four times daily), ranitidine (150 mg via nasogastric tube twice daily, 50 mg intravenously every six to eight hours, or a 6.25 mg per hour continuous intravenous infusion), or omeprazole (40 mg intravenously, or via nasogastric tube daily). Finally, patients should receive nutritional support, preferably enteral, within 24 to 48 hours of admission to the ICU.

**Mechanical ventilation**

Respiratory failure and hypoxemia are the main problems of ARDS. Oxygen delivery by mechanical ventilation remains a very important objective in the management of these patients. They are more prone for multiorgan failure. Even though higher tidal volume (10 to 15 ml/kg) maintains effective ventilation and oxygenation, the incidence of VALI was high in animal models. Small retrospective and prospective uncontrolled trials suggested a benefit from limiting tidal volume and peak airway pressures in patients with ARDS. Numerous larger, randomized trials comparing traditional and lower tidal volumes have since been conducted, each trial differing in its methodology and results. The larger randomized, multicentre trial to date, conducted by the ARDS Network, ultimately demonstrated a significant reduction in mortality when using a tidal volume of 6 mL per kg of predicted ideal body weight and a target plateau pressure of 30 cm H_2O or less (mortality 31%) as opposed to a tidal volume of 12 mL per kg and a target plateau pressure less than 50 cm H_2O (mortality 39.8%).

Low tidal volume ventilation improves outcome by avoiding over distention of normal alveoli thereby preventing volutrauma. Low tidal volume ventilation also improves outcome by reduced activation of inflammatory cascades associated with VILI and multiorgan failure. In ARDS Network trial studies, it was found that higher plasma levels of soluble receptors of TNF-α were associated with higher mortality. Furthermore the low tidal volume strategy was associated with lower levels of soluble TNF-α receptors. In another study from the same patient population, elevated plasma levels of IL-6, interleukin-8 (IL-8), and IL-10 were also linked to increased mortality.
while lower tidal volume was associated with a greater drop in IL-6 and IL-8 by day 3 of enrolment.  

In low tidal volume ventilation there is a reduction in minute ventilation causing increase in partial pressure of arterial carbon dioxide (PaCO$_2$) which leads to a strategy of permissive hypercapnia. Some guidelines acknowledge permissive hypercapnia as an acceptable practice when necessary to limit tidal volumes, but also stress that its use is limited in patients with preexistent metabolic acidosis, and contraindicated in patients with increased intracranial pressure. Because no firm guidelines have been established, current options range from a allowing for an arterial pH as low as 6.8, to increasing respiratory rate up to 35 and buffering with intravenous bicarbonate when pH drops below 7.3. Despite ongoing controversy and the delayed adoption low tidal volume strategy in clinical practice, the current evidence has led professional societies to recommend the use of lower tidal volumes at goal plateau pressures less than 30 cm H$_2$O in patients with established ARDS. Because calculations based on total body weight may be partly responsible for the documented underuse of lower tidal volumes for patients with ARDS, the importance of using predicted ideal body weight (IBW), based upon measured height and sex, cannot be overstressed. Although no firm guidelines exist regarding patients without established ARDS there is clinical evidence that a low tidal volume strategy may help prevent progression to ARDS in patients at risk. Yet to be determined is whether a more optimal or “best” strategy exists beyond that employed in the ARDS Network sponsored study. Although data suggest that tidal volumes lower than 6 mL per kg may confer even greater protection from VILI, there is no general consensus on this practice. However, in the original ARDS Network trial, the lower tidal volume assignment started with a goal of 6 mL per kg, but patients in this arm were oftentimes adjusted to as low as 4 mL per kg as needed to maintain plateau pressures less than 30 cm H$_2$O.

**Recruitment**

Recruitment manoeuvers (RM) are traditionally delivered as sustained inflations with peak inflation pressures limited to between 30 and 40 cm H$_2$O, and held for a period ranging from 15 to 40 seconds. In some patients the physiologic abnormalities in ARDS can be reversed by a recruitment maneuver (RM), and typically delivered as a sustained deep inflation with the intention of reopening collapsed regions of the lung. However, because of the unusually high surface tension within affected alveoli, the benefit is often transient, especially if not followed by sufficiently high levels of PEEP. Periodic RMs also have the potential to worsen oxygenation by shunting blood flow to poorly aerated regions and impair cardiac output by limiting venous return and cardiac preload. Furthermore, RMs could conceivably contribute to lung injury through excessive over distention or repeated opening of collapsed lung. Many clinical studies have yielded mixed results regarding beneficial effects of RMs on oxygenation and lung function. Although earlier clinical studies demonstrated the benefits of recruitment to be negligible or short-lived, recent larger trials have demonstrated more promising improvements in lung function and oxygenation but still failed to demonstrate any reduction in mortality.

**Positive end-expiratory pressure**

Positive end-expiratory pressure (PEEP) is another widely employed strategy shown to retard alveolar derecruitment in the injured lung. Several studies have demonstrated the ability of PEEP to prevent or delay alveolar derecruitment and attenuate VALI.
However, the protective effect of higher PEEP was questioned after a multicentre randomized trial failed to demonstrate an improvement in outcomes using a higher PEEP strategy during low tidal volume ventilation in ARDS patients. The amount of recruitable lung varies significantly among ARDS patients, some have suggested that setting PEEP levels without first determining the level of recruitable lung may offset the potential benefits of PEEP. In a recent randomized trial, the selection of PEEP was more patient-directed and set at a level required to maintain plateau pressures of 28 to 30 cm H₂O. This higher PEEP strategy again failed to demonstrate a reduction in mortality, but did demonstrate lasting improvements in oxygenation and compliance and an increase in ventilator-free and organ failure-free days.

Others have shown that more directly targeting PEEP to transpulmonary pressure by measuring esophageal pressures may be a safer and more effective means of determining optimal PEEP. Optimal PEEP

It has been often observed that lower inflection point (LIP) on the inspiratory limb of the PV curve obtained from ARDS patients is the point beyond which the slope of the curve dramatically increases (Figure 2). This dramatic increase in compliance at the LIP was initially believed to represent a sudden increase in lung volume and hence maximal alveolar recruitment. Thus, many have advocated using the LIP to guide the setting of “optimal” PEEP. However, several studies have demonstrated significant recruitment beyond the LIP, a concept supported by mathematical models and CT imaging. Data from CT imaging in ARDS patients has recently lent strong support to setting “optimal PEEP” at the point of maximal curvature (PMC) along the deflation limb of the PV curve (Figure 2). Nevertheless, the concept of “optimal PEEP” has likely been oversimplified and controversy remains over how alveolar recruitment is best served by PEEP.

High frequency oscillation ventilation: High-frequency oscillation ventilation (HFOV), with very small tidal volumes equal to or less than dead space and delivered at a very high rate, would seem to be an ideal ventilatory strategy in ARDS. How adequate ventilation is achieved with tidal volumes less than or equal to dead space is unknown. Proposed mechanisms include a pendelluft effect of mixing gases between lung regions of differing impedances, coaxial flow with net center inflow and net peripheral outflow, mixing of fresh and residual air along the leading edge of gas flow, and simple molecular diffusion through relatively still air. HFOV first demonstrated clinical benefits among infants with respiratory distress syndrome. Although early smaller studies of HFOV in adult ARDS were promising, a larger multicentre-controlled trial failed to demonstrate any reduction in mortality from HFOV over conventional ventilation.

Extracorporeal membrane oxygenation

Extracorporeal membrane oxygenation (ECMO) used alone or in combination with HFOV, uses cardiopulmonary bypass to facilitate gas exchange while minimizing ventilation of the lung to limit barriers to
healing. Despite demonstrated efficacy in neonates with severe respiratory distress syndrome,\textsuperscript{110} ECMO had until recently failed to demonstrate any reduction in adult mortality.\textsuperscript{111,112}

**Prone position ventilation**

Previously in mid 70s, prone positioning was shown to improve oxygenation in patients with hypoxic respiratory failure.\textsuperscript{113} Proposed mechanisms have centered around the potential reversal of gravitationally distributed perfusion to the better ventilated ventral lung regions\textsuperscript{114} and improved ventilation of previously dependent dorsal lung,\textsuperscript{115} both of which would improve ventilation/perfusion matching. The largest randomized clinical trial to date also demonstrated an improvement in oxygenation and a reduced incidence of ventilator-associated pneumonia with prone positioning, but again no benefit in survival.\textsuperscript{116} This study, however, brought greater attention to safety concerns by demonstrating a higher incidence in pressure sores and inadvertent endotracheal tube displacement.

**Pharmacological interventions**

**Vasodilators**

Initial studies examined the use of intravenously administered vasodilators such as nitroglycerin and prostacyclin,\textsuperscript{117,118} but simultaneous and nonselective reductions in systemic and pulmonary vascular resistance led to systemic arterial hypotension with increases in cardiac output and shunt. After the once described “endothelial-derived relaxing factor” was discovered to be nitric oxide (NO),\textsuperscript{119} it was found that inhaled NO (iNO) could selectively dilate the pulmonary vasculature within well-ventilated regions of the lung,\textsuperscript{120} helping reverse both hypoxic vasoconstriction and physiologic shunt. Subsequently, two small-randomized controlled trials demonstrated a significant but transient improvement in oxygenation and shunt in ARDS patients in response to iNO, but these benefits did not last past 24 hours, and there was no improvement in outcomes.\textsuperscript{121,122} Most studies have demonstrated minimal adverse effects of iNO other than dose-dependent methaemoglobinemia.\textsuperscript{123} At the present time, iNO has been approved by the Food and Drug Administration for use in neonates with hypoxic respiratory failure accompanied by pulmonary hypertension but is not approved for use in adult ARDS.

**Surfactant**

Surfactant replacement is to help restore the natural surfactant film and reduce surface tension at the air–liquid interface, thus reducing the tendency for alveolar collapse and improving oxygenation through a reduction in shunt. The evidence in support of surfactant replacement therapy for neonatal RDS is abundant.\textsuperscript{124,125} Results from its investigated use in adult ARDS patients have been less promising.\textsuperscript{126-128} The largest multicentre randomized clinical trial in adult ARDS failed to demonstrate any improvement in mortality with continuous aerosol delivery of the synthetic surfactant, Exosurf.\textsuperscript{127}

**Corticosteroids**

Numerous uncontrolled trials had initially suggested a potential benefit of corticosteroids for late or persistent ARDS.\textsuperscript{129-131} However, treatment with corticosteroids during the acute phase of ARDS has since been proven ineffective.\textsuperscript{132,133} The first randomized controlled trial of corticosteroids for late ARDS demonstrated improved lung injury scores and oxygenation, decreased multiorgan dysfunction scores, and reduced ICU and in-hospital mortality in the group receiving steroids.\textsuperscript{134}

**Anticoagulants/fibrinolysis**

Minimizing microvascular thrombosis could conceivably improve oxygenation through improved ventilation-perfusion matching\textsuperscript{135} and increase survival through prevention of multiorgan failure.\textsuperscript{136} Thus, the importance of
coagulation in the pathogenesis of ARDS has become widely appreciated, and the use of anticoagulant therapy in ARDS has in turn gained attention. The most encouraging clinical evidence to support this therapeutic target initially came from a multicenter trial demonstrating a mortality benefit from activated protein C (APC) in severe sepsis. However, because randomized trials of other potent anticoagulants, such as antithrombin III and tissue factor pathway inhibitor (TFPI), yielded no mortality benefit in sepsis, the postulated benefits from APC may be unrelated to its anticoagulant activity.

Nutritional therapy

Nutritional supplements containing omega 3 fatty acids like eicosapentaenoic acids (EPA) are helpful in directly suppress monocyte production of inflammatory cytokines and incorporate into cell membrane phospholipids to compete with omega-6 fatty acids to promote the production of more favorable prostaglandins and leukotrienes. Many studies supporting omega-3 fatty acids in ARDS came initially from small randomized trials comparing a standard isonitrogenous, isocaloric enteral diet with one supplemented with a proprietary mixture of EPA, gamma-linolenic acid (borage oil), and other antioxidants. These studies demonstrated an improvement in gas exchange and lung function, a reduction in bronchoalveolar lavage fluid (BALF) levels of IL-8, leukotriene B4, and neutrophils and a reduction in ICU stay and mechanical ventilation days with the EPA-rich supplement.

Fluids

Optimal fluid management in patients with acute lung injury is unknown. Diuresis or fluid restriction may improve lung function but could jeopardize extrapulmonary-organ perfusion. Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing nonpulmonary-organ failures. These results support the use of a conservative strategy of fluid management in patients with acute lung injury. Fluids administration is controversial in ARDS. Liberal fluid administration in these patients can increase pulmonary oedema. Limiting fluids in such patients with multi organ dysfunction can lead to decreased tissue perfusion. Diuretic therapy (furosemide) combined with albumin has been shown to improve oxygenation and haemodynamics in hypo-proteinemic ARDS patients but does not reduce mortality. The use of PA catheters came into question after a large observational study of 5,700 critically ill patients actually suggested a higher mortality rate associated with PA catheter use. However, subsequent prospective trials have contradicted these findings. So fluid administration should be optimized based on haemodynamic stability and urine output.

Airway pressure release ventilation

Airway pressure release ventilation (APRV) is a ventilator mode that uses sustained high airway pressures and spontaneous breathing to maximize lung recruitment, with transient periods of “pressure release” to facilitate ventilation while minimizing derecruitment during exhalation. Proponents assume that the periods of pressure release are brief enough to avoid alveolar closure and reexpansion, and efficacy relies heavily on the presence of spontaneous ventilation, which is believed to generate regionally variable transpulmonary pressures that favor recruitment of dependent lung regions.

Ketoconazole

Ketoconazole acts through inflammatory signaling modification. It is an imidazole
antifungal agent with anti-inflammatory properties. It blocks the synthesis of proinflammatory mediators such as the eicosanoid leukotrienes and thromboxane A2 and also reduces macrophage proinflammatory cytokine production. Early small studies were successful in preventing ARDS in high risk patients, however a later study by the ARDSnet group of ketoconazole in 234 patients with ARDS was negative.

**Ibuprofen**

Ibuprofen inhibits cyclo-oxygenase and it is a non-steroidal anti-inflammatory agent. In a study of 448 patients with sepsis ibuprofen diminished prostanoid production and was associated with trends towards decreased duration of pulmonary dysfunction and ARDS, but this did not reach statistical significance. Modulation of other inflammatory mediators has also been investigated.

**Insulin**

Insulin has anti-inflammatory effects *via* inhibition of the pro-inflammatory transcription factor NFkB. A landmark trial of intensive insulin therapy (IIT) in critical care reported a large decrease in mortality by maintaining serum glucose levels between 80 and 110 mg/dL. Subsequent critical care studies have had mixed results, and a significant risk of hypoglycaemia was apparent upon meta-analysis of intensive insulin therapy studies. In a rat model of endotoxin induced ARDS tight glycaemic control to 90-110mg/dl reduced the severity of lung injury. The role of intensive insulin therapy in preventing ARDS by maintaining tight glycaemic control (80 to 110 mg/dL) is currently being studied.

**Statins**

Apart from their cholesterol lowering effects statins improve epithelial and endothelial function to reduce alveolar capillary permeability and decrease pulmonary oedema. Statins modulate the inflammatory cascade; regulate inflammatory cell recruitment, activation and apoptosis; and lessen cytokine and protease activity. This may improve outcomes, as high levels and persistence of inflammatory mediators in ARDS are associated with poor outcome.

**Others**

IL-8 is a chemoattractant for neutrophil migration into the alveolus. In a rat model of gastric aspiration anti-IL-8 antibody significantly reduced neutrophil recruitment to the alveolus and reduced the severity of lung injury.

ARDS is a process of diffuse pulmonary inflammation with increased vascular and alveolar permeability. The physiologic process is restrictive lung disease and hypoxemia occurs due to oedema and V/Q mismatch. The ventilatory treatment involves increasing positive pressure ventilation to improve oxygenation. Ventilator induced lung injury can be minimized by maintaining high PEEP, low tidal volume, peak pressures less than 35 cm H\(_2\)O, and FiO\(_2\) less than 60%. Death is primarily due to multi-organ dysfunction (usually cardiovascular collapse), and not ARDS primarily. Therefore, all other supportive measures should be optimized. Since its first published description in 1967, our understanding of the pathogenesis and pathophysiology of ARDS has grown appreciably, and ongoing research efforts continue to provide hope for exciting new therapies in the future. The improved understanding of this condition has already resulted in improved outcomes for patients suffering from ARDS, but the prognosis for those acutely afflicted in the hospital, and those fortunate enough to survive, leaves room for ongoing progress in the management of these patients. Aside from the obvious importance of reducing mortality from this condition, a
reduction in days on the ventilator and subsequent stay in the intensive care unit represent some of the other tangible and intangible benefits to both patients and society in general. 172,173

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