Review Artical

Management of acute respiratory distress syndrome

B. K. Bhattarai

Department of Anaesthesiology and Critical Care, B. P. Koirala Institute of Health Sciences (BPKIHS), Ghopa, Dharan-18, Sunsari, Nepal.

Correspondence to: Dr. Balkrishna Bhattarai, Associate Professor, Department of Anaesthesiology & Critical Care, BP Koirala Institute of Health Sciences (BPKIHS), Ghopa, Dharan-18, Sunsari, Nepal.

e-mail: bhattaraibk@yahoo.com

Background: Managing patients with acute respiratory distress syndrome (ARDS) still remains a challenge to the intensivists despite huge accumulation of basic and clinical data and better understanding in its management. The evolution of the concept of ventilator associated lung injury (VALI) in mechanically ventilated patients with ARDS has changed the approach to ventilatory management. Survival of the patients with ARDS may be improved by modifying the mechanical ventilation such that VALI is kept to a minimum. Protective strategy in mechanical ventilation with limited volume and pressure is the only accepted treatment or supportive measure shown to affect the outcome in ARDS patients. Low tidal volume ventilation has been recommended for every patient with ARDS to be used routinely. Protective ventilatory strategy has been accepted as a new gold standard and is being used to evaluate and compare other techniques and modalities. Use of approaches such as prone position ventilation, inhaled nitric oxide and surfactant has failed to improve survival in clinical studies. But these approaches may confer benefits if used in conjunction with the protective strategy.

Key words: Acute respiratory distress syndrome (ARDS); Protective ventilatory strategy; Ventilator associated lung injury (VALI)

Introduction

The reported prevalence of acute respiratory distress syndrome (ARDS) is high in the order of 5-10% of all ICU admissions.[1] It is associated with mortality as high as up to 74%.[2] Managing patients with ARDS still remains as an extreme challenge to the intesivists despite huge accumulation of basic and clinical data and better understanding in its management. Mechanical ventilation is indispensable in support of the patients with ARDS in respiratory failure. The approach to selecting tidal volume, positive end expiratory pressure (PEEP) and ventilatory modes are changing with reported improved pulmonary functions and survivals. There are further additions to the pharmacological therapies to offer improvement in the management of ARDS. Recently, the interest of the researchers has been focused on the study of damage to the lungs due to application of pressure, positive or negative, known as ventilator associated lung injury (VALI) or ventilator induced lung injury (VILI). By modifying mechanical ventilation such that VALI is kept to a minimum may improve survival of patients with ARDS.

In this article, attempt has been made to include definition of ARDS, brief pathophysiology of ARDS, VALI, ventilatory and clinical strategies, alternative and adjunctive modalities and therapies and the general approach to the management of ARDS patients.

Definition

The American-European Consensus Conference defined acute respiratory distress syndrome (ARDS) as "a condition or conditions resulting in impaired gas exchange with ratio of arterial partial pressure to fraction of inspired oxygen (PaO_2/FIO_2) less than 200, regardless of the level of the PEEP; bilateral lung infiltrates on the chest radiograph; and a pulmonary capillary wedge pressure PCWP less than 18mmHg or if not directly measured, the clinical absence of

elevated left atrial pressure". [3] This definition is comprehensive and covers ARDS patients in wide variety of setting. The criteria of diagnosing ARDS include: i) insult to the lung from epithelial (e.g. aspiration) or endothelial (e.g. sepsis) side, ii) bedside finding of tachypnoea, dyspnoea, crackles, iii) diminished lung compliance (<40ml/ cmH_2O), iv) impaired gas exchange (PaO_2/FIO_2 <200), v) diffuse (three or four quadrants) airspace filling on the chest radiograph and vi) exclusion of high-pressure pulmonary oedema (e.g. PCWP <18mmHg, echocardiographic examination).

Acute respiratory distress syndrome (ARDS) is a syndrome, not a disease and can have several causes fulfilling the above criteria. The syndrome may be the manifestation of several pathophysiologic pathways. The cause for ARDS due to acid aspiration could be direct chemical injury whereas ARDS associated with sepsis and pancreatitis is probably due to systemic inflammation. The details of the pathways remain poorly understood.

Diagnosing the existence of ARDS does not mean diagnosing patient's underlying problem. While the patient is being given the supportive management, diagnostic and therapeutic interventions must go side by side. Appropriate supportive therapy may transiently make the patient stable but if for example, the underlying source of sepsis in the abdomen is not recognized with appropriate tests (e.g. CT scan), the patient will definitely succumb.

Lung Injury Score (LIS), developed by Murray and colleagues[4] in 1988, based on chest x-ray, hypoxaemia (PaO_2/FIO_2) score, lung compliance and PEEP, is the most widely accepted scoring system although several systems have been developed to compare the severity of ARDS in various studies and settings.[5]

An exhaustive list can be prepared to enumerate the causes of ARDS, but by far the most common causes encountered in ICU are pneumonia and gastric acid aspiration through direct injury and sepsis and trauma through indirect injury.[6] The mortality in ARDS is more related to the causes of ARDS than to the lung injury itself.[7] ARDS associated with sepsis has higher mortality as compared to that associated with air embolism.[8]

Pathophysiology

Prevailing knowledge supports that acute lung injury (ALI) and ARDS are the spectrums of the same pathophysiologic processes[9] and will be used as synonyms in this article. It is well known that ARDS results from a pulmonary capillary leak that causes flooding of the lung interstitium and alveolar space with protein rich fluid despite normal pulmonary intravascular pressure, regardless of cause. Obviously this flooding diminishes the lung compliance, which can be evidenced by increased pressure in the monitor. This results in substantial fraction of mixed venous blood passing through the non-ventilated airspaces resulting into right to left intrapulmonary shunt that is relatively refractory to oxygen therapy.

The early phase of ARDS is characterized by the capillary leak or also called non-cardiogenic pulmonary oedema. Pathologically there is diffuse alveolar damage (DAD), [10] that leads to progressive lung inflammation and cellular injury. The early phase of DAD is also called exudative due to the predominance of pulmonary oedema and its consequences. This condition may resolve or progress to diffuse lung fibrosis.

The tracheal fluid at the onset of ARDS has high protein content (70-90% of serum level) in contrast to cardiogenic pulmonary oedema and can have diagnostic value early in the course of oedemagenesis but not later.[11]

The chest x-ray finding in ARDS is described as diffuse lung infiltrates. Marked inhomogeneity of alveolar flooding is evidenced in CT scan.[12] This suggests that the application of large tidal volumes and PEEP may result in over distension of relatively spared lung regions before recruitment of flooded alveoli thus demanding the newer protective strategy to be discussed later.

Hyaline membrane formation in the alveolar space becomes prominent over the days following acute lung injury due to precipitation of serum proteins. Increase in the number of inflammatory cells in the insterstitium and necrosis of the type I pneumocytes may occur. Abnormal collagen deposits may follow this by 7-10 days. This phase is also known as proliferative phase of ARDS. The ventilated patients show evidence of large dead space and requirement of large minute ventilation and pulmonary hypertension. There is overall restriction of the lung mechanics. The time course of recovery from profilerative phase may be relatively variable with some patients making a nearly complete recovery in a relatively brief period of time and other showing protracted lung derangements taking many months.[13]

Ventilator Strategies

Ventilator Associated Lung Injury (VALI) and Evolution of Protective Strategy

In 1985, Dreyfuss and co-workers[14] could reproduce the experiments, reported earlier by Webb and Tierney, [15] demonstrating that mechanical ventilation using large tidal volumes and high inflation pressures could cause a fatal lung injury in rats with otherwise normal lungs. They hypothesized that mechanical ventilation with large tidal

volume or high inflation pressure might exacerbate or perpetuate the lung injury in patients suffering from ARDS. This raised two important questions: Did the high inflation pressure or large tidal volume excursions cause the lung injury? Did PEEP attenuate or worsen the injury? Further investigations by Dreyfuss and colleagues[16] in animals (rats) showed that large tidal volumes were associated with lung injury, but the high inflation pressure in the absence of large tidal volume was not. They were surprised to observe that PEEP had the effect of limiting the injury that occurred in animals ventilated with large tidal volumes and high pressures. The results have been verified in larger animals also. Corbridge and co-workers[17] in a canine model of oleic acid injury showed that mechanical ventilation with large tidal volume and low PEEP was associated with a worsening of intrapulmonary shunt compared with ventilation with high PEEP and small tidal volumes. This was the first observation that the pattern of ventilation used had an effect on the evolution of acute lung injury.

Other studies[18] have also supported the idea that PEEP level that maintains lung inflation above a lower inflection point (LIP) on the static pressure-volume curve of the lung results in less lung injury than a PEEP and tidal volume setting that causes the lung to be deflated and inflated repeatedly across the LIP. This is attributed to the larger shear force due to opening and closing during the respiratory cycle. Maintaining tidal inflation above the LIP with PEEP set above the LIP has been termed the "open lung" approach and has been evaluated extensively. However, production of static pressure-volume curve for patients with ARDS is technically difficult, does not always provide clear inflection points, and is of unproven benefits.[19]

Many clinical studies[20, 21, 22, 23] have been conducted comparing the outcome of ventilation with small tidal volumes (5-7ml/kg), lower target pressure (peak and plateau- 35cmH_2O) also called protective strategy with that of ventilation with conventional strategy with higher tidal volume and target pressure (peak and plateau). Whether the conventional groups were ventilated in accordance with best practice in the trials is debatable since prescribed limits were exceeded. One of the studies (ARDS Network Study) with 861 patients showed benefit from the protective strategy.[23] This study perhaps more convincingly shows the negative effect of high tidal volumes and pressures on outcome. This study established the need to limit tidal volume and inflation pressure in ARDS patients. The death rates of patients ventilated with high and conventional (low) PEEP did not differ significantly and optimum PEEP in patients with ARDS could not be defined. We still cannot define the best pressure or the physiological criteria by which PEEP should be adjusted.[24]

Results of clinical studies[25, 26, 27] have suggested that mechanical stress is important in determining the outcome of the patients with ARDS. Mechanical ventilation continues to damage the injured lungs despite adopting strategy to maintain low tidal volume. The ventilator associated lung injury (VALI) can have many components[28] viz. a) volutrauma- damage caused by over distension, b) atelectotrauma- injury associated with repeated recruitment and collapse, theoretically prevented by using PEEP above LIP, c) biotrauma- pulmonary and systemic inflammation caused by the release of mediators from lungs subjected to injurious mechanical ventilation, d) oxygen toxic effects-damage caused by high concentration of inspired oxygen and e) barotraumas-high pressure induced lung damage.

When protective strategy termed 'open lung approach' is followed, PEEP is set 2cmH_2O above the LIP. If LIP cannot be determined then a PEEP of 16cmH_2O is used. The driving pressure, defined as plateau pressure minus PEEP is kept below 20cmH_2O, peak pressure restricted to 40cmH_2O and the respiratory rate kept below 30 breaths per minute. When the patient is disconnected from the ventilator, a recruitment manoeuvre (RM) with use of continuous positive airway pressure (CPAP) of 35cmH_2O is applied for 40 seconds before re-instituting the previous PEEP.[29] Recruitment manoeuvres are the processes of periodically briefly raising the transpulmonary pressure to higher level than are achieved during tidal ventilation. Clinical investigators have reported that the possible derecuitment due to reduction in tidal volume while using protective strategy can also be prevented and oxygenation improved by using recruitment manoeuvres.[29, 30] A recent clinical study[31] to evaluate the effects of RMs in patients with acute lung injury ventilated with high PEEP has shown that the duration of RM induced recruitment is brief. Greater and more sustained effects are likely with higher RM pressure and with improved RM techniques and effects of RM may be greater in patients in whom there is greater potential for recruitment. Role of RM has been described in children also.[32]

Permissive Hypercapnia

In a retrospective review, Hickling and colleagues[33] in 1990, reported their experience using low tidal volume pressure limited ventilation (peak inflation pressure not greater than 45cmH_2O, ideally less than 30cmH_2O) and permissive hypercapnia (tolerance of $PaCO_2$ elevation of 20-30 mmHg or even more and the associated acidosis, as long as the goal of the airway pressure is achieved). It was followed by a prospective descriptive study using the same ventilatory strategy and published the report in 1994.[34]They excluded the patients with contraindications to hypercapnia and observed that the use of permissive hypercapnia was

associated with far better survival than predicted by APACHE-II score. Similar reports have been published others[25] but the most compelling of all is by Amato and colleagues[18] who using the 'open lung' approach (VT <6ml/kg, PC-IRV mode, Ppeak <40cmH_2O, PEEP 2cmH_2O above the LIP) and permissive hypercapnia demonstrated more rapid recovery of pulmonary compliance, decreased requirements of high FIO_2, high rate of liberation from ventilator and decreased death associated with respiratory failure. But there are a number of controversial points to be considered in the study. Small sample size, sepsis not as causes of ARDS in both treatment and control arms (mostly leptospirosis and pneumonia), multiple differences between the two groups (PEEP strategy, CO2 levels, ventilatory modes, minute ventilation) are the issues of concern. In spite of these questions, this study must be considered an important investigation in the ventilatory management of patients with ARDS.

Permissive hypercapnia can be incorporated in the alternative approach to use of open lung PEEP also known as 'least PEEP strategy' for the management of patients with ARDS.[35] In this approach, the least PEEP required to maintain haemoglobin saturation of 90% on non-toxic FIO_2 (60-70%). There is less likelihood of alveolar overdistension at any given tidal volume. Since the PEEP is much below LIP, there is chance of lung damage by shear forces of recruitment and collapses.

There may be deleterious effects of permissive hypercapnia, although $PaCO_2$ as high as 250mmHg (pH as low as 6.72) has been reported to be well tolerated in volunteers.[36] Bronchial asthma patients also frequently have $PaCO_2$ higher than 100mmHg without showing significant systemic effects. But what happens in the patients with underlying metabolic acidosis by superimposing with respiratory acidosis is not known but can be anticipated to be significantly deleterious.

To avoid unwanted high level of $PaCO_2$, two simple methods have been advocated. The first one is to reduce circuit dead space, and one may prefer for this reason using a heated humidifier instead of a heat and moisture exchanger, which can add almost 100ml of dead space to ventilator circuit.[37]The other simple feature consists in increasing respiratory frequency above the conventional settings of 12-20/min. This may be achieved by a high respiratory peak flow and no end-inspiratory pause to optimize the inspiratory to expiratory time ratio as used in ARDS Network trial.[23]

Permissive hypercapnia should not be attempted in patients with definite contraindications to its use i.e. elevated intracranial pressure (e.g. cerebral oedema or severe head injury), seizures, pulmonary hypertension and cardiovascular deterioration associated with permissive hypercpnia.

Alternative and Adjunctive Protective Strategies

Prone Position Ventilation

Prone position oxygenation in ARDS patients is not a new but accepted modality.[38] It has been shown to have improved oxygenation but without survival benefit[39]. However, it remains as underutilized modality mainly due to difficulty of providing nursing and other care. Different hypotheses have been proposed[40] to explain the improvement in oxygenation including increased FRC (functional residual capacity), change in the regional diaphragm motion, better clearance of secretion, and redistribution of perfusion.[41,42, 43] Another possible reason for the improvement in oxygenation could be improved lymphatic drainage in prone position. Specially designed ICU beds may be used for ventilating the patient in prone position. Being effective and safe, prone position ventilation should be attempted in patients with severe ARDS more commonly.

Airway Pressure Release Ventilation (APRV)

APRV has been shown to provide higher mean airway pressure still allowing spontaneous breathing thereby providing better gas exchange and haemodynamics with less need of sedation.[44]

Inverse Ratio Ventilation (IRV)

When inspiration to expiration ratio (I: E) is made more than one in either volume cycled or pressure cycled ventilation, it is called inverse-ratio ventilation (IRV). IRV has been found to improve oxygenation in a small subset of patients refractory to conventional ventilation.[45, 46] But there is no way to prospectively identify the patients likely to respond to IRV. The mechanism believed to improve oxygenation in IRV is that it causes alveolar recruitment at lower airway pressure and more optimal distribution of ventilation[47] by recruiting alveoli with longer time constants.[48] Pressure controlled IRV has been employed in open lung strategy but the role of volume-controlled IRV remains poorly defined and used only as the last resort in hypoxia refractory to conventional modes of ventilation.

High Frequency Ventilation (HFV)

It can be considered logical that ventilation with very small tidal volume at higher frequencies should be associated with less VALI and better outcome if excessive lung excursion is associated with damage of the injured lung in ARDS patients. The tidal volumes and ventilatory rates can be variable in high frequency ventilation. Gas exchange is

poorly understood in high frequency ventilation but it is believed that it occurs through augmented axial diffusion and through bulk flow.[49,50] Unfortunately, multiple trials of HFV have failed to demonstrate benefit over mechanical ventilation.[51, 52,53,54]

Extra corporeal Membrane Oxygenation (ECMO)/ Intravenous Oxygenation (IVOX)

Theoretically, oxygenation by ECMO and allowing the lung to rest can be attractive strategy for patients with lung injury. This, however, is not supported by recent outcome study.[55] Use of intravenous oxygenation (IVOX) has been reported in ARDS patients.[56] In this technique, small membrane lung is actually inserted into the vena cava. This, however, is capable of only limited gas exchange and hence of limited usefulness. ECMO/ IVOX remain only as last resorts in hypoxia refractory to conventional ventilation.

Liquid Ventilation

Breathing through liquid medium can be expected to be advantageous when the surface tension at the air-liquid interface of lungs is increased, as it occurs in acute lung injury. When special liquid medium (capable of dissolving large amount of respiratory gases) is used for ventilating the lungs it can offset the collapsing force, decrease the alveolar surface tension with exogenous surfactant and eliminate air-liquid interface by filling the lung with a fluid. The only group of liquids that has the capacity to dissolve respiratory gases and is devoid of significant toxic effects is per fluorocarbons (PFC). PFC passively dissolves oxygen and other respiratory gases. Oxygen solubility is inversely proportional to the number of fluorine atoms present.[57]The first use of liquid ventilation with PFC in human was in babies and was described by Greenspan and colleagues[58] in 1989. Hirschl and co-workers[59] first reported partial liquid ventilation (PLV) in a mixed group of adult, paediatric and neonatal patients in uncontrolled single centre study and concluded that it can be safely used in patients with severe respiratory failure and may improve lung function. Potential benefits of PLV described are improvement in oxygenation, producing liquid PEEP, improvement in lung mechanics and reduction in inflammation. The described problems encountered include pneumothorax, ET tube blocking and uncertain long-term effect.[60]

Although liquid ventilation has been shown to be safe in patients with acute lung injury, there has been no improvement in survival or decrease in ventilator requirement. No evidence was found from randomized controlled trials to support partial liquid ventilation in children in a recent review.[61] We do not know, if some subset of patients with ARDS responds to partial liquid ventilation. Researches are on the way to evaluate other possible uses of liquid ventilation such as pulmonary drug delivery.

Pharmacotherapy

Better understanding of the pathophysiology of ARDS has contributed to development and use of various pharmaco-therapeutic adjuncts in ARDS patients. Pharmaco-therapeutic adjuncts are used not only for improving oxygenation but also to limit the acute lung injury.

Inhaled Nitric Oxide (NO)

Nitric oxide has been extensively studied, as a therapy for ARDS after Roissant and co-workers[62] published their initial work using inhaled NO. NO is the final common mediator of vascular smooth muscle relaxation previously known as endothelial derived relaxing factor (EDRF). The activity of NO seems to be terminated in vivo by binding to haemoglobin resulting into the formation of methaemoglobin, which is regarded as the most important risk, associated with its use.

The beneficial effects in the lungs of ARDS patients is produced by selective vasodilatation of pulmonary capillaries and arterioles adjacent to the ventilated alveoli and thus diverting blood to those alveoli which are away from areas of shunt. Initially the pulmonary vascular resistance decreases which is accompanied by decrease in the pulmonary artery pressure at a concentration of approximately 0.1ppm in patients with ARDS whereas improvement in oxygenation occurs at a concentration of 1 to 10ppm.[63] Systemic haemodynamic effects do not occur due to rapid inactivation of inhaled nitric oxide by binding to haemoglobin in the blood. This requires it to be given by continuous gas delivery through ventilator circuits.

Some patients with ARDS do not respond to inhaled NO and investigators have speculated increased pulmonary phosphodiesterase type-5 to be partially responsible for its decreased responsiveness and sildenafil is likely to improve the responsiveness.[64] Inhaled NO completely reverses the effects of permissive hypercapnia.[65] It has been demonstrated that NO decreases H_2O_2 production and release of IL-6 and IL-8 in neutrophils after 4 days of therapy in ARDS patients.[66] NO may also inhibit platelet function at concentrations commonly administered.

Although abundance of literature describing the beneficial physiologic effects of inhaled NO exists, no mortality benefits were shown in a study with 385 ALI/ARDS patients.[67] Nonetheless, it is a safe therapy with appropriate monitoring in patients with severe hypoxaemia despite usual measures. Interruption of continuous delivery of NO can

precipitate life threatening hypoxaemia and right heart failure.[68]

Prostaglandins

It was thought that prostaglandins might be of some benefit in ARDS patients, since prostaglandin E_1 (PGE_1) is known to dilate pulmonary artery. But PGE_1 is reported to decrease in pulmonary artery pressure and increase in shunt[69] and outcome studies failed to demonstrate improvements.[70] But some researchers believe that PGE_1 may improve oxygen delivery.[71] Prostaglandin is associated with hypotension, diarrhoea and fever. Newer mode of delivery by aerosolizing the PGE_1 has raised renewed interests of its use again.[72] It is associated with enhanced efficacy and diminished side effects.

Surfactants

Clinical investigators of adult ARDS have been interested by the result of surfactant therapy in infants with the respiratory distress syndrome (RDS) of prematurity. In RDS of prematurity, surfatant therapy is associated with improved gas exchange, improved lung mechanics, decreased requirements for continuous positive airway pressure (CPAP), and less barotraumas.[73] But prospective study of surfactants in adult ARDS patients showed no benefits with surfactant therapy.[74] Exogenous surfactant can still be considered experimental in ARDS patients.

Corticosteroids

Corticosteroids by virtue of their ability to attenuate cell mediated immunity and decrease cytokine release and activation, appear to be ideal agents to interrupt the detrimental cascade of immunologic events that accompany sepsis and ARDS. Corticosteroids have been shown to significantly improve outcome in animals treated with endotoxin[75] but, unfortunately, failed to demonstrate benefits in human studies.[76] This discrepancy may be due to the fact that animals that obtained a beneficial response was a consequence of earlier treatment with steroids in course of disease than it is possible with human patients. Steroid therapy has not only failed to demonstrate a benefit in outcome but also in gas exchange or lung mechanics. The only condition, which fulfills the criteria of ARDS and responds to steroid therapy, is acute eosinophilic pneumonia.[77] Any patient showing high eosinophils count in broncho-alveolar lavage (BAL) should be treated with high doses of steroids. Although it has been anecdotally claimed that high dose steroid therapy may be of some benefit in the proliferative phase of ARDS, it is difficult to discern their role during proliferative phase of ARDS in the absence of well-controlled, randomized trials in debilitated, infection-prone ARDS patients. Recently, use of low dose steroids in acutely ill patients with sepsis has shown a reduction in mortality.[78]

Activated Protein C

Recently, clinical evaluations have shown those drugs specifically targeting the inflammatory markers are effective. Recombinant human activated protein C, an anticoagulant, is the first anti-inflammatory agent that has been found to be in sepsis[79] and hence can be expected to be useful in ARDS associated with sepsis.

Activated protein C inactivates factor Va and VIIIa, thereby preventing the generation of thrombin which in turn decreases inflammation by inhibiting platelet activation, neutrophil recruitment and mast cell degranulation. The direct anti-inflammatory properties include blocking the production of cytokines by monocytes and blocking cell adhesion. Before starting therapy with activated protein C there must be a) proven or suspected infection, b) evidence of systemic response to infection, and c) evidence (criteria) for acute organ dysfunction in clinical practice. Activated protein C is associated with the risk of increased incidence of serious bleeding (intracranial bleeding or requirement of 3 or more than 3 units of blood) as compared to placebo. Activated protein C must be used with caution in patients with international normalized ratio (INR) of more than 3 or a platelet count less than 30,000/cmm. Currently, use of activated protein C is restricted to the more seriously patients who are at eminent risk of death. Activated protein C should be used as an adjunct to supportive therapy when standard care has failed to show improvement and that there are no contraindications.

General Approach of Management[35, 80]

After identifying a patient suffering from ARDS, 100% oxygen should be administered through a high flow mask until trachea can be intubated and mechanical ventilation started. Oxygen supplementation acts as both diagnostic and therapeutic manoeuvre. Hypoventilated patients show dramatic improvement in oxygenation, patients with substantial V/Q mismatching show moderate response, and patients with significant shunt (ARDS patients) show only minimal response.

Non-invasive ventilation is rarely appropriate as the course of ARDS is usually longer than the time that intensivists want to use non-invasive ventilation. The ventilatory mode may depend on the availability of the ventilator and the experience of the intensivists.

Every effort should be made to minimize oxygen consumption by controlling fever and use of sedation and muscle relaxants. To keep the mixed venous oxygen saturation higher, the haemoglobin should be kept at a

minimum of 12gm/dl. Attempts must be made to maintain optimal cardiac output but keeping in mind that excess volume loading can worsen the respiratory condition.

Endotracheal suctioning should be performed without disconnecting the endotracheal tube from the circuit through a sample valve of the connector. Systemic detection of airway colonization of bacteria should be done at least once weekly using broncho-alveolar lavage, since there is high incidence of nosocomial pneumonia and difficulty in diagnosing ventilator-associated pneumonia (VAP) in these patients.[81] Weaning of high pressures, FIO_2 and sedation might be started early on and should be tested repeatedly on daily basis.[82]

Conclusion

Basic science investigations and clinical studies have brought significant change in the understanding and practice of managing the patients of ARDS in the recent years. The evolution of the concept of VALI in mechanically ventilated patients with ALI or ARDS has changed the approach to ventilatory management. Protective strategy in mechanical ventilation is the only accepted treatment or supportive measure that has been shown to affect the outcome in the patients with ARDS. It is recommended to use low tidal volume ventilation routinely for patients with injured lungs with few exceptions to conditions exacerbated by hypercapnia (e.g. raised ICP). Protective ventilatory strategy (volume and pressure limited) has been accepted as a new gold standard against which newer supportive modalities including partial liquid ventilation, high frequency ventilation, ECMO etc should be tested. Other approaches intended to improve gas exchange in the injured lung that have failed to improve survival in clinical studies, including prone positioning, inhaled NO, surfactants etc could confer benefit if used in conjunction with this protective ventilatory strategy. Based on the present knowledge, it can be concluded that limiting the tidal volume and airway pressure can give the best chances of survival to the ARDS patients.

References

1. Roupie E, Lepage E, Wysocki M et al. Prevalence, etiologies, and outcome of the acute respiratory distress syndrome among hypoxaemic ventilated patients. Intensive Care Med 1999; **25:** 884-86.
2. Fan E, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. JAMA 2005; **294:** 2889-2896.
3. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference of ARDS: Definitions, mechanisms, relevant outcomes, and clinical trial co-ordinations. Am J Respir Crit Care Med 1994; **149:** 818-824.
4. Murray JF, Matthay MM, Luce J, et al. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis 1988; **138:** 720
5. Moss M, Goodman PL, Heinig M, et al. Establishing the relative accuracy of three new definitions of adult respiratory distress syndrome. Crit Care Med 1995; **23:** 1629-1637.
6. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000; **342:** 1334
7. Doyle RL, Szaflarski N, Modin GW, et al. Identification of patients with acute lung injury: predictors of mortality. Am J Respir Crit Care Med 1995; **152:** 1818- 1824.
8. Kollef MH, Schuster DP. The acute respiratory distress syndrome. N Engl J Med 1995; **332:** 27
9. Shapiro BA, Perruzi WT. Changing practice in ventilator management: A review of literature and suggested clinical correlations. Surgery 1995; **117:** 121
10. Maitra A, Kumar V. The lung and the upper respiratory tract. In: Kumar V, Cotran RS, Robbins SL (Eds). Robbins Basic Pathology (7th ed). Philadelphia, Saunders (An Imprint of Elsevier),2003: 467
11. Matthay MA, Weiner-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar oedema in humans. Am Rev Respir Dis 1990; **142:** 1250-1257
12. Gattinoni L, Bombino M. Relationship between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. Anesthesiology 1988; **69:** 824-832
13. Elliot CG. Pulmonary sequelae in survivors of the adult respiratory distress syndrome. Clin Chest Med 1990; **11:** 789-800
14. Dreyfuss D, Basset G, Soler R, et al. Intermittent positive pressure hyperventilation with high inflation pressure produces pulmonary microvascular injury in rats. Am Rev Respir Dis 1985; **132:** 880-884
15. Webb HH, Tierney DF. Experimental pulmonary oedema due to intermittent positive pressure ventilation with high inflation pressure: Protection by positive end expiratory pressure. Am Rev Respir Dis 1974; **110:** 556-565

16. Dreyfuss D, Soler P, Basset G et al. High inflation pressure pulmonary oedema. Am Rev Respir Dis1988; **137:** 1159-1164

17. Corbridge TC, Wood LDH, Crawford GP et al. Adverse effects of large tidal volumes and low PEEP in canine acid aspiration. Am Rev Respir Dis 1990; **142:** 311-315

18. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the 'open lung approach' with low distending pressure in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. Am J Respir Crit Care Med1995; **152:** 1835-1846

19. Ward NS, Lin DY, Nelson DL, et al. Successful determination of lower inflection point and maximal compliance in a population of patients with acute respiratory distress syndrome. Crit Care Med 2002; **30:** 963-968

20. Stewart TE, Meade MO, Cook DJ, et al, for the pressure- and volume-limited ventilation strategy group. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. N Engl J Med1998; **338:** 355-361

21. Brower RG, Shanholtz CB, Fessler HE, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. Crit Care Med 1999; **27:**1492-1498

22. Brochard L, Roudot-Thoraval F, Roupie E et al, for the Multicenter Trial Group on Tidal Volume Reduction in ARDS. Tidal volume reduction for prevention of ventilator induced lung injury in acute respiratory distress syndrome. Am J Respir Crit Care Med 1998; **158:** 1831-1838

23. Network ARDS. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome: the acute respiratory distress syndrome network. N Engl J Med 2000; **342:** 1301-1308

24. Dries DJ, Marini JJ. Optimized positive end expiratory pressure-an elusive target. Crit Care Med 2002; **30:** 1159-1160

25. Roupie E, Dambrosio M, Servillo G, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. Am J Respir Crit Care Med 1995; **152:** 121-128

26. Weg JG, Anzueto A, Balk RA, et al. The relation of pneumothorax and other air leaks to mortality in the acute respiratory distress syndrome. N Engl J Med 1998; **338:** 341-346

27. Eisner MD, Thompson BD, Schoenfeld D, Anzueto A, Matthay MA. Airway pressure and early barotraumas in patients with acute lung injury and acute respiratory distress syndrome.Am J Respir Crit Care Med 2002; **165:** 978-982

28. Pinhu L, Whitehead T, Evans T, Griffith M. Ventilator associated lung injury. Lancet 2003; **361:** 332-340

29. Amato MBP, Barbas CSV, Medeiros DM, et al. Effects of protective ventilator strategy on mortality in acute respiratory distress syndrome. N Engl J Med 1998; **338:** 347-354

30. Foti G, Cereda M, Sparacino ME, et al. Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome patients. Intensive Care Med 2000; **26:** 501-507

31. The ARDS Clinical Trial Network, national Heart, Lung, and Blood Institute, National Institute of Health. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end expiratory pressure. Crit Care Med 2003; **31:** 2592-2597.

32. Desai AR, Deep A. Ventilatory strategy and adjunctive therapy in ARDS. Indian J Pediatr. 2006; **73:** 661-668.

33. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe acute respiratory distress syndrome. Intensive Care Med 1990; **16:** 372-377

34. Hickling KG, Walsh J, Henderson S, et al. Low mortality rate in adult respiratory distress syndrome using low volume, pressure limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 1994; **22:** 1568-1578

35. O'Connor MF, hall JB. ARDS: Current treatment and ventilator strategy. Anesthesiol Clin North Am 1998; **16:** 155-180

36. Frumin MJ, Epstein RM, Cohen G. Apnoeic oxygenation in man Anesthesiology 1959; **20:** 789-798

37. Pelosi P, Solca M, Ravagnan I, Tubiolo D, Ferrario L, Gattinoni L. Effect of heat and moisture exchanger minute ventilation, ventilatory drive, and work of breathing during pressure support ventilation in acute

respiratory failure.Crit Care Med 1996; **24:** 1184-1188

38. Douglas W, Rehder K, Beynen RM, et al. Improved oxygenation in patients with acute respiratory failure: the prone position. Am Rev Respir Dis 1977; **115:** 559-566.
39. Guerin C, Gaillard S, Lemasson S, et al. Effects of systematic prone positioning in hypoxaemic acute respiratory failure: a randomized controlled trial. JAMA 2004; **292:** 2379-2387.
40. Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. Am J Respir Crit Care Med 1994; **150:** 184- 193
41. Langer M, Masheroni D, Marcolin R, et al. The prone position in ARDS patients: a clinical study. Chest 1988; **94:** 103-107
42. Pappert D, Roissant R, Slama K, et al. Influence of positioning on ventilation-perfusion relationship in severe adult respiratory distress syndrome. Chest 1994; **106:** 1511-1516
43. Pelosi P, Croci M, Calappi E, et al. The prone positioning during general anaesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. Anesth Analg 1995; **80:** 955-960.
44. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. Crit Care Med. 2005; **33:** 5228-5240.
45. Tharratt RS, Allan RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe respiratory failure. Chest 1988; **94:** 755-762
46. Cole AGH, Wellse SF, Sykes MK. Inverse-ratio ventilation compared with PEEP in adult respiratory failure. Intensive Care Med 1984; **10:** 227-232
47. Manthous CA, Schmidt GA. IRV in ARDS: Improved outcome without auto PEEP. Chest 1993; **103:** 953- 954.
48. Gore DC. Hemodynamic and ventilatory effects associated with increasing inverse inspiratory-expiratory ventilation. Journal of Trauma-Injury Infection & Critical Care 1998; **45:** 268-272.
49. Fredberg JJ. Augmented diffusion in the airways can support pulmonary gas exchange. J Appl Physiol 1980; **49:** 232-238
50. Klocke RA, Saltzman AR, Grant BJB, et al. Role of molecular diffusion in conventional and high frequency ventilation. Am Rev Respir Dis1990; **142:** 802-806
51. Borg UR, Stoklosa JC, Siegel JH, et al. Prospective evaluation of combined high frequency ventilation in post-traumatic patients with adult respiratory distress syndrome refractory to optimized conventional ventilatory management. Crit Care Med 1989; **17:** 1129-1141
52. Holzapfel L, Rober D, Perrin F, et al. Comparison of high frequency jet ventilation to conventional ventilation in adults with respiratory distress syndrome. Intensive Care Med 1987; **13:** 100-105
53. McIntyre NR, Follet JV, Dietz JL, et al. Jet ventilation at 100 breaths per minute in adult respiratory failure. Am Rev Respir Dis 1986; **134:** 897- 901.
54. Bollen CW, van Well GT, Sherry t, et al. High frequency oscillatory ventilation compared with conventional mechanical ventilation in adult respiratory distress syndrome: a randomized controlled trial. Crit Care 2005; **9:** R430-R439.
55. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure controlled inverse ratio ventilation and extracorporeal CO2 removal for adult respiratory distress syndrome. Am J Respir Crit Care Med 1994; **149:** 295-305
56. High KM, Snider MT, Richard R, et al. Clinical trial of an intravenous oxygenator in patients with adult respiratory distress syndrome. Anesthesiology 1992; **77:** 856-863
57. Lowe KC. Per-fluorinated blood substitutes and artificial oxygen carriers. Blood Rev 1999; **13:** 171-184
58. Grenspan JS, Wolfson MR, Rubenstein DS, Shaffer TH. Liquid ventilation of pre-term neonates. J Pediatr 1990; **117:** 106-111
59. Hirschl RB, Pranikoff T, Ganger P, Schreiner RJ, Dechert R, Bartlett RB. Liquid ventilation in adult, children, and full term neonates. Lancet 1995; **346:** 1201-1202
60. Kaisers U, Kelly KP, Busch T. Liquid ventilation. Br J Anaesth 2003; **91:**143-151.
61. Davies MW, Sargent PH. Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome. The Cochrane Database of Systematic Reviews 2004, issue 4.
62. Roissant R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory syndrome. N Engl J Med1993;

328: 399-405

63. Lowson SM, Rich GF, McArdle PA, et al. The response to varying concentration of inhaled nitric oxide in patients with acute respiratory distress syndrome. Anesth Analg 1996; **82:** 574-581
64. Molony ED, Evans TW. Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome. Eur Respir J 2003; **21:** 720-727.
65. Puybasset L, Stewart T, Rouby J, et al. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. Anesthesiology 1994; **80:** 1254-1267
66. Chollet-Martin S, Gatecel C, Kermarrec N, et al. Alveolar neutrophils function and cytokine levels in patients with the adult respiratory distress syndrome during nitric oxide inhalation. Am J Respir Crit Care Med 1996; **153:** 985-990.
67. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. JAMA 2004; **291:** 1603-1609.
68. Lavoie A, hall JB, Olson DM, et al. Life threatening effects of discontinuing inhaled nitric oxide in severe respiratory failure. Am J Respir Crit Care Med 1996; **153:** 1985-1987
69. Radermacher P, Santak B, Becker H, et al. Prostaglandin E1 and nitroglycerin reduce pulmonary capillary pressure but worsen ventilation- perfusion distributions in patients with adult respiratory distress syndrome. Anesthesiology 1989; **70:** 601-606
70. Bone RC, Slotman G, Maunder R, et al. Randomized Double-blind, multicenter study of prostaglandinE1 in patients with adult respiratory distress syndrome. Chest1989; **96:** 114-119
71. Silverman HJ, Slotman G, Bone RC, et al Effects of prostaglandin E1 on oxygen delivery and consumption in patients with the adult respiratory distress syndrome. Chest 1990; **98:** 405-410
72. Walmrath D, Schneider T, Schermuly R, et al. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. Am J Repir Crit Care Med 1996; **153:** 991-996
73. Horbar JD, Soll RF, Sutherland JM, et al. A multicenter, randomized, placebo-controlled trial of surfactant therapy for respiratory distress syndrome. N Engl J Med 1989; **320:** 959-965
74. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactants in adults with sepsis induced acute respiratory distress syndrome. N Engl J Med 1996; **334:** 1417-1421
75. White GI, Archer LJ, Beller BK, et al. Increased survival with methyl prednisolone treatment in canine endotoxin shock. J Surg Res 1978; **25:** 357-364
76. Luce JM, Montgomery B, Marks JD, et al. Ineffectiveness of high dose methyl-prednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. Am Rev Respir Dis 1988; **138:** 62-68
77. Allen JN, Pacht ER, Gadek JE, et al. Acute eosinophilic pneumonia as a reversible cause of non-infectious respiratory failure. N Engl J Med 1989; **321:** 569-574
78. Annane D, Briegel J, Sprung CL, et al. Corticosteroid insufficiency in acutely ill patients. N Engl J Med 2003; **348:** 2157-2159
79. Bernard GR, Vincent JL, Laterre PF, et al. Efficiency and safety of recombinant human activated protein C in severe sepsis. N Engl J Med 2001; **344:** 649-
80. Brochard L. Management of mechanically ventilated patients with ARDS. In: Proceeding Book, International Critical Care Congress-2002; 2002: 1-15.
81. Delclaux C, Roupie E, Blot F, Brochard L, Lemaire F, Brum-Buisson C. Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome. Am J Respir Crit Care Med 1997; **156:** 1092-1098.
82. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusion in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; **342:** 1471-1477.