CHAPTER 7

# Acute Respiratory Distress Syndrome

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*A 28-year-old male is brought to the casualty with complaints of high-grade fever, upper respiratory tract infections (URTI), dry cough and loose stools of 1-week duration. Over the past 2 days, he is progressively worsening and now has respiratory distress. On examination, he is tachycardic [heart rate (HR) of 96 beats/min], normotensive [blood pressure (BP) 116/80 mm Hg] and tachypneic (respiratory rate 35 breaths/min). His $SpO_2$ is 80% on room air, which falls to 70% on minimal exertion. Bilateral coarse crepitations are present. Chest X-ray shows bilateral consolidation, more on the right side. A throat swab sent 2 days back for H1N1 has come positive today.*

**What is the likely diagnosis? What should be the initial workup?**

The patient is a young male with history of high-grade fever and lung infiltrates with impaired oxygenation. The most likely diagnosis is pneumonia with acute hypoxemic (type I) respiratory failure (AHRF). The pathophysiologic mechanisms that account for the hypoxemia observed are low ventilation/perfusion (V/Q) ratio and shunt. These two mechanisms lead to widening of the alveolar-arterial $PO_2$ gradient (normal <15 mm Hg) while breathing room air. The difference between the two mechanisms is the response of the patient on breathing 100% oxygen. Hypoxemia predominantly due to low V/Q responds to oxygen supplementation, whereas hypoxemia due to shunt does not respond well to oxygen supplementation. The common causes for hypoxemic respiratory failure include the following:

- Pneumonia
- Chronic obstructive pulmonary disease (COPD)
- Pulmonary edema
- Pulmonary fibrosis
- Asthma
- Pneumothorax
- Pulmonary embolism
- Pulmonary arterial hypertension
- Pneumoconiosis
- Granulomatous lung diseases
- Cyanotic congenital heart disease
- Bronchiectasis
- Acute respiratory distress syndrome (ARDS)
- Fat embolism syndrome
- Kyphoscoliosis
- Obesity.

*Initial workup:*

Acute hypoxemic respiratory failure may be associated with a variety of clinical manifestations, including tachypnea and dyspnea. However, these are nonspecific and respiratory failure may be present without dramatic signs or symptoms. Therefore, analysis of arterial blood gas is extremely important in patients in whom AHRF is suspected.

Chest radiography is essential. Electrocardiography (ECG) should be performed to evaluate the possibility of a cardiovascular cause of respiratory failure. ECG may also detect dysrhythmias resulting from hypoxemia or acidosis.

Arterial blood gas analysis should be performed to confirm the diagnosis and to assess the severity of respiratory failure and guide management.

Presence of anemia on complete blood count in these patients will contribute to tissue hypoxia, whereas polycythemia may indicate chronic hypoxemic respiratory failure. Leukocytosis or leucopenia point to an infectious etiology.

Evaluation of renal and hepatic function may be helpful in the evaluation and management of a patient in respiratory failure, and to assess the presence of any multi-organ dysfunction. Abnormalities in electrolytes such as potassium, magnesium and phosphorus may aggravate respiratory failure due to muscle weakness and also can affect functions of other organ systems such as cardiovascular and gastrointestinal systems.

**What is ARDS?**

Acute respiratory distress syndrome (ARDS) is a life-threatening condition requiring intensive care unit (ICU) admission and ventilatory support. It is defined by presence of non-cardiogenic pulmonary edema and hypoxemia due to direct or indirect injury to lung parenchyma. It is a common endpoint of various direct and indirect insults. ARDS was first described by Ashbaugh and Petty in 1967. It was first described as adult respiratory distress syndrome to distinguish it from the neonatal respiratory distress syndrome, but after recognition of ARDS in pediatric patients, the nomenclature has been changed to acute respiratory distress syndrome.[1]

The incidence of ARDS varies in different studies due to variations in definitions and association with a lengthy list of causes and comorbidities. The National Institute of Health in 1977 had described an incidence of 75 per 100,000 population.[2] The **L**arge observational study to **UN**derstand the **G**lobal impact of **S**evere **A**cute respiratory **F**ailur**E** (LUNG SAFE) study found that ARDS was present in >10% of ICU patients and incidence was >20% patients requiring invasive mechanical ventilation.[3]

ARDS is always associated with a risk factor, the risk increasing with multiple risk factors. These factors can injure the lung directly or indirectly; accordingly, the risk factors are categorized as direct or indirect **(Table 1)**. This categorization is amply justified by the differences in pathogenesis, physiologic difference and differing outcomes.[4]

**Table 1:** Risk factors associated with ARDS.[4]

| *Factors causing direct lung injury* | *Factors causing indirect lung injury* |
|---|---|
| Pneumonia | Sepsis |
| Aspiration | Multisystem trauma |
| Lung contusion | Transfusion of plasma and other products |
| Inhalational injury | Acute pancreatitis |
| Reperfusion injury | Drug overdose |
| Near drowning | Cardiopulmonary bypass |
| Fat embolism | Other surgeries |

Sepsis is the most common cause of ARDS and is associated with the worst outcomes, while trauma-related ARDS has a significantly lower mortality.[4-6]

**What is the pathogenesis of ARDS? What are the pathophysiologic consequences of ARDS?**

*Pathogenesis:*

ARDS is a condition initiated or triggered by injury to the alveolar epithelium and/or capillary endothelium. While alveolar epithelial injury is the initial insult in the conditions associated with direct lung injury, capillary endothelial injury is the initial trigger in the conditions associated with indirect lung injury. Ultimately both mechanisms play role in ARDS, hence both events can be identified on histopathology at the time of diagnosis.[7] Alveolar epithelial cells are of two types; flat type I and cuboidal type II. Type I cells are most abundant (90% of epithelial cells) and are prone to damage. Type II cells are responsible for production of surfactant, proliferation and production of type I cells and transport of ions and are less prone to damage.[8] Loss of type II cells lead to loss of usual transport and removal of fluid across the membrane.

There are three phases of ARDS identified on histopathology:[9,10]

1. Exudative phase occurs due to the injury to alveolar epithelium and capillary endothelium
2. Proliferative phase starts 7–14 days after the initial insult and leads to repair of damaged epithelium/endothelium, restoration of barrier function and proliferation of fibroblasts
3. Fibrotic phase occurs in some patients as chronic inflammation sets in leading to fibrosis of alveoli.

The most prominent feature in ARDS is widespread loss of alveolar epithelial type I cells due to sloughing and apoptosis. One of the well-known markers for epithelial injury, the receptor of advanced glycosylation end-product (RAGE) is highly expressed on alveolar epithelial cells type I. Endothelial injury is also widespread. It causes increased permeability leading to leakage of plasma in the interstitial space and airspaces. Therefore, the alveolar fluid in ARDS is rich in protein, in contrast to the alveolar fluid in cardiogenic-pulmonary edema, which has low-protein content. Injury to endothelium also causes release of inflammatory molecules, increased expression of cell surface adhesion molecules (e.g. selectin, intracellular

adhesion molecule-1) and activation of procoagulant pathways by increased release of von Willebrand factor (vWF), especially in patients with sepsis and bacteremia. These in turn helps in binding and transmigration of neutrophils across the endothelium.[11]

In addition, the other abnormalities contributing to pathogenesis of ARDS are as follows:

- Neutrophilic infiltration leading to inflammatory cascade
- Surfactant dysfunction
- Dysregulated intravascular and extravascular coagulation cascade.

Although neutrophils are not critical for the pathogenesis of ARDS, as evidenced by incidence of ARDS in neutropenic patients, they play a crucial role in initial inflammatory cascade. Neutrophils release a variety of proteases, e.g. elastase, collagenase, gelatinase A and gelatinase B, reactive oxygen species, in addition to proinflammatory cytokines and chemokines. All these markers lead to a widespread inflammatory response, both pulmonary and extrapulmonary. Proinflammatory cytokine surge and further recruitment of neutrophils by resident macrophages also add to the inflammatory response.[11-13]

Surfactant dysfunction is the combined result of injury to type II epithelial cells, intra-alveolar flooding with proteinaceous fluids and increased proteolysis. Both lipid and protein components of surfactant are abnormal. Surfactant dysfunction leads to abnormality in host defense and lung mechanics.[14-16]

Dysregulated intravascular and extravascular coagulation is mainly due to activated leukocytes and endothelial cells. Both increased procoagulant activity and impaired fibrinolysis have been described in ARDS. Tissue factor expression is increased on the surface of alveolar epithelium and resident macrophages leading to increased procoagulant activity in the edema fluid. Elevated levels of plasminogen activator inhibitor-I (PAI-I) and reduced levels of protein C have been implicated in the impaired fibrinolysis.[17]

*Pathophysiologic consequences:*

The pathophysiologic consequences of ARDS include the following:

- Refractory hypoxemia and shunt
- Decreased lung compliance
- Pulmonary hypertension.

*Refractory hypoxemia and shunt*: Physiological shunt increases in ARDS due to the following reasons:

- Flooding of the alveolar space with protein, exudates and fluid
- Alveolar collapse due to increase surface tension in absence of surfactant
- Non-cardiogenic pulmonary edema due to leaky alveolar-capillary membrane.

All these lead to a mismatched V/Q as blood flowing through capillaries in the alveoli which are collapsed are not taking part in gas exchange. The inflammatory edema also leads to widened alveolar septum leading to decreased diffusion across the alveolar capillary membrane.[18-20]

*Decreased compliance:* Alveolar flooding and atelectasis along with alveolar capillary membrane inflammation makes the alveolar spaces very stiff, resulting in non-compliant lungs. In late stages of ARDS, fibrosis also decreases the compliance of the lung.

*Pulmonary hypertension and RV failure:* The development of pulmonary hypertension is a common occurrence in ARDS. It further worsens the hypoxemia by increasing dead-space ventilation and hypercarbia. Pulmonary hypertension develops due to hypoxic pulmonary vasoconstriction[21] and also due to local production of endothelin-1 and thromboxane A2. ARDS also causes remodeling of arterial, venous and lymphatic circulation, leading to decrease in cross-section of the lumens due to deposition of fibrin and collagen.[21,22] Formation of microthrombi and macrothrombi in pulmonary vessels is also common in ARDS. Microthrombi and macrothrombi had been demonstrated in 95% and 86% of autopsy specimens, respectively.[22] Pulmonary hypertension can lead to further hypoxia by right-to-left shunting across a patent foramen ovale and end-organ hypoperfusion due to right ventricular failure leading to reduced cardiac output.[23]

**What is the clinical definition of ARDS?**

*Clinical definition:*

Murray and colleague's proposed diagnostic criteria which included; hypoxemia [(partial pressure of oxygen in arterial blood ($PaO_2$)/fraction of inspired oxygen ($FiO_2$)], chest radiographic opacities (number of quadrants), positive end-expiratory pressure (PEEP) level, and low respiratory system compliance (Crs). Murray further expanded their definition to describe the time course; which addressed prognostic and treatment implications of different phases and causes of ARDS.[24]

The American European Consensus Conference (AECC) on ARDS in 1994 definition considered four parameters to identify ARDS, viz. timing of onset, oxygenation, absence of cardiac failure and chest radiograph findings. ARDS was defined as impaired oxygenation of acute onset with $PaO_2/FiO_2$ (PF) ratio less than 200 and a pulmonary capillary wedge pressure less than 18 mm Hg. Acute lung injury (ALI) with PF ratio less than 300 was identified separately by AECC. ALI represented a broader spectrum of lung injury to include processes other than ARDS which were associated with impaired gas exchange.[25]

*The Berlin definition 2012* ***(Table 2)****:*

Meta-analysis of data from 4,188 patients, taken from four multicenter and three single-center datasets of ARDS patients were used. All the four elements of AECC definition were updated. It also evaluated ancillary variables to update the definition and to increase the predictive validity in predicting clinical outcomes. It differs from AECC definition in each of the elements. It specifies the timing of onset within 7 days of a known insult.[26,27] To improve the interobserver agreement in interpretation of chest radiograph consistent with ARDS, the Berlin definition further described the chest opacities in ARDS not be fully explained by effusions, lobar collapse or nodules. In addition, 12 sample radiographs with interpretations as consistent, inconsistent and equivocal for diagnosis of ARDS can be used.[27] The new definition has removed the term ALI and uses only ARDS. ARDS has been classified into three degrees of severity based on the PF ratio.[26] To meet the definition of PF ratio, patient must be receiving ≥5 cm $H_2O$ of continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP). In mild ARDS, this CPAP can be delivered through noninvasive ventilation (NIV):

- Mild ($PaO_2/FiO_2$: 201 to 300 mm Hg with PEEP or CPAP ≥5 cm $H_2O$)
- Moderate ($PaO_2/FiO_2$: 101 to 200 mm Hg with PEEP ≥5 cm $H_2O$)
- Severe ($PaO_2/FiO_2$: ≤100 mm Hg with PEEP ≥5 cm $H_2O$).

For the calculation of PF ratio, arterial blood sample is needed. Recent studies have shown good correlation between $SpO_2/FiO_2$ ratio and PF ratio.[28] $SpO_2/FiO_2$ ratio of 235 had been shown to correspond to PF ratio of 200 and $SpO_2/FiO_2$ ratio of 315 to PF ratio of 300. One limitation of $SpO_2/FiO_2$ ratio is that, it is reliable only when $SpO_2$ is less

**Table 2:** Berlin definition of ARDS.[26,27]

| | |
|---|---|
| Timing | Within 1 week of a known clinical insult or new or worsening respiratory symptoms |
| Chest radiograph | Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules |
| Cause of edema | Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic edema, if no risk factor present |
| Severity | Oxygenation criteria |
| Mild | 200 mm Hg <$PaO_2/FiO_2$ ≤300 mm Hg with PEEP or CPAP ≥5 cm $H_2O$ (Formerly ALI by AECC Criteria) |
| Moderate | 100 mm Hg <$PaO_2/FiO_2$ ≤200 mm Hg with PEEP ≥5 cm $H_2O$ (Formerly ARDS by AECC criteria) |
| Severe | $PaO_2/FiO_2$ ≤100 mm Hg with PEEP ≥5 cm $H_2O$ (Formerly ARDS by AECC Criteria) |

(AECC: American European Consensus Conference; ALI: acute lung injury; ARDS: acute respiratory distress syndrome; CPAP: continuous positive airway pressure; $FiO_2$: fraction of inspired oxygen; $PaO_2$: partial pressure of oxygen in arterial blood; PEEP: positive end-expiratory pressure)

**Table 3:** Differences between AECC and Berlin definitions of ARDS.[25,26]

| ***Components*** | ***AECC definition*** | ***Berlin definition*** |
|---|---|---|
| Timing | Acute onset | Acute onset <1 week of inciting event |
| Chest imaging | Bilateral infiltrates on chest X-ray | Bilateral infiltrates on chest imaging not fully explained by effusion, lobar/lung collapse or nodules |
| Origin of edema | No evidence of left atrial hypertension or PCWP <18 mm Hg | Respiratory failure not fully explained by cardiac failure or fluid overload |
| Oxygenation | $PaO_2/FiO_2$ <300 is acute lung injury<br>$PaO_2/FiO_2$ <200 is ARDS | $PaO_2/FiO_2$ 200–300 with PEEP or CPAP ≥5 cm $H_2O$: mild ARDS<br>$PaO_2/FiO_2$ 100–200 with PEEP or CPAP ≥5 cm $H_2O$: moderate ARDS<br>$PaO_2/FiO_2$ <100 with PEEP or CPAP ≥5 cm $H_2O$: severe ARDS |

(ARDS: acute respiratory distress syndrome; CPAP: continuous positive airway pressure; $FiO_2$: fraction of inspired oxygen; $PaO_2$: partial pressure of oxygen; PCWP: pulmonary capillary wedge pressure; PEEP: positive end expiratory pressure)

than 98% because the oxyhemoglobin curve is flat above $SpO_2$ of 100%. The advantage with $SpO_2$ measurement is, it is noninvasive and can be done continuously and is widely available in all setups.[29] However, $SpO_2$ has yet not been incorporated in definition of ARDS.

**How will you differentiate ARDS from cardiogenic pulmonary edema?**

The initial definition from AECC for ARDS required a pulmonary artery wedge pressure (PAWP) of less than 18 mm Hg without any clinical evidence of left atrial hypertension. This definition missed the diagnosis of ARDS in patients with left atrial hypertension or heart failure, whereas both can exist together. The Berlin definition allows for considering the presence of both hydrostatic and non-hydrostatic pulmonary edema provided the respiratory failure cannot be explained by heart failure alone, even clinical vignettes were added in the supplementary article. Use of bedside echocardiography to rule out cardiogenic pulmonary edema has been encouraged if no identifiable precipitating factor for ARDS could be identified.[26] Till date, no laboratory study had been reliably able to differentiate between cardiogenic pulmonary edema and ARDS. B-type natriuretic peptide (BNP) levels at the time of admission could not differentiate between cardiogenic and non-cardiogenic edema, and it also did not correlate with the measurements found on invasive hemodynamic monitoring.[30] Even N-terminal pro BNP levels do not correlate with PAWP.[31]

Recently, lung ultrasound has been extensively used in the bedside assessment of critically ill patients in ICU.[32,33] In ARDS, usually a nonhomogeneous B-pattern and pleural line abnormality (shred sign) are usually found.[32] Bilateral B-pattern can be present in both cardiogenic and non-cardiogenic pulmonary edema.[33-36]



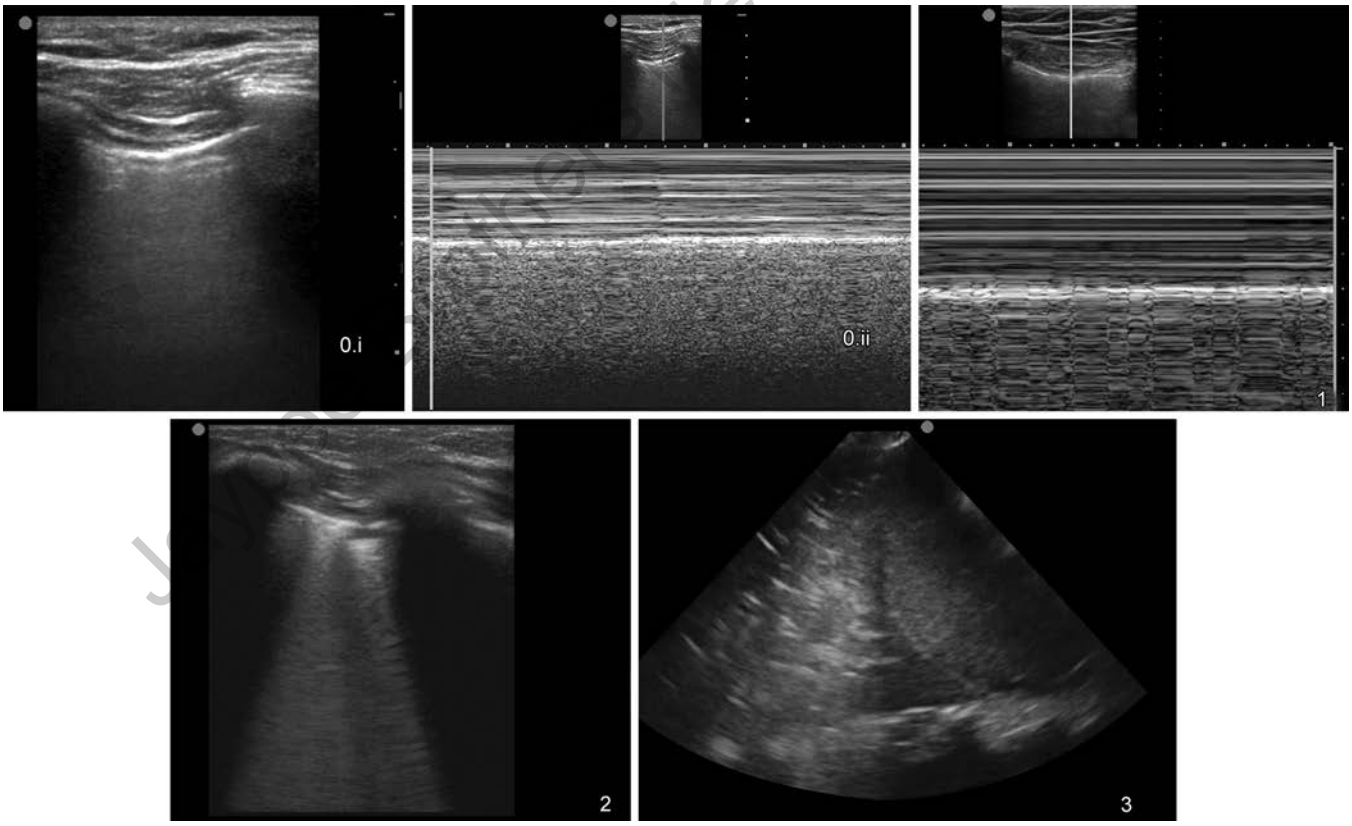



**Fig. 1:** Possible findings at ultrasonographic lung examination. **0**: Normal aeration with normal sliding, (i) B mode with A-lines pattern and (ii) M mode showing sea shore sign; **1**: M mode showing lung pulse indicating lack of ventilation; **2**: B-lines indicating alveolar-interstitial syndrome (AIS); **3**: Lung consolidation, hyperechoic area with air-bronchogram.

**Table 4:** Clinical differences between ARDS and CPE.[32-36]

| ***Clinical parameter*** | ***ARDS*** | ***Cardiogenic pulmonary edema (CPE)*** |
|---|---|---|
| History | Variable | History of heart disease or previous history of CPE |
| Signs of cardiac failure | Usually absent | Commonly present |
| X-ray | Opacities are more or less uniformly distributed. Opacification persist for days to weeks (retrospective) | Opacities begin/prominent in bilateral perihilar areas Opacities clear rapidly within hours with treatment (retrospective) |
| ***Ultrasound findings*** | | |
| Pleural line | May be reduced, thickened or appear coarse | Normal |
| Lung sliding | May be absent | Present |
| Lung pulse during ventilation | Can be seen | Not seen |
| B lines-alveolar interstitial syndrome (AIS) | AIS with air bronchograms and spared areas | Homogeneous AIS with no spared areas |
| Consolidation | Signs-like shred sign, tissue-like sign are seen | Not seen |
| Pleural effusion | Uncommon and exudative | Common and large transudative |
| Echocardiography | No new change in left ventricular function | New or worsening left ventricular systolic dysfunction |
| IVC diameter | Usually normal and collapsing with respiration | Usually dilated and non-collapsible |
| Pulmonary vascular permeability index (PVPI) using the transpulmonary thermodilution (TPTD) technique[37] | >3 | <2 |



**How will you manage this patient in ICU?**

*Treatment:*

The treatment of ARDS is respiratory support and identification and treatment of the predisposing cause. With substantial improvement in supportive therapies there has been a gradual decline in mortality attributable to ARDS over the last few decades. The most crucial step in treating ARDS is the identification of the predisposing factor and prompt therapy for it, e.g. in sepsis associated ARDS, early resuscitation, appropriate antibiotic and early source control has shown good outcome.[38]

The supportive therapy for ARDS mainly focuses on providing adequate gas exchange with lung protective ventilation and minimizing ventilator-induced lung injury (VILI). The strategies to reach this objective can be pharmacologic, non-pharmacologic or a combination of both **(Table 5)**.

**Table 5:** Supportive strategies for ARDS.

| ***Nonpharmacologic strategies*** | ***Pharmacologic strategies*** |
|---|---|
| Mechanical ventilation<br>Noninvasive ventilation/high flow nasal cannula (HFNC)<br>Invasive ventilation with low tidal volumes<br>PEEP application | Muscle relaxation<br>Corticosteroids<br>Diuretics to achieve negative fluid balance in the absence of shock |
| ***Rescue therapies***<br>Recruitment maneuvers<br>Prone positioning<br>High frequency oscillation (HFO)<br>Extracorporeal carbon dioxide removal ($ECCO_2R$)<br>Extracorporeal membrane oxygenation (ECMO) | ***Rescue therapy***<br>Inhaled vasodilators |

*Noninvasive ventilation (NIV)/High flow nasal cannula (HFNC):*

NIV can reduce intrapulmonary shunt and the work of breathing, thus improving oxygenation. The advantages of NIV include avoiding deep sedation, allowing spontaneous breaths, minimal risk of nosocomial pneumonia, improved hemodynamics and better V/Q matching. In a meta-analysis of 13 heterogeneous studies of NIV in ALI/ARDS (n = 540), there was 50% NIV failure rate.[39] Appropriate selection of patient for NIV is of paramount importance. NIV seems to be a reasonable choice in the subset of ARDS patients with a $PaO_2/FiO_2$ >

150 due to lower failure rate.[40] On the other hand, patients with *de novo* ARF (without previous cardiac or respiratory disease) have almost two times more chances of NIV failure compared with the patients with previous cardiac or respiratory disease.[41] Other predictors of failure of NIV include higher heart rate, lower PF ratio, lower bicarbonate, high sepsis-related organ failure assessment (SOFA) score and worsening of lung infiltrate 24 hour after admission. Likelihood of NIV failure is 2–3 times more in hypoxemic respiratory failure than cardiogenic pulmonary edema or acute exacerbation of chronic obstructive pulmonary disease. Higher hospital mortality is observed in patients with acute hypoxemic respiratory failure who failed NIV.[42] Possible consequent risk of delaying tracheal intubation in patients managed with NIV also have worse outcome. With the given amount of evidence NIV should be avoided in *de novo* ARF and patients with severe ARDS. In other patients, NIV can be given with close monitoring for the signs of NIV failure.

High-flow nasal cannula (HFNC) can deliver warmed and humidified high oxygen flow through the nose which improves patient comfort.[43] It improves oxygenation, $CO_2$ clearance, end-expiratory lung volume and thus decreases work of breathing. In the FLORALI trial, Frat et al. compared the efficacy of high flow nasal cannula, NIV and oxygen through standard facemask in patients with acute hypoxemic respiratory failure without hypercapnia. They looked at the proportion of patients intubated at 28 days, all-cause mortality at 90 days and ventilator free days at 28 days. This trial also showed a high rate of failure with NIV with an intubation rate of 50%. Though the difference in intubation rate was not statistically significant in the three groups, the number of ventilator free days was significantly higher in HFNC group. On post-hoc analysis the intubation rate was significantly low in HFNC group in the group of patients with PF ratio less than 200. All-cause mortality was also lower in HFNC group. Overall subjective patient-comfort was much higher in HFNC group.[44]

*Invasive mechanical ventilation:*

Hypoxemic respiratory failure is the hallmark of ARDS. The alveolar spaces are flooded with proteinaceous exudative inflammatory fluid leading to impaired oxygenation and a stiff lung with low lung compliance leads to increasing work of breathing. Almost all patients of ARDS need some respiratory support and a significant proportion of them need endotracheal intubation and invasive mechanical ventilation. There have been a substantial evidence through clinical and experimental studies that mechanical ventilation leads to functional and structural alteration in lung.[45] Mechanical ventilation perpetuates the lung injury in ARDS and contributes to the morbidity and mortality associated with ARDS.[46-48] Webb and Tierney in 1970 showed that high peak inspiratory pressure (PIP) produced severe damage in lungs of rats which was attenuated by use of PEEP. Gattinoni first described the concept of "baby lung".[49] The ARDS lung was considered homogeneous lung in radiographs but it appeared inhomogeneous in computed tomography (CT) scans with most of the densities present in the dependent parts of the lungs. The lungs comprised of normally aerated, poorly aerated, nonaerated and overinflated tissues. Effectively, the lung is divided into three zones: a nonrecruitable zone, in the bases, an injured but recruitable midzone, and a spared though potentially overdistended zone in the apices. On quantitative estimation from the CT images, the volume of the normally aerated lungs in adult patients of severe ARDS was equivalent to the normally aerated lung of a healthy boy of 5–6 years age, supporting the concept of baby lung. The shunt fraction, degree of hypoxemia and pulmonary hypertension relate to the nonaerated tissue of lungs. Respiratory compliance correlates well with the remaining normally aerated lung tissue. Thus, compliance truly measures the volume of baby lung. In other words, we can say that the ARDS lung is not stiff but small. The modern mechanical ventilation strategy focuses mainly on minimizing ventilator-induced lung injury and near normalization of blood gases. It involves protective lung ventilation and keeping the lung open with the appropriate use of PEEP.

*Lung protective ventilation:*

Historically, a tidal volume of 12–15 mL per kg was routinely used for mechanical ventilation, but now it is well established that a low tidal volume, plateau-pressure limited ventilation has shown reduced mortality after the NIH ARDS Network published their first multicenter randomized control trial (RCT) in 2000.[50] Mortality in traditional tidal volume group was 39.8% and 31% in lower tidal volume [6 mL/kg predicted body weight (PBW) and plateau pressure <30 cm $H_2O$) group ($p = 0.007$)

*Permissive hypercapnia:*

In order to prevent VILI, target tidal volume was decreased in the algorithm provided by the ARDSNet. This in turn led to $CO_2$ retention and hypercapnic acidosis (HCA). In view

**Table 6:** Ventilatory management of ARDS (ARDSnet Protocol).[50]

***Calculate predicted body weight (PBW):***
- *Males:* PBW (kg) = 50 + 2.3 [(height in inches) − 60] or 50 + 0.91 [(height in cm) − 152.4]
- *Females:* IBW (kg) = 45.5 + 2.3 [(height in inches) − 60] or 45.5 + 0.91 [(height in cm) − 152.4]

Ventilator Mode
Volume Assist/Control until weaning

***Tidal Volume (Vt):***
- *Initial Vt:* 6 mL/kg predicted body weight
- Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hr and after each change in PEEP or Vt
- If Pplat >30 cm $H_2O$, decrease Vt to 5 or to 4 mL/kg
- If Pplat <25 cm $H_2O$ and Vt <6 mL/kg PBW

***Respiratory rate (RR):***
- With initial change in Vt, adjust RR to maintain minute ventilation
- Make subsequent adjustments to RR to maintain pH 7.30–7.45, but do not exceed RR = 35/min and do not increase set rate if $PaCO_2$ <25 mm Hg

I:E Ratio
Acceptable range, 1:1–1:3 (no inverse ratio)
$FiO_2$, PEEP, and Arterial Oxygenation
Maintain $PaO_2$ = 55–80 mm Hg or $SpO_2$ = 88%–95% using the following PEEP/$FiO_2$ combinations:

| **$FiO_2$** | 0.3 | 0.4 | 0.5 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1 |
|---|---|---|---|---|---|---|---|---|---|
| **PEEP** | 5 | 8 | 10 | 12 | 14 | 16 | 18 | 18–24 | |

***Acidosis management:***
- If pH <7.30, increase RR until pH ≥ 7.30 or RR = 35/min
- If pH remains <7.30 with RR = 35, consider bicarbonate infusion
- If pH <7.15, Vt may be increased (Pplat may exceed 30 cm $H_2O$)

***Alkalosis management:***
If pH >7.45 and patient not triggering ventilator, decrease set RR but not below 6/min.

***Fluid management:***
- Once patients are out of shock adopt a conservative fluid management strategy
- Use diuretics or fluids to target a central venous pressure (CVP) of <4 mm Hg or a pulmonary artery occlusion pressure (PAOP) of <8 mm Hg

***Liberation from mechanical ventilation:***
- Daily interruption of sedation
- Daily screen for spontaneous breathing trial (SBT)
- SBT when all of the following criteria are present:
  - $FiO_2$ <0.40 and PEEP <8 cm $H_2O$
  - Not receiving neuromuscular blocking agents
  - Patient is awake and following commands
  - Systolic arterial pressure >90 mm Hg without vasopressor support
  - Tracheal secretions are minimal, and the patient has a good cough and gag reflex.

***Spontaneous breathing trial:***
Place patient on 5 cm $H_2O$ PEEP with 5 cm $H_2O$ pressure support ventilation or T-piece
Monitor HR, RR, oxygen saturation for 30–90 min
Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).



of proven mortality benefit with protective lung ventilation, this $CO_2$ rise is accepted as long as there is no harm with this respiratory acidosis. This practice is known as permissive hypercapnia.[51] The limits for $PCO_2$ and pH in permissive hypercapnia are not yet clear but in the data from clinical trials on permissive hypercapnia, $PCO_2$ levels of 60–70 mm Hg and arterial pH of 7.20–7.25 has been found safe.[52]

*Positive end-expiratory pressure (PEEP):*
PEEP and/or recruitment maneuvers have been universally used to improve oxygenation in ARDS patients since the first description of ARDS. Over last 50 years the use of PEEP has shifted more toward minimizing lung injury than improving hypoxemia. The mechanisms explaining the beneficial effects of PEEP in ARDS lungs are:

- Alveolar recruitment leading to increased FRC leading to improvement in ventilation-perfusion match
- Stabilization of recruited lung and prevention of atelectrauma by avoiding cyclical alveolar collapse by splinting open alveoli.
- Extravascular lung water redistribution.

Even with all the evidences gained over the years about the beneficial effects of PEEP, one of the most debatable issue is to select the ideal or optimal PEEP. If PEEP is too low, recruitment will not be enough to improve hypoxemia, and if PEEP is too much, it will overstretch the normal baby lung leading to VILI and increased dead space.

*PEEP titration:*

Setting right PEEP is important as it not only helps in recruitment and oxygenation but also prevents VILI. An optimal PEEP is one which will help in recruitment, prevent cycles of recruitment and decruitment and prevent alveolar overdistention. No single method has been optimized to set right PEEP. Multiple methods have been used and proposed for setting optimal PEEP.

*Oxygenation:*

In all ARDS Network studies, a combination of PEEP and $FiO_2$ were set to achieve and maintain a target $SpO_2$ (>88%). The tables proposed for ARDS Network trial were based on expert opinion and not on robust evidence. At the same time, this table did not consider individual lung mechanics. These tables were easy to use and had a face validity, as they were routinely used in all the trials by ARDS Network. It is largely believed that higher PEEP should be limited to patients with high recruitability to extract maximal benefit and to avoid lung injury. Chiumello et al.[53] concluded that simple PEEP selection methods such as Lung Open Ventilation Strategy study table correlated recruitability better than the complex PEEP selection methods based on lung mechanics like ExPress (progressively increasing PEEP until the airway plateau pressure of 28–30 cm), stress index less than 1 (discussed below), and esophageal pressure (PEEP set equal to the absolute value of esophageal pressure), as judged by whole lung CT scans in static conditions at 5 and 45 cm $H_2O$.

*Pressure–volume loop:*

Pressure –volume loop is the graphical representation of relationship between pressure and volume as the lung inflates and deflates **(Fig. 2)**.

The lower inflection point mainly represents the point where alveolar recruitment starts. The rapid rise after LIP represents alveolar recruitment. PEEP above LIP increases compliance of the lung by recruitment. Upper inflection point is the pressure above which the compliance decreases, here the lungs starts to get overdistended. The rapid rise in pressure at the beginning of inspiration,

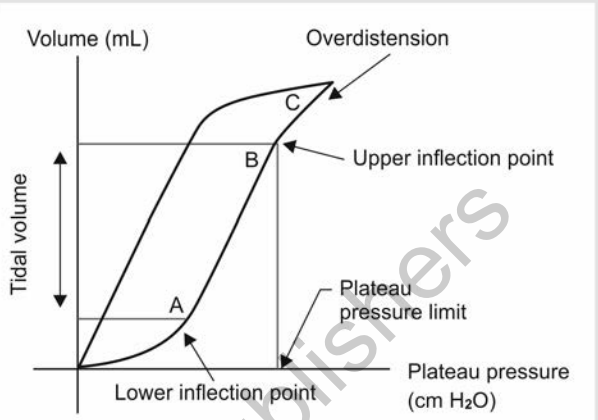



**Fig. 2:** Pressure–volume loop showing inflection points.

after the LIP indicates alveolar recruitment. This pressure is high as reinflation of collapsed alveolus needs higher pressure than distending an inflated one. The part of the loop which is linear from LIP to UIP represents the ideal pressure at which the alveoli are open and continue to distend gradually with rise in pressure with increasing compliance. This is known as the curve of optimal compliance.

Amato and colleague[54] popularized the concept of setting ideal PEEP based on the PV curve and identification of LIP and UIP. They recommended to set PEEP at a level 2 cm $H_2O$ more than the LIP. A number of issues are faced while using this method to set ideal or optimal PEEP:

- Deep sedation (and often paralysis) is required to get a correct PV curve
- In a mechanically ventilated patient, a quasi-static pressure–volume (PV) loop maneuver is required with low flow rate (<10 L/min), to minimize the effects of airway resistance on the peak pressure, and bring it closer to the plateau pressure
- It is often difficult to identify the LIP and UIP.
- Esophageal manometry is required to calculate the actual lung compliance instead of respiratory system compliance
- The inflation limb may not be indicative of recruitment, rather it can be some other mechanics, e.g. inflation of an edematous lung.

*Driving pressure:*

Driving pressure ($\Delta P$) is the ratio of tidal volume to static compliance of respiratory system.

ΔP = Tidal volume (Vt)/Respiratory system compliance (Crs)

Clinically, driving pressure is the difference between alveolar plateau pressure and PEEP, i.e. ΔP = Pplat – PEEP

Pplat – PEEP = Vt/Crs

Crs = Vt/Pplat – PEEP

Both PEEP and tidal volume are independent variables and can be altered by physician, but plateau pressure and compliance are dependent variables, so any change in independent variable affects the dependent variable.

When increasing the tidal volume or PEEP, if there is recruitment then driving pressure will decrease and compliance increases but if there is over distension then worsening of compliance and increase in driving pressure occurs. Driving pressure and compliance are interrelated. Driving pressure may be defined better as the amount of cyclical alveolar deformation imposed on ventilating lung units.

When we measure compliance (Crs), we are actually measuring the compliance of thorax as a whole, and lungs are just a part of it. Hence if we need to know the distending pressure of lungs alone, we need to measure transpulmonary pressure (alveolar – pleural pressure/esophageal pressure) which is clinically not feasible.

Ventilator-induced lung injury is due to lung stress and strain which is proportional to the pressure applied to the lung. As lung stress and strain is difficult to measure in clinical practice airway driving pressure can be used to predict lung injury. Higher the driving pressure greater the lung injury.[55]

Recently Amato et al. showed in their multilevel mediation analysis of 3,562 ARDS patients from 9 previous RCTs that ΔP is a better predictor of ARDS outcome.[56] The independent variables associated with improved outcome were driving pressure, $PaO_2/FiO_2$ ratio at entry, pH at entry, risk of death (APACHE, SAPS). The authors did multiple resampling considering subgroups of patients with matched mean levels for one variable but different mean level for another ranking variable and found that increased driving pressure was associated with increased mortality.

Thus, driving pressure is an independent predictor of survival in patients with ARDS and that the reduction in tidal volume or increase in PEEP was found beneficial, only if associated with decrease in driving pressure (ΔP).

Low driving pressure is associated with improved survival but achieving lower driving pressure may be a challenge. In patients with ARDS with good recruitable lung after applying recruitment maneuver and appropriate PEEP, the functional lung size increases and transpulmonary pressure gets evenly distributed leading to better compliance and lower driving pressure.

*Stress index:*

Another easy bedside surrogate method to know the change in compliance is the stress index **(Fig. 3)**.[57] It is noted from the terminal part of pressure time curve of volume-controlled breath with constant flow in a paralyzed patient. When the terminal part of pressure time curve is concave downward, it represents good compliance (stress index <1), concave upwards it represents poor compliance (stress index >1) whereas flat shape represents normal compliance (stress index = 1). To know the real stress on lung, we need to measure transpulmonary stress index and is clinically challenging. Transpulmonary stress index can be substituted by airway pressure stress index since there is good correlation between them.[58,59]

Airway stress index is a simple bedside tool to track respiratory compliance to ventilator adjustments and hence used to predict lung injury during ventilation.[60] Both tidal volume and PEEP can be titrated to stress index to limit lung injury.[61] Stress index reflects the respiratory compliance which in turn has an impact on driving pressure **(Crs = Vt/Pplat – PEEP)**; so low stress index will have low driving pressure and vice versa. So, both stress index and driving pressure can be used as an

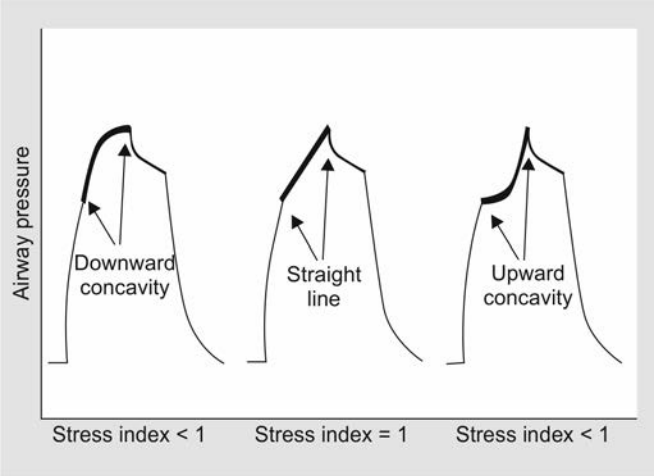



**Fig. 3:** Pressure time Scalar Waveforms showing stress index. *Courtesy:* Ventilator-induced lung injury. Kulkarni AP, Divatia JV, in Critical Care Update 2009. Pages 48-58. Editors. V Nayyar, et al. Published by M/s Jaypee Brothers Medical Publishers (New Delhi, India). ISBN 978-81-8448-972-9

indicator of lung stress. Transpulmonary driving pressure is more important and real indicator of lung stress. Driving pressure has shown to have close correlation with transpulmonary driving pressure and reflect lung stress.[62] So, airway driving pressure (ΔP) can practically replace transpulmonary driving pressure as an indicator of lung stress. Driving pressure is easy to measure, more objective and easier to keep a trend as compared to stress index.

*Other supportive measures:*

*Sedation:* Sedation is usually mandatory in ARDS patients receiving lung protective ventilation. Deep sedation is preferred in the initial stages to improve synchrony, to prevent VILI, especially when neuromuscular blockade is warranted. Secondary analysis of large ICU database has shown that benzodiazepines, as compared to Propofol, were associated with higher days of ventilatory support, longer duration of ICU stay and higher mortality.[63] Lighter levels of sedation are targeted once there is no requirement of muscle paralysis. Pain and sedation score should be frequently assessed using validated scales.[64] In conclusion, sedation should be adequate and deep enough in the early stages of ARDS, especially when patients are receiving neuromuscular blockade, analgesia and lighter sedation or no sedation are preferred when the clinician starts preparing for weaning from mechanical ventilation.

*Fluid management:* Pulmonary edema is the hallmark of ARDS, hence logically keeping the patient 'dry' may help in oxygenation and outcome. At the same time, presence of circulatory shock warrants adequate fluid resuscitation to maintain the peripheral perfusion in the initial stages. In hemodynamically stable ARDS patients (FACTT trial), the conservative strategy of fluid management improved lung function and shortened the duration of mechanical ventilation and intensive care without increasing non-pulmonary organ failures, without any change immortality.[65]

*Nutrition:* As in any other ICU patient, management of ARDS patient also includes nutrition. The enteral route of nutrition is safer and better than the parenteral route.[66] No individual dietary component or composition has yet been proven to be of particular benefit over others in ARDS. The goal of nutritional support is the provision of sufficient nutrients along with correction and prevention of deficiency of micro-or macronutrients.[67] Various combinations of omega-3-fatty acids, ribonucleotides, glutamine and arginine have been investigated in ARDS for immunomodulation. There was a beneficial effect on infection rate but there was no mortality benefit.[68] Even one large study of omega-3-fatty acid and antioxidants was terminated early in view of excess mortality in patients receiving omega-3-fatty acid.[69] One study found that a high fat, low carbohydrate diet reduced the duration of mechanical ventilation in patients with respiratory failure. The authors suggested that the reason for the beneficial effect was a decrease in respiratory quotient with decrease in $CO_2$ production, though the most common reason for high respiratory quotient remains to be overfeeding.[70] A study of clinical outcomes in 1,000 ARDS patients randomized to full calorie versus trophic (10 cc/hr) enteral feeds did not show any difference in mortality or other clinical outcomes.[71] Overall, there is still no compelling evidence to support the use of anything other than standard (enteral) nutritional support, with avoidance of overfeeding.

**What is the role of steroids in ARDS?**

The anti-inflammatory actions of corticosteroids have made these drugs the most studied. Alveolar fibrosis in ARDS and the antifibrotic properties of steroids have been investigated.

*Steroids in early ARDS:* Earlier studies investigated the use of high-dose methylprednisolone in early ARDS. Bernard et al. in 1987 used methylprednisolone (4 doses of 30 mg/kg) and found no improvement in oxygenation, lung compliance or severity of ARDS at 45 days, as compared with the placebo group.[72] Similar results were seen when high dose steroids were used in septic shock patients.[73] Further trials used a lower dose of steroids. In the 2002 trial by Annane which investigated low dose steroids in septic shock, a retrospective subgroup analysis of ARDS patients, showed a reduction of mortality in those patients who had received 7 days of low dose corticosteroids and mineralocorticoids.[74,75] Meduri published the results of a double-blind, placebo-controlled trial, in which patients of early severe ARDS were randomized to receive methylprednisolone infusion (1 mg/kg/day) versus placebo for 28 days.[76] They observed downregulation of systemic inflammation, significant improvement in both pulmonary and extra pulmonary organ dysfunction and reduction in duration of mechanical ventilation and ICU length of stay with methylprednisolone. On long-term follow-up of 12 months, they found no difference in the mortality between the groups. Higher incidence of septic

shock patients in placebo group may have contributed to this.

*Steroids in late ARDS:* The effectiveness of steroids in late fibroproliferative phase of ARDS became the area of interest for researchers after the initial trials showed lack of favorable outcome in early stages of ARDS. Meduri and colleagues reported a case series of 9 patients with ARDS and fibrotic changes on open lung biopsy.[77] The use of 2–3 mg/kg/day of methylprednisolone resulted in improvement in lung injury scores, chest X-ray appearance and oxygenation in all patients. A larger case series of 25 patients was published by the same author in 1994 using similar doses of methylprednisolone followed by a tapering dose over 6 weeks, resulting in marked improvement in most indices of lung function.[78]

The ARDS Clinical Trials Network conducted a multicenter trial of steroids in late persistent ARDS. About 180 ARDS patients were recruited 7–28 days after the diagnosis and randomly assigned to receive either methylprednisolone or placebo. The steroids were tapered over a 3-week period unless the patient remained ventilated at 21 days when the steroids were tapered over 4 days. There was no mortality benefit at day 60 and day 180. There was increased 60-days and 180-days mortality in patients who were started on steroids at least 14 days after diagnosis. Methylprednisolone increased ventilator-free days, shock-free days with improvement in oxygenation and respiratory system compliance. As compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness. Thus, they concluded against the routine use of steroids in ARDS and also warned about the increased rate of death in ARDS, if steroids were started after 14 days of diagnosis of ARDS.[79]

The use of steroids in ARDS still remains controversial. Meta-analysis and cohort studies both reported trend toward improved outcome with steroids. No excess adverse events were found. Marked heterogeneity was seen in the included studies.[80]

*Timing of steroid dosing:* Evidence suggests that fibrosis starts at very early stage of ARDS. Inflammatory cytokines have been documented in bronchoalveolar lavage fluid and plasma of ARDS patients from the outset of their disease. Experimental studies and animal studies suggest that earlier use of steroids is more likely to prevent progression of ARDS.[81]

The timing of steroid differed significantly in two major studies. The ARDSnet study recruited patients at least 7 days into the course of their disease, whereas Meduri's group recruited patients within 3 days of diagnosis.[76,79] One interpretation of these trials is that steroids may only be effective, if given early in lung injury, before the inflammatory process has caused irreversible damage to the alveoli.

*Steroid dose:* Very little data is available on the relationship between steroid dose and response in critically sick patients. It will be immature to say that a "one-dose-fits-all-strategy" will be successful because of:

- Extremely complex and multifaceted nature of inflammatory response
- Wide variance in metabolism and tissue distribution among individuals
- Uncertainty about the targets of steroids—whether local or systemic.

**What are the rescue therapies for refractory hypoxemia?**

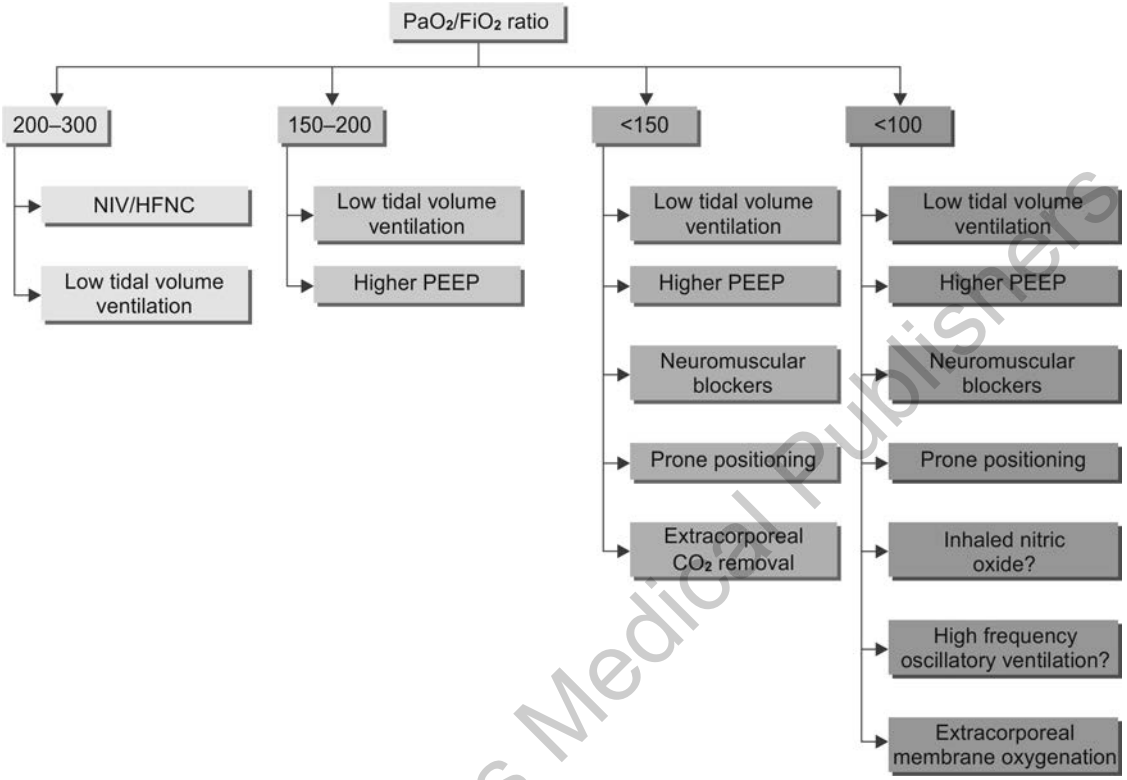
*Rescue therapies* ***(Flowchart 1)****:*

Rescue measures or rescue therapies are required in the patients who are profoundly hypoxemic with maximum ventilatory support. Initially, these patients are managed with deep sedation and neuromuscular blockade to prevent asynchrony and improve recruitment. Rescue therapies have been used in patients with persistent hypoxemia in spite of deep sedation and neuromuscular blockade; however, benefits of many of these therapies are yet to be proven.

*Neuromuscular blockade:*

Neuromuscular blockade is the first step before using any rescue therapy. Neuromuscular blockade used in initial stage of severe ARDS (defined as PF ratio <150) has been shown to reduce mortality. In the ACURYSYS trial[82] the effect of neuromuscular blockade for 48 hours started within 48 hours of diagnosis of severe ARDS has shown to improve outcome. Crude 28- and 90-day mortality were significantly lower in the group receiving Cisatracurium, hazard ratio (HR) ratio for death at 90 days in the Cisatracurium group was 0.68. Cisatracurium group had more ventilator-free days without an increase in muscle weakness. The explanation for the improved outcome in the group with neuromuscular blockade is not clear. Neuromuscular blockade leads to abolition of spontaneous efforts, there was improved control of inspiratory volume

**Flowchart 1:** Therapies in ARDS.






preventing volutrauma and reduction in transpulmonary pressure which reduced the incidence of barotrauma. In terms of lung mechanics, improved synchrony led to better recruitment, reduced atelectrauma, improved compliance and oxygenation. All these led to less pulmonary and systemic inflammation producing better outcome.[83]

*Recruitment maneuver (RM):*

Lung protective ventilation with low tidal volume limits injury due to overdistension. PEEP is applied to avoid atelectrauma by splinting open alveoli and preventing cyclical alveolar collapse. In hypoxemic ARDS, recruitment maneuver is applied to reopen the recruitable lung. Recruitment maneuvers are used to recruit collapsed but potentially recruitable alveoli.[84] Recruitment maneuver is followed by constant application of higher (than before) PEEP to keep the lungs open to increase end-expiratory lung volume. This will help the patient by preventing cyclical collapse.[85] Moreover, recruitment may reduce VILI caused by overdistention of healthy alveoli. However, RMs may directly over distend aerated lung units and could, paradoxically, lead to increased VILI.[84-86] Several methods of recruitment have been employed in clinical and experimental settings with varying results.

*Sustained inflation:*

The most common approach is to set the ventilator on CPAP mode and increase the pressure to 30–40 cm $H_2O$ for 30–40 sec. Severe hemodynamic compromise may happen during this maneuver and requires proper hemodynamic monitoring. This can even be done with pressure-controlled ventilation.[87] The effects of recruitment maneuver were variable in the patients with ARDS and had higher adverse effects (hypotension and desaturation occurred in 22% of patients receiving RMs, while serious complication like increased air leak through chest tube occurred in <5% patients).[88-90] Due to the uncertainty of benefits with RMs and the potential for complications with repeated RMs, it is unjustified to use scheduled RMs.

*Stepwise recruitment maneuver or decremental PEEP method (open lung approach):*

In this approach, both plateau pressure and PEEP are gradually increased with the driving pressure kept constant (e.g. 15 cm $H_2O$). After the recruitment, the PEEP

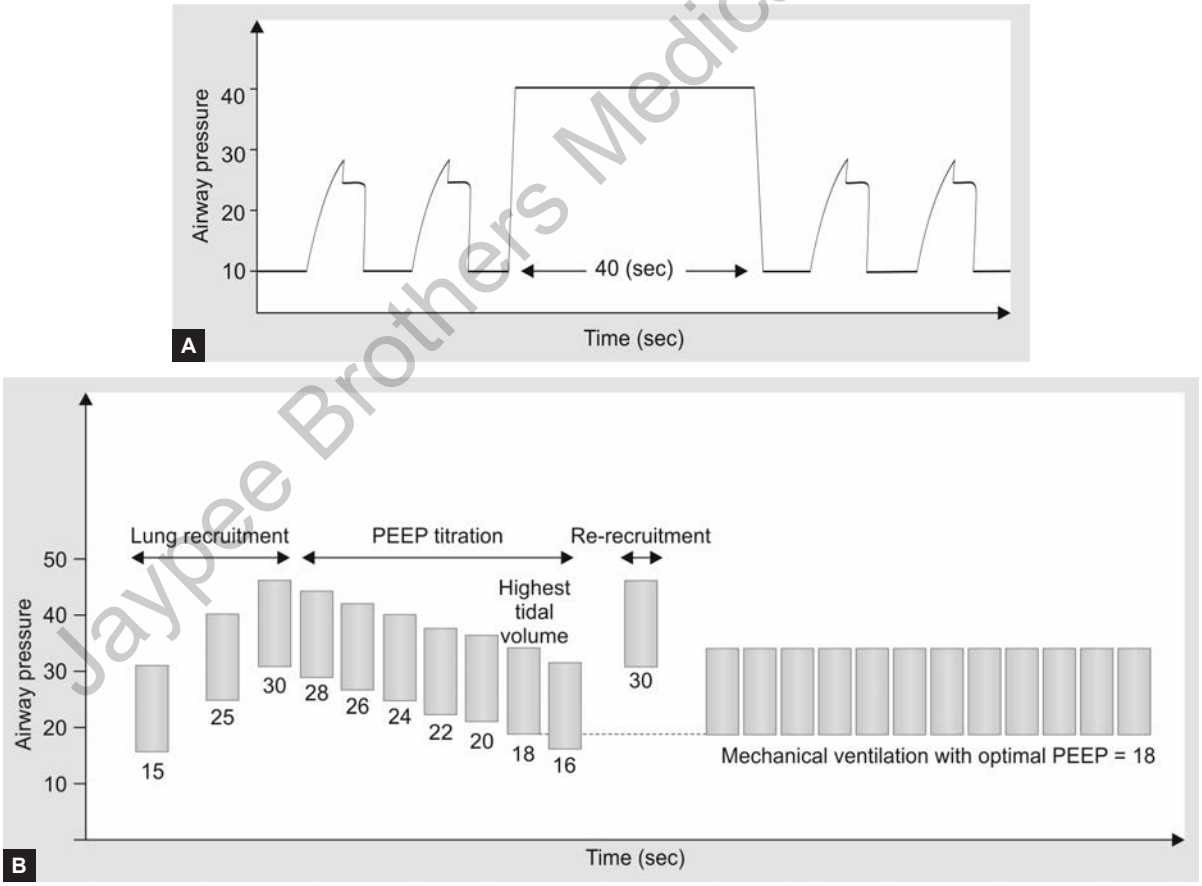
is kept high (e.g. 20–25 cm $H_2O$). PEEP is then gradually decreased in 2 cm decrement and the compliance is measured at each step, to get the best compliance.[91] Some have used arterial oxygenation or even dead space to identify the optimal PEEP while decreasing the PEEP.[92,93] After identifying the PEEP at which the best compliance or oxygenation is not maintained, the recruitment maneuver is applied again. After this second recruitment, PEEP is set 2 cm above the PEEP level identified with the best compliance. Marini[94] suggested that the stepwise approach is much better than the sustained inflation, as it is better tolerated from a hemodynamic point of view **(Figs. 4A and B)**. One alternative way for recruitment is to keep the patient in PCV with the inspiratory pressure fixed and gradually increasing the PEEP.

*Recruitment maneuver in prone position:*

Prone position helps facilitation of recruitment. Kacmarek showed that oxygenation was better with recruitment maneuver in prone position than in supine position, also lesser amount of PEEP was needed in prone position to maintain the same PF ratio.[95] Lim et al. also showed in canine lung injury models that prone position increased the effect of low PEEP recruitments, at the same time the hemodynamic impairment duet to high PEEP was decreased in prone position.[96] Similarly, Cakar et al. found that recruitment maneuvers with lower PEEP were more effective in prone position.[97]

*Prone-positioning:*

As in the case of application of PEEP, the indications and applications of prone ventilation has changed




**Figs. 4A and B:** Pressure-time curve with recruitment maneuvers: (A) Sustained inflation with CPAP of 40 cm $H_2O$ for 40 sec; (B) Stepwise recruitment using decremental peep keep driving pressure constant to obtain optimal peep.

over time. Prone positioning was first utilized in mid-1970s.[98] Proposed mechanisms by which prone-ventilation helps in improving oxygenation are as follows:[98,99]

- Recruitment and improved ventilation of the previously dependent dorsal lung via regional changes in chest wall mechanics and reduced lung compression by the heart and mediastinum
- Gravitationally distributed better perfusion toward the better ventilated previously ventral lung
- Better ventilation-perfusion matching with better clearance of $CO_2$
- More homogeneous ventilation and reduced chances of VILI.

*Indications for prone position:*

The beneficial effect of prone positioning is not only by the improvement in oxygenation, but also prevention of VILI with reduction in transpulmonary pressure and more homogenous distribution of stress and strain throughout the lungs.[99,100] Accordingly, it should be applied at the early stage as first line therapy.

Despite the physiological advantages with prone ventilation, earlier trials did not show any mortality benefit, though these trials were not done with the ideal body weight driven tidal volumes.[101,102] The Proning Severe ARDS Patients (PROSEVA) study group showed significant reduction in mortality with prone ventilation.[103] They had given prone position in patients with PF ratio <150, for 16 consecutive hr and ventilated with protective lung ventilation strategy. There was significant reduction in 28-day and 90-days mortality. After these trials, a meta-analysis of the combined data of these studies found that there was a significant benefit of prone ventilation patients ventilated with tidal volume more than 8 mL/kg of ideal body weight (IBW).[104]

*Timing and duration for prone ventilation:*

Prone ventilation should be started in hypoxemic ARDS as soon as possible.[105] In initial trials, proning sessions were of 7–8 hours which was later increased to >12 hour.[106,107] In the PROSEVA trial proning was given as 17 hours sessions and was used for 4 days on average. In PSII trial, it was further increased to 18 hours and 8 days.[107]

*Risk management/safety:*

Given the high rates of complications [e.g. dislocation of endotracheal tube (ETT), pressure sores, etc.] experts have concluded that prone-positioning should be limited to patients with severe hypoxemia and undertaken only in high expertise centers with experience in safe technique.[102,107]

*Contraindications:*

Absolute contraindication is an unstable spine fracture. Other relative contraindications are enumerated in the **Table 7**. Acute abdomen is not a contraindication for prone position ventilation.

*High frequency oscillatory ventilation (HFOV):*

High frequency oscillatory ventilation (HFOV) has also been used to improve oxygenation by increasing mean airway pressure to promote alveolar recruitment. At the same time, small tidal volumes avoids risk of overdistention. HFOV has been successfully used in neonates and pediatric patients, since 1983. Studies have shown higher survival rates for patients in premature infants with acute respiratory distress syndrome (ARDS). There was a resurgence of interest in HFOV for adults after low tidal volume strategy was shown to be effective. HFOV delivers tidal volumes of 1–3 mL/kg at very high rates, usually between 100–600/min. HFOV use has failed to demonstrate improvement in outcomes in adults.[108]

*Initial settings and management of a patient on HFOV **(Table 8)**:*

*Bias flow* is the continuous flow of gas responsible for replenishing oxygen and removing carbon dioxide ($CO_2$) from the patient circuit and it is started at 20 L/min. A large number of patients will need to be paralyzed at this flow rate. The need for neuromuscular block (NMB) may be eliminated by increasing the bias flow rate, but $CO_2$ retention is a potential concern. Bias flow is set between 25–40 L/min.

*Inspiratory time is* usually set at 33%.

*Mean airway pressure (mPaw)* is set at 25–34 cm $H_2O$ or at 3–5 cm above the patient's previous conventional ventilator mPaw.

**Table 7:** Contraindications to prone positioning.

| ***Absolute*** | ***Relative*** |
|---|---|
| • Unstable spinal fractures<br>• Unmonitored increased intracranial pressure | • Open abdominal wound<br>• Multiple trauma with unstable fractures<br>• Pregnancy<br>• Severe hemodynamic instability<br>• Severe facial trauma or facial surgery in last 15 days |

**Table 8:** Initial and ongoing assessment of the patient on HFOV[111]

| | |
|---|---|
| ABG | 30 min postinitiation<br>Frequency based on clinical status<br>Within an hour of any major change in setting |
| CXR | Within an hour post-initiation<br>Daily<br>Whenever lung hyperinflation or collapse is suspected |
| CWF | Check for degree of vibration noted and symmetry<br>*Changes in CWF:*<br>Increases with improvement in compliance<br>Decreases with worsening of compliance<br>Noted only on one side of chest, if tube gets migrated to one lung or in presence of unilateral pneumothorax |
| Auscultation | Breath sounds cannot be heard<br>Listen for changes in intensity of the piston sound |
| Heart and GI sounds | Stop piston temporarily,<br>Lung inflation and oxygenation will be maintained |
| Vital signs | HR, BP, MAP and urine output hourly |
| Perfusion | Monitor adequate perfusion status by monitoring capillary refill time, skin turgor and color, urine output changes, base excess |
| Secretions | Secretions are suspected, if there is:<br>Rapid rise in $PaCO_2$<br>Decrease in oxygenation<br>Decrease in CWF<br>Suctioning should be done, whenever needed to minimize de-recruitment |

(ABG: arterial blood gas; CWF: chest wiggle factor; CXR: chest X-ray; GI: gastrointestinal; $PaCO_2$: partial pressure of oxygen)

*Frequency (f):* Initial frequency should be based on the most recent arterial blood gas:

pH <7.10 = 4 Hz
pH 7.10–7.19 = 5 Hz
pH 7.20–7.35 = 6 Hz
pH >7.35 = 7 Hz

*$FiO_2$:* Initially set at 1.0, it is gradually reduced as per improvement in oxygenation.

Tidal volume (Vt) depends on the oscillatory pressure amplitude (ΔP) and frequency. Lowering the frequency allows more time for gas exchange leading to larger Vt.[109,110]

*Mechanisms of gas exchange in HFOV:*

During HFOV, the alveolar minute ventilation increases exponentially with tidal volume but unlike conventional ventilation, alveolar ventilation decreases with increase in frequency and vice versa. Increase in frequency decreases the delivered tidal volume by dampening the pressure delivery, thus decreasing alveolar ventilation giving rise to $CO_2$ retention. The mechanism of gas exchange at such a very low tidal volume involves several phenomena, which are as follows:[112-114]

- *Bulk flow:* Bulk flow or bulk convention is the most important mechanism in HFOV. It also helps in gas exchange in areas with low regional dead space volumes, such as in proximal gas exchange units. The importance of bulk flow has been shown in anesthetized canine models where $PaCO_2$ rose significantly once the volume delivered per oscillation was decreased to lower than the volume of rebreathing circuit. Even in clinical practice, the volume delivered per oscillation changes much more than expected, depending on the changes in applied frequency.[114,115]
- *Convective gas exchange:* The spatial distribution of inspiratory gas flow and expiratory gas flow are different in HFOV, as a result, convection in opposing currents happen in the same airway, giving rise to convective gas exchange which is more pronounced at the bifurcation of airways.[116]
- *Pendelluft* means 'swinging air'. It describes the movement of gas within the lung because of dynamic pressure gradients between lung units through differences in the timing of inflation and deflation. Regional differences in inertance and compliance of the peripheral airways and lung units—and hence differences in local respiratory time constants—result in differences in the timing of inflation and deflation at steady state during HFOV. Lung units that are inflating even as others are deflating may receive gas from the deflating lung units. This inter-regional airflow increases gas mixing and enhances gas exchange.[117]
- *Cardiac contractions* also enhance gas mixing and contribute to gas exchange during HFOV. The strong contractions of the heart act as a percussive force for gas mixing. Indeed, during apneic ventilation, cardiac oscillations may account for over 50% of oxygen uptake and nearly 40% of $CO_2$ clearance.[118]

*Evidence against the use of HFOV:*

The OSCILLATE trial, an international study from the Canadian Critical Care Trials Group, compared HFOV in early, moderate-to-severe ARDS ($PaO_2/FiO_2$ ratio ≤200 mm Hg) with conventional protective ventilation.[119] The study

was terminated early following interim analysis as they found that in-hospital mortality was higher in the HFOV group which was quite significant. Patients who received HFOV were more likely treated with neuromuscular blockade and vasopressors and received higher doses of sedatives compared with controls.

The OSCAR study was conducted simultaneously in the United Kingdom and involved a similar population of patients.[120] The investigators reported a higher 30-day mortality rate with HFOV compared to conventional group. There did not appear to be any differences between the groups in terms of vasopressor support or fluid administration. It is unclear why the HFOV trials failed. The relatively high mean airway pressures may have been associated with increased regional overdistension and VILI. Alternatively, increased intrathoracic pressures may have resulted in hypotension, right ventricular dysfunction, fluid overload, hypoperfusion, and multiple organ dysfunction syndrome (MODS).

In conclusion, on the basis of current evidence, HFOV should not be used as a primary mechanical ventilation mode in ARDS, and its use as rescue therapy should be reserved until after proven strategies have been exhausted.

*Extracorporeal membrane oxygenation:*
Extracorporeal membrane oxygenation (ECMO) removes blood from the body, oxygenates it, removes $CO_2$ and returns it back to the body. This comprises of a mechanical system and can be used to support failing lung or heart or both. In case of failing lung (as in ARDS) blood is withdrawn from a central vein into the extracorporeal circuit through a mechanical pump and then passed through an oxygenator where blood passes along one side of a membrane, which provides the interface for diffusion of gases. The oxygenated blood is (after proper warming or cooling) returned to another central vein. This is known as veno-venous ECMO (VV-ECMO). In patients with cardiac dysfunction or with cardiopulmonary dysfunction, blood is collected through a central vein and returned to a central artery and thus both oxygenation and support to systemic circulation is maintained. This is known as veno-arterial ECMO (VA-ECMO).[121]

*Indications and contraindications for ECMO in ARDS:*[122,123]
*Indications:*

- Severe hypoxemia (e.g. PF ratio <80, despite the application of high levels of PEEP [15–20 cm $H_2O$]) for at least 6 hour in patients with potentially reversible respiratory failure
- Uncompensated hypercapnia with acidemia (pH <7.15) despite the best possible ventilator settings
- Excessively high end-inspiratory plateau pressure (>35–45 cm $H_2O$)
- Very severe ARDS defined as any one of the three criteria PF ratio~50 mm Hg for >3 hours; a PF ratio <80 mm Hg for more than 6 hours; or an arterial blood pH of less than 7.25 with a partial pressure of arterial carbon dioxide of at least 60 mm Hg for >6 hours.

*Contraindications for ECMO in ARDS:*
*Absolute:*
Any condition that precludes the use of anticoagulation therapy.

*Relative:*

- High-pressure ventilation (end-inspiratory plateau pressure >30 cm $H_2O$) for >7 days
- High $FiO_2$ requirements (>0.8) for >7 days
- Limited vascular access
- Any condition or organ dysfunction that would limit the likelihood of overall benefit from ECMO, such as severe, irreversible brain injury or untreatable metastatic cancer.

*Evidence for utility of ECMO in ARDS:*
Older studies with technology of ECMO did not find significant difference in survival with extracorporeal $CO_2$ removal.[124,125] Peek et al. (CESAR trial) studied outcome of referral to ECMO center in patients with severe, potentially reversible respiratory failure as judged by Murray score >3·0 or pH <7·20. The ECMO patients had significantly better chance of survival without severe disability.[126] A recent study (EOLIA trial 2018) of early initiation of ECMO in severe ARDS (PF ratio <50 mm Hg for more than 3 hr; or <80 mm Hg for >6 hr; or an arterial blood pH <7.25) was designed to demonstrate an absolute mortality reduction of 20% and relative risk reduction of 33%. It was terminated prematurely after 75% recruitment. There was a statistically nonsignificant reduction in mortality (46% versus 35%).[127] This amounts to a clinically important 24% relative reduction in mortality, and could have been demonstrated in an adequately powered trial. Further, the results of this trial should not undermine role of ECMO as rescue therapy.[128]

*Airway pressure release ventilation in ARDS:*
*APRV (Airway pressure release ventilation):* This allows patients to breathe spontaneously while receiving high airway pressure with an intermittent pressure release.

The high pressure is used for alveolar recruitment. By promoting spontaneous breathing, it might improve alveolar recruitment to the dorsal caudal regions of the lungs.[129] Although arterial oxygenation might be better with airway pressure release ventilation, evidence is lacking to support improved outcomes.[130] Given that the transalveolar distending pressures are probably high during spontaneous breathing with airway pressure release ventilation, the potential for lung injury is of concern.[131]

APRV is a mode of ventilation, which is based on open lung approach and provides partial ventilatory support.[132] This mode provides both safety and comfort. Safety in terms of low chances of VILI and hemodynamic compromise while providing adequate ventilatory support without dangerously high pressures in the lung. Comfort in terms of unrestricted spontaneous breathing with greater patient-ventilator synchrony. Despite its theoretical advantages, it has not been used widely and is still thought to be a rescue mode for poor oxygenation in ARDS.[133] APRV had been historically viewed as CPAP at two alternate pressure levels, and accordingly the mandatory breath is known as 'P high" and the duration of mandatory breath is called "T high". In a similar manner, the expiratory pressure and time (release time) are known as "P low" and "T low", respectively.

In a small study of 24 patients with acute respiratory distress syndrome (ARDS), ventilation-perfusion (V A/Q) distribution was better with airway pressure release ventilation (APRV) with spontaneous breathing compared to pressure support ventilation (PSV).[134]

It is important to stress that APRV has not been subjected to large scale randomized controlled investigation and there are concerns allowing spontaneous breathing, in patients with $PaO_2/FiO_2$ <150. In the current scenario, APRV may have a role as rescue therapy (after prone positioning) or as a bridge to ECMO similar to HFOV.

*Pulmonary vasodilators:*

Inhaled vasodilators such as nitric oxide, prostacyclin, prostaglandin E1 selectively dilate the vessels which are present in the well-ventilated regions of lung. These drugs decrease pulmonary vascular resistance and pulmonary vascular pressure while improving the right ventricular function and result in improved oxygenation due to better ventilation-perfusion matching and reduction in shunting. These drugs act locally and have very short half-lives; hence they do not usually cause systemic hypotension.[135]

*Inhaled nitric oxide (iNO):* Causes modest and transient improvement in oxygenation, which did not translate into improvements in mortality, duration of mechanical ventilation or days without ventilation. Oxygenation did not improve in all the patients receiving iNO but there was increased risk of renal injury.[135,136] Though the factors deciding responsiveness to iNO are uncertain, in retrospective cohort studies, absence of sepsis or septic shock, baseline high pulmonary pressures and responsiveness to PEEP had been found to be predictive of responsiveness to iNO.[137] Thus, the uncertainty of response, lack of proven benefits and associated potential harms warrant against the routine use of iNO in ARDS.

*Prostacyclin:* The effects of inhaled prostacyclin are comparable to iNO. Prostacyclin also leads to transient increase in oxygenation and reduction in pulmonary pressures but without any decrease in morbidity and mortality.[138] The advantage of inhaled prostacyclin over iNO is that it does not need sophisticated devices for delivery. Preliminary studies of inhaled Iloprost, a prostacyclin analog, in patients with ARDS and pulmonary hypertension reported improved oxygenation without adverse effects on lung mechanics or systemic hemodynamics.[139]

*Stem cell therapy and keratinocyte growth factor:*

There has been recent interest in embryonic pluripotent stem cells, adult derived multipotent stem cells and progenitor cells in their potential for attenuating inflammation and accelerating tissue repair in ARDS. Enthusiasm first came from findings suggesting a favorable rate of engraftment and epithelial differentiation of infused bone marrow–derived stem cells in the injured lungs of mice, but recent works suggest these results are not as robust as expected.[140] In multiple animal experiments, mesenchymal stem cells derived from human bone marrow, helped in early recovery from ARDS, pneumonia and VILI.[141,142] Keratinocyte growth factor (KGF) may help promote healing in ARDS lung by accelerating type II pneumocyte proliferation, increased surfactant production and repair of oxidative damage. One group of investigators has shown the protective effect of Mesenchymal stem cells (MSC-derived from human bone marrow) on *ex vivo* perfused human lung preparation injured by *E. coli* endotoxin. Their explanation was that the healing was promoted by the release of KGF from the

MSCs.[143] However, a double-blind, phase 2 trial, KGF did not show improvement in oxygenation index and had three times higher mortality at 28 days.[144] Currently, KGF is not recommended for treatment of ARDS.

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