Pulmonary: Respiratory Failure, ARDS and Mechanical Ventilation

Pauline K. Park MD, FACS, FCCM
Lena M. Napolitano MD, FACS,FCCM
University of Michigan, Ann Arbor, MI

I. INTRODUCTION. Acute respiratory failure (ARF) is respiratory system failure or dysfunction resulting in abnormalities of gas exchange, including oxygenation and/or carbon dioxide elimination. Common etiologies in trauma and acute care surgery patients include pulmonary contusions, pneumonia, atelectasis, aspiration, pulmonary edema, acute respiratory distress syndrome (ARDS) [1] and pulmonary embolus (**Table 1**). Mechanical ventilation and noninvasive ventilation are the primary therapies for treatment of ARF.

II. CLASSIFICATION and EPIDEMIOLOGY. ARF is classified as either hypoxemic or hypercapneic. Severe hypoxemic ARF should raise concern for possible ALI or ARDS.

A. Hypoxemic respiratory failure (Type I), defined as arterial partial pressure of oxygen (PaO_2) < 60 mm Hg on room air, is the most common form of respiratory failure, and hypoxemia is a major immediate threat to organ function.

B. Hypercapneic respiratory failure (Type II), defined as arterial partial pressure of carbon dioxide ($PaCO_2$) of > 50 mm Hg on room air.

C. ARDS (Definitions in **Table 2**) is a syndrome of acute hypoxemic respiratory failure that arises from ***direct*** (pulmonary) or ***indirect*** (extrapulmonary) insults (**Table 3**) that induce pulmonary inflammation, damage the cells of the alveolar-capillary membrane, and lead to severe acute respiratory failure. [2] The recently proposed Berlin Definition [3] removes the previous category of acute lung injury (ALI) and classifies ARDS into mild, moderate and severe stages., Objective evidence of volume status is required when a clear ARDS risk factor is not present. Compared with the AECC definition, the Berlin Definition had better predictive validity for mortality and higher disease severity correlated with increased mortality, decreased ventilator-free days, and increased lung weight by CT scan.

1. A prospective population-based study showed a crude incidence of ALI of 78.9 per **100,000 person-years**, which extrapolates to a national annual incidence of 190,600 cases with an estimated 74,000 deaths from ALI annually in the United States, and associated **with** an in-hospital mortality rate of 38.5%, with the mortality rate increasing with age. [4] A single-center 5 year observational study reported that the rate of ARDS in trauma has decreased significantly, with a > 50% reduction in the incidence of ARDS after injury, despite similar patient demographics and injury severities with use of prudent ventilator strategies.[5]

2. ARDS is associated with pathologic changes in the lung with diffuse alveolar damage (DAD) that includes alveolar flooding, characteristic hyaline membranes, resulting in the loss of the gas exchange and barrier functions of the lung as a result of injury to the endothelial and epithelial layers of the alveolar-capillary membrane (**Figure 1**). Parenchymal injury is not a truly "diffuse" process and has significant regionalization of the inflammation, injury, and subsequent mechanical abnormalities. This heterogeneity can have significant impact on a mechanical ventilation strategy since

there is preferential delivery of ventilatory breaths to pulmonary regions with higher compliance and lower resistance (i.e., the more normal regions) rather than to diseased parenchyma resulting in potential regional overdistention. ARDS stages include ***exudative***, ***proliferative***, and ***fibrotic*** phases.[6]

III. TREATMENT – Noninvasive Ventilation (NIV)

A. NIV provides positive pressure ventilator support without the need for an invasive airway. NIV should be considered first-line therapy in ARF due to chronic obstructive pulmonary disease (COPD) exacerbation, since it is associated with decreased mortality, decreased need for intubation, decreased complications and reduced length of hospital stay. [7] Similarly, NIV is an effective and safe treatment of adult patients with ARF due to acute cardiogenic pulmonary edema; a systematic review of 21 studies documented NIV was associated with reduced hospital mortality and endotracheal intubation and reduced ICU length of stay. [8]

B. NIV as a weaning strategy for intubated patients with ARF uses early extubation with immediate application of NIV. A recent systematic review of 12 trials documented that NIV significantly decreased mortality, ventilator-associated pneumonia, ICU and hospital length of stay, and total duration of mechanical ventilation. [9]

C. The role of NIV for treatment of ARF due to severe exacerbations of asthma is less clear, and should be used with caution, and careful monitoring for need for intubation. [10]

D. NIV can also be used to treat ARF from other conditions such as severe pneumonia, obesity hypoventilation and to improve respiratory outcome in post-surgical patients. [11]

IV. TREATMENT – Intubation

A. Endotracheal intubation is required, and the orotracheal route is recommended with direct laryngoscopy or the glidescope vs. awake fiberoptic intubation for patients with potential difficult airway. Short-acting sedative/hypnotics with neuromuscular blockade are required in awake patients. Caution should be used with propofol (which can cause significant hypotension) and etomidate (which is associated with adrenal insufficiency), particularly in elderly patients and patients with hypotension or hemodynamic instability.

B. Chest radiograph should be obtained to confirm position, and generally the endotracheal tube should be inserted to 23 cm in men and 21cm in women (measured at the incisor). with the aim of positioning the end of the endotracheal tube 2 to 5 cm above the carina. Cuff pressures should be monitored, and closed-circuit suction catheters used.

C. Sedation is required for endotracheal tube and MV tolerance, and intravenous infusions of short-acting narcotics and sedatives are used most commonly. A sedation scale and daily sedation holidays should be used to reduce sedation to the least amount required. We transition to enteral narcotics and sedatives as soon as gastrointestinal tract function is confirmed. Emerging data document that benzodiazepines are associated with increased delirium, and caution should be used with these agents, particularly in the elderly and in those critically ill patients with organ dysfunction or failure.

V. TREATMENT: VAP Prevention

A. All efforts to prevent ventilator-associated pneumonia (VAP) should be implemented immediately after intubation and initiation of mechanical ventilation. [12] The key components of the Ventilator Bundle for VAP prevention are:

- Elevation of the Head of the Bed
- Daily "Sedation Vacations" and Assessment of Readiness to Extubate
- Daily Oral Care with Chlorhexidine
- Peptic Ulcer Disease Prophylaxis
- Deep Venous Thrombosis Prophylaxis

B. Other evidence-based strategies for VAP prevention can be considered in ICUs with a high prevalence of VAP, including continuous aspiration of subglottic secretions (CASS) tubes, silver-coated endotracheal tubes, and selective oral decontamination (SOD) or digestive tract decontamination (SDD),

VI. TREATMENT – Mechanical Ventilation (MV)

A. Effective strategies in MV must ensure adequate oxygenation and alveolar ventilation, reduce work of breathing without ventilator-induced lung injury (VILI).

B. The treatment for hypoxemic ARF (Type I) is to improve oxygenation and reverse/prevent tissue hypoxia by achieving adequate oxygen delivery to tissues with a goal of arterial oxygen saturations > 90% on the lowest FiO_2 concentration possible. The treatment of failure to ventilate, i.e. hypercapneic ARF (Type II), is to increase alveolar ventilation by achieving adequate minute ventilation.

C. MV can lead to additional lung injury, i.e. VILI. [13] VILI mechanisms include direct injury from elevated airway pressure (barotrauma), diffuse alveolar injury resulting from overdistention (volutrauma), injury caused by repeated cycles of recruitment/derecruitment (atelectrauma), and the most subtle form of injury related to the release of local mediators in the lung (biotrauma) (**Figure 2**).[14]

D. Variables that can be adjusted for mechanical ventilation include:

- Mode of ventilation
- Tidal volume (Vt)
- Respiratory rate (RR)
- Supplemental oxygen, (FiO_2)
- Inspiration/expiration ratio (I:E)
- Inspiratory flow rate
- Positive end-expiratory pressure (PEEP)
- Trigger sensitivity (effort required to trigger the ventilator to deliver a breath)
- Rise time (determines speed of rise of flow or pressure in each breath)
- Temperature and humidity of inspired air.

E. Oxygen uptake via the lungs is dependent on both PaO_2 (FiO2, alveolar pressure) and ventilation-perfusion matching (reversing atelectasis, reduce intra-pulmonary shunting). To improve oxygenation, three main strategies are utilized:

1. Increase FiO_2. High levels (>50%) have been associated with oxygen toxicity, absorptive atelectasis, and other issues.
2. Increase mean alveolar pressure by increasing mean airway pressure (increase PEEP or increase I:E ratio, increase inspiratory time
3. Recruitment maneuver with PEEP (i.e., 30cm H_20 PEEP for 30 seconds, 40cm H_20 PEEP for 40 seconds, or pressure control RM with high PEEP 40, low PEEP 20, I:E 1:1 for 2 minutes)

F. Ventilation describes carbon dioxide elimination via the lungs and is largely dependent on alveolar ventilation. Alveolar ventilation = respiratory rate x (tidal volume – dead space). To improve CO_2 elimination:

a. Increase minute ventilation (increasing tidal volume or respiratory rate)

VII. MODES of MECHANICAL VENTILATION

- Controlled MV is commonly used initially to ensure adequate alveolar ventilation, arterial oxygenation, reduce work of breathing, and reduce further lung damage. Recent studies suggest a benefit when early conversion to spontaneous breathing modalities during MV is employed. Therefore spontaneous breathing is desired whenever possible.
- Mechanical positive pressure ventilation can be delivered via a volume or pressure target.
- No single mode of MV for ARF is superior in terms of clinical outcomes

A. Volume Modes: Tidal volume is set and airway pressure is variable. The airway pressure will be variable based upon the rate of delivery of the tidal volume, pulmonary compliance (plateau pressure), and airway resistance (peak pressure). This variability in airway pressure may result in barotrauma if high peak airway pressures occur. [15]

1. **Controlled mechanical ventilation mode (CMV):** Set respiratory rate and tidal volume to achieve an exact minute ventilation; does not allow patient interaction. CMV may result in diaphragmatic inactivity, promoting atrophy and contractility dysfunction in this important inspiratory muscle, so is not commonly used.
2. **Assist-control ventilation mode (AC):** A commonly used mode of MV that is patient- or time-triggered, flow-limited and volume-cycled. The tidal volume of each delivered breath is the same, whether triggered by the ventilator or the patient. The ventilator delivers breaths in coordination with the respiratory effort of the patient. If a patient triggering event does not occur in a set time interval, then the ventilator will deliver a breath similar to control mode. This allows for patient participation with regards to breath initiation. AC is associated with low work of breathing, as every breath is supported and tidal volume is guaranteed.
3. **Synchronous intermittent mandatory ventilation mode (SIMV):** The ventilator delivers both mandatory (set rate, tidal volume) breaths delivered in coordination with the respiratory effort of the patient, and pressure support (set pressure) breaths to support spontaneous breathing. Most SIMV modes will default to a control-mode setting in the event that the patient does not trigger the ventilator in a certain time window around the preset respiratory rate. Synchronization of the tidal volume delivery with the patient's inspiratory effort attempts to limit barotrauma that may

occur with non-synchronized IMV when a preset breath could be delivered to a patient who is already maximally inhaled (breath stacking) or is forcefully exhaling.

B. Pressure Modes: Airway pressure is set and tidal volume is variable. The tidal volume will be affected by any factor that changes the airway pressure including thoracic compliance and pulmonary resistance, and by the inspiratory time. As the lung inflates, the inspiratory flow tapers which results in a more homogenous gas distribution throughout the lungs. Since tidal volume is variable in pressure control modes, a sudden decrease in pulmonary compliance can cause a rapid reduction in tidal volume and minute ventilation resulting in acute respiratory acidosis, and this mode necessitates close monitoring of the minute ventilation and possible intrinsic- or auto-PEEP (**Figure 3**). [16]

1. **Pressure Control Ventilation (PC):** Set an inspiratory pressure and inspiratory time rather than tidal volume and inspiratory flow rate. Tidal volume is dependent on set pressure, inspiratory time and patient's compliance/resistance. In patients with hypoxemic ARF or ARDS, changing from a volume control mode to pressure control mode may result in lower peak airway pressures.

2. **Pressure Support Ventilation (PSV):** Breaths are assisted by a set inspiratory pressure, which is delivered until inspiratory flow drops below a pre-determined threshold (e.g., 25% of peak flow). Respiratory rate and tidal volume are determined by the patient. Can be a stand-alone mode or with SIMV (PSV only with spontaneous breaths). Apnea alarms are required to ensure patient safety. Some ventilators may have a set back-up IMV rate should spontaneous respirations cease. PSV has been advocated to limit barotrauma and decrease the work of breathing. PSV is also used at low levels (5 cm H_2O) during spontaneous breathing trials.

3. **Pressure-regulated Volume Control (PRVC) or Volume Control Plus (VC+):** Automatically adjusts inspiratory pressure in response to dynamic changes in patients mechanics to guarantee a set tidal volume in a pressure-control breath. Constant pressure is applied throughout inspiration (like pressure control), but the ventilator will adjust the inspiratory pressure with each breath (compensating for changes in airway resistance and compliance) to deliver a set tidal volume. PRVC is a patient- or time-triggered, pressure-limited, time-cycled mode.

4. **Airway Pressure Release Ventilation (APRV):** This is an inverse-ratio pressure mode of MV that alternates between High PEEP (generally set between 25-30 cm H_2O) and Low PEEP (usually 0 cm H_2O), with a longer inspiratory time (Time-High), I:E commonly 7:1 to 10:1, and a very short expiratory time or "release" (Time-Low). APRV achieves high mean airway pressures resulting in improved alveolar recruitment without high plateau pressures. Tidal volume is determined by the difference between High/Low PEEP. Spontaneous breathing can occur, and APRV is well-tolerated both hemodynamically and in terms of patient comfort.

5. **BiLevel or Biphasic Ventilation:** Similar to APRV, mandatory breaths are pressure-controlled and spontaneous breathing can occur at Time-High or Time-Low (**Figure 4**). Spontaneous breaths may be pressure-supported. Compared to APRV, BiLevel Time-Low is generally longer, which allows for more spontaneous breaths during Time-Low.

C. ADVANCED MODES OF MECHANICAL VENTILATION in the ICU

- Newer modes of MV are focused on improving the patient-ventilator interface, resulting in decreased ventilator dsynchrony and improved patient comfort, allowing greater time in spontaneous breathing. [17]

1. **Proportional Assist Ventilation (PAV):** During PAV, the airway pressure is proportional to the instantaneous effort of the patient, and is amplified according to the patient respiratory mechanics (pulmonary compliance and airway resistance) and the chosen level of assistance (0-100%) for the respiratory muscles. Caution must be exercised in patients who are not reliably initiating spontaneous breaths (i.e., in the presence of altered mental status, or apneic periods) A recent advance is the development of PAV+, a mode that provides intermittent automated measurements of the patient's compliance and resistance which are used by the ventilator to adjust the specific support for the patient. No studies have yet documented improved outcome using PAV.

2. **Adaptive Support Ventilation (ASV):** This mode can deliver both controlled (like pressure-control) and assisted (like pressure support) pressure cycles related to a minute ventilation target set by the clinician and based on automated measurements of the patient's respiratory mechanics.

3. **Neurally adjuted Ventilatory Assist (NAVA):** Like PAV, the level of ventilator assistance is proportional to the patient's effort, but the signal is a diaphragmatic electromyogram signal from diaphragmatic contraction obtained from electrodes on an esophageal catheter. A significant benefit of NAVA is improvement in patient-ventilator synchrony and reduced work of breathing by ensuring the respiratory muscles are supported throughout inspiration when compared with other commonly used MV modes. NAVA is not yet in widespread use, and the patient groups most likely to benefit are yet to be defined.

4. **SmartCare:** This closed loop system provides automated adaptation of the level of PSV and initiates an automated weaning protocol to decrease the level of PSV and initiate spontaneous breathing trials when a low level of PSV is attained. The first multicenter study comparing automated weaning to standard of care (n=144) documented that automated weaning reduced the total duration of mechanical ventilation and weaning duration, and the proportion of patients requiring NIV after extubation. [18] Additional clinical trials are underway.

D. MECHANICAL VENTILATION STRATEGIES FOR ARDS

- Many recent advances have been made in developing protective MV strategies for patients with ARDS. [19] These include low tidal volume ventilation, permissive hypercapnia, open lung strategy, and high frequency oscillatory ventilation (HFOV).

- The only ventilator strategy demonstrated to lower mortality in ARDS is the ARDNet "lung protective" strategy (lower tidal volume (6 ml/kg), plateau pressure limited) and this should form the basis for initial management. Higher PEEP, "open lung" strategies have been associated with improved non-mortality outcomes.

1. **Low Tidal Volume Ventilation:** Alveolar stretch from high tidal volumes can result in VILI through stimulation of an exaggerated alveolar and systemic inflammatory response. High tidal volumes are associated with high plateau pressures, which are associated with increased mortality. The ARDS-Network landmark ARMA multicenter, randomized controlled trial documented that low tidal volume (6 ml/kg) versus high tidal volume (12 ml/kg) ventilation in ARDS patients was associated with a significantly lower mortality (31% vs. 40%; p = 0.007) in the low tidal volume group. Ventilator-free days and number of days without non-pulmonary organ system failures was also decreased in the low tidal volume group. The incidence of barotrauma was similar at 10% vs. 11%. [20] The "*Guidelines for Mechanical Ventilation of the Trauma Patient*" from the participants of the 'Inflammation and Host Response to Injury Large Scale Collaborative Research Program' standardized clinical management in trauma patients to ensure that a low tidal volume, lung-protective strategy is used for patients with ARDS. This also provides guidelines for the PEEP and weaning of mechanical ventilation **(Table 4)**.[21]

2. **Permissive Hypercapnia:** Low tidal volume ventilation to reduce volutrauma can result in decreased minute ventilation leading to hypercapnia and acute respiratory acidosis. Permissive hypercapnia accepts deliberate hypoventilation in order to reduce alveolar overdistension and pressures in ARDS patients with severe hypoxemia. Resultant hypercarbia and respiratory acidosis is managed medically. Hypercapnia may worsen intracranial pressure and should be avoided in patients with traumatic brain injury. Tidal volume is gradually reduced to allow a slow increase in $PaCO_2$. Therapy with sodium bicarbonate or tromethamine (THAM) can be used to treat any resultant acute respiratory acidosis.

3. **Optimizing PEEP, esophageal pressure (Pes) protocol:** In patients with chest and abdominal wall compression, measured transpulmonary pressure may reflect higher transpleural pressures, rather than elevated airway pressures. In a pilot randomized trial, Talmor measured esophageal pressure (Pes) with an esophageal balloon catheter as a surrogate approximation of pleural pressure in estimating transpulmonary pressure. [22] Patients in whom PEEP titration was based on Pes sustained statistically significant improvements in oxygenation and respiratory-system compliance and decreased mortality after adjustment for baseline APACHE scores when compared to patients managed with the standard ARDSNet FiO_2/PEEP table. The authors suggest that this method may allow optimal, safe PEEP titration by individualizing adjustments for a given patient's specific torso compliance. This hypothesis will be tested in an upcoming larger randomized, clinical trial.

4. **Open Lung Strategy:** Combining the use of low-volume tidal volume strategies, with the application of PEEP at levels above the lower inflection point, and permissive hypercapnia has been termed the "open-lung approach" **(Figure 5)**. Depletion of surfactant and low levels of PEEP lead to cyclic atelectasis with repeated collapsing and opening of the remaining function alveoli in ARDS patients. Cyclic opening and closing of alveoli can lead to leukocyte activation, VILI, and loss of functional residual lung capacity (FRC). Increased levels of PEEP lead to recruitment of collapsed alveoli, reducing ventilation-perfusion mismatch, improved arterial oxygenation, and increased FRC. By maintain end-expiratory pressure, alveoli

that are unstable and prone to collapse will remain open. The optimal PEEP level is difficult to determine but evidence suggests that maximal recruitment and lung volume maintenance occurs when the PEEP is set at a level just above the inflection point (Pflex) on the pressure-volume curve in ARDS patients. A recent meta-analysis confirmed that higher vs. lower levels of PEEP was associated with improved survival among patients with ARDS. [23] Despite the use of increased PEEP, it has been demonstrated that decreasing plateau pressures (Pplat) results in a lower mortality in ARDS patients **(Figure 6)**. The study does not reveal a safe threshold for Pplat in ARDS patients. A bivariate analysis also showed that lower Pplat quartiles were associated with reduced mortality compared to higher Pplat quartiles (p=0.039) suggesting that tidal volume reduction benefits patients even when Pplat is already <30-35 cm H_2O **(Figure 7)**.

5. **High-Frequency Oscillatory Ventilation (HFOV):** HFOV delivers small tidal volumes at frequencies of 3-15 Hz to maintain adequate minute ventilation. Oxygenation is manipulated by adjusting mean airway pressure similar to the use of PEEP in conventional mechanical ventilation. Ventilation and carbon dioxide elimination is controlled by changing the tidal volume, by amplitude or power, or by adjusting the frequency. Increasing the amplitude or decreasing the frequency will cause an increase in carbon dioxide elimination. Amplitude or power is set to achieve appropriate chest wall movement and adequate CO_2 elimination. HFOV was initially used as a rescue strategy when other modes of mechanical ventilation had failed.[24],[25] A recent meta-analysis concluded that HFOV in adults with ARDS is a safe and may improve outcome (RR 0.77, 95% CI 0.61-0.98, (**Figure 8**) and was associated with improved oxygenation compared to conventional MV, but more study is needed. [26] HFOV may also be considered for use in patients with bronchopleural fistulae or tracheobronchial injuries to maintain low mean airway pressures in an effort to resolve air leaks within the tracheobronchial system.

   HFOV is, in theory, the ideal 'lung protective' method, and may have a larger margin of safety in keeping the lung open within the desired target range of alveolar over distention in heterogeneously injured ARDS lungs, but outcome benefits have not yet been proven in a large prospective, randomized trial. [2728] Two such studies are underway: the Oscillation for ARDS Treated Early (OSCILLATE) Trial [29] by the Canadian Critical Care Trials Group with a target sample size of 1200 patients, and the High Frequency Oscillation in ARDS (OSCAR) Trial [30] ongoing in the United Kingdom with a target sample size of 802 patients.

   Although the exact severity threshold at which to initiate a trial of HFOV remains unclear, an emerging approach includes the following severity criteria: [31]

   a. FiO_2 >0.60 and SpO_2 <88% on CMV with PEEP >15 cm H_2O, or
   b. Plateau pressures >30 cm H_2O, or
   c. Mean airway pressure 24 cm H_2O, or APRV with High pressure 35 cm H_2O

6. **Airway Pressure-Release Ventilation (APRV):** APRV is a pressure-limited, time-cycled mode of mechanical ventilation that allows the patient unrestricted spontaneous breathing during application of continuous positive airway pressure (CPAP) with a very short release time, resulting in open lung MV. APRV has two

settings of pressure. The high pressure setting allows spontaneous breathing and accounts for 80-95% of the cycle time creating an open lung. The remainder of the cycle allows for a periodic pressure release to the low pressure setting to allow for ventilation and carbon dioxide clearance while preventing alveolar collapse. APRV is used when patients are able to spontaneously breathe, yet high mean airway pressure is required for alveolar recruitment for severe hypoxemia.

E. ADJUNCTS to MECHANICAL VENTILATION in ARDS & SEVERE HYPOXEMIA

- In patients with severe life-threatening hypoxemia, a number of strategies are used, including fluid management, recruitment maneuvers, neuromuscular blockade, prone position, inhaled nitric oxide and extracorporeal membrane oxygenation (ECMO). [32] [33]

1. **Recruitment Maneuvers:** Alveolar recruitment is aimed at improving pulmonary gas exchange, preventing ventilator-induced lung injury, atelectasis, and atelectrauma. Recruitment maneuvers (RMs) can increase alveolar FRC and PEEP can then maintain the alveoli to prevent collapse. Recruitment refers to the dynamic process of reopening unstable airless alveoli through an intentional transient increase in transpulmonary pressure, accomplished via many methods. A common method for RMs is to provide sustained inflation with 30cm H_2O PEEP for 30 seconds or 40 cm H_2O PEEP for 40 seconds; alternatively, the use of a pressure control RM with high PEEP 40, low PEEP 20, I:E 1:1 for 2 minutes is effective. The optimal methods of RMs (sustained inflation versus incremental PEEP) and optimal pressure, duration and frequency of RMs have not been tested in large clinical trials. A recent systematic review concluded that RMs were associated with a significant increase in oxygenation with few serious adverse events. [34] Transient hypotension and desaturation during RMs is common but is self-limited without sequelae. Given the uncertain benefit and lack of information regarding impact on clinical outcomes, RMs should be considered for use only in patients with life-threatening hypoxemia.

2. **Fluid Management:** A conservative fluid management strategy was superior to a liberal strategy in ARDS patients with improved lung function and oxygenation and decreased duration of MV and ICU stay, but no difference in 60-day mortality. [35] Diuretic therapy should be considered in severe hypoxemia (PaO_2/FiO_2 ratio $\leq$ 100). A careful assessment of adequacy of perfusion and cardiac performance should be completed before initiation of diuretic therapy, and re-assessment continued while diuresis is ongoing.

3. **Neuromuscular Blockade**: A multicenter, double-blind trial of 340 patients with severe ARDS confirmed that early administration of a neuromuscular blocking agent (cisatracurium) improved 90-day survival and increased time off mechanical ventilation without increasing muscle weakness compared to placebo. [36] Enthusiasm for this approach must be tempered with concern for critical illness polyneuropathy.

4. **Inhaled Nitric Oxide (NO)**: Nitric oxide is a selective pulmonary vasodilator leading to decreased pulmonary vascular resistance, pulmonary arterial pressure, and right ventricular afterload. Low-dose inhaled NO has shown improved short-term oxygenation in ARDS patients without affecting duration of mechanical ventilatory support or mortality. [37] Inhaled NO may be considered a salvage therapy in patients

who continue to have life-threatening hypoxemia despite optimization of all other treatment strategies.

5. **Prone Positioning:** Changes in patient positioning can have a dramatic effect on oxygenation and ventilation in severe ARDS and severe hypoxemia. Prone position can improve the distribution of perfusion to ventilated lung regions, decreasing intrapulmonary shunt and improving oxygenation. The use of intermittent or extended prone positioning can significantly improve oxygenation in 60% to 70% of patients. [38] Prone positioning can be performed safely by trained and dedicated nursing staff that are aware of its potential benefits in critically ill patients with severe hypoxemia. Prone positioning is a useful tool for treatment of hypoxemia, can sometimes prevent the need for extracorporeal membrane oxygenation (ECMO), and is used for lung recruitment in patients undergoing ECMO. Recent meta-analyses in ARDS patients documented significantly decreased mortality with prone positioning, with an absolute mortality reduction of 10% in severely hypoxemic ARDS patients. [39] [40] [41] Prone positioning clearly serves a role as rescue therapy for patients with ARDS and refractory life-threatening hypoxemia.

6. **Extracorporeal Membrane Oxygenation (ECMO):** ECMO is considered in patients with severe ARDS and hypoxemia with reversible lung disease who have failed other rescue strategies. ECMO provides oxygenation, ventilation with total extracorporeal CO2 clearance, minimizes barotrauma with complete lung rest, and is accomplished via veno-venous ECMO support, until the patient's endogenous lung function improves. [42] Substantial progress in ECMO has been achieved. ECMO potential complications include bleeding (including intracranial hemorrhage), coagulopathy, thrombosis, and mechanical complications. Of 1473 adults with severe ARDS, ECMO was associated with a 50% survival to discharge. [43] Patients with severe ARDS and hypoxemia should be referred to an ARDS center with ECMO experience to achieve the best outcomes possible. Adult patients are cannulated percutaneously with large 21-31 French venous catheters for drainage of deoxygenated blood and infusion and oxygenated blood. Anticoagulation is necessary, and heparin continuous infusion is common, and monitored with ACT or PTT studies.

   The CESAR trial (Conventional Ventilation or ECMO for Severe Adult Respiratory Failure) was a prospective randomized trial (n=180) in the United Kingdom. Of the 90 patients assigned to ECMO treatment, only 68 received ECMO; others were managed with mechanical ventilation and rescue strategies. 63% of patients transferred to an ECMO center survived to 6 months without disability vs. 47% in the conventional management group (RR 0.69, CI 0.05-0.97, p = 0.03). A criticism of this study is that the conventional cohort was not managed with low tidal volume, low plateau pressure, open lung protective MV. Another multicenter ECMO clinical trial, ECMO to Rescue Lung Injury in Severe ARDS (EOLIA), is being initiated in France to address this issue. [44]

VIII. INCREMENTAL APPROACH TO THE MANAGEMENT OF SEVERE ARDS

- Development of ICU protocols reduces undesirable variability, mandates best evidence practice, promotes action and timeliness, and facilitate multi-disciplinary communication.

- We have developed an algorithm (**Figure 9**) for management of critically ill patients with severe ARDS/severe hypoxemia at the University of Michigan to provide evidence-based care.
- In ARDS patients, initial low tidal volume ventilation should be initiated, set at 6-8 mL/kg of predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of 2 hours until the tidal volume is set at 6 mL/kg. Goal: SpO_2 88-95%, PO_2 55-80 mmHg, plateau pressures < 30 cm H_2O while using lowest FiO_2 possible.
- If no improvement, recruitment maneuvers should be considered. If oxygenation improves during recruitment maneuvers, the PEEP should be increased until optimal PEEP is achieved.
- If no improvement, evaluation for a possible intracardiac shunt and/or pulmonary hypertension should be initiated. Diagnostic strategies include pulmonary artery catheter placement and/or transthoracic or transesophageal echocardiogram. Inhaled nitric oxide should be considered as a therapeutic strategy to improve oxygenation. If there is still no improvement in oxygenation, prone positioning should be considered.
- At this point, for a patient with persistent severe hypoxemia, transfer of the patient to an ARDS Referral Center with experience in other ARDS treatment modalities, including rescue strategies, APRV, HFOV and ECMO should be considered**.** [45]

IX. WEANING and LIBERATION from MECHANICAL VENTILATION

- Mechanical ventilation has significant potential risks such that efforts should be focused on liberation from mechanical ventilation once adequate lung recovery has occurred.
- Nearly half of the time spent with mechanical ventilation is spent weaning the patient.
- A daily Spontaneous Awakening Trial (SAT) followed by a Spontaneous Breathing Trial (SBT) should be performed in all patients on MV. A randomized multicenter trial that compared this "wake up and breathe" protocol (paired SAT/SBT) vs. usual care plus a daily SBT in the control cohort confirmed that SAT/SBT resulted in improved outcomes with reduced mortality, increased ventilator-free days and reduced ICU and hospital length of stay. [46]
- Continuous protocols for weaning from mechanical ventilation directed by respiratory therapists are associated with shorter duration of ventilation and ICU length of stay.Patients who fail a SAT/SBT trial are returned to their previous ventilator settings and re-screened for another SAT/SBT trial in 24 hours. The patient must be carefully evaluated to determine the etiology of the SAT/SBT failure with assessment for anxiety, pain, secretions, muscle weakness, atelectasis, hypoxemia, hypercarbia, and all other potential etiologies for lack of resolution of ARF.
- Patients who complete a paired SAT/SBT trial [CPAP with low pressure support (5cm H_2O) or automatic tube compensation, or T-piece] should be assessed to determine readiness for extubation. At the completion of the SAT/SBT trial, the rapid shallow breathing index (RSBI), the ratio of respiratory frequency to tidal volume (f/VT, respiratory rate x tidal volumes in liters), is calculated and an arterial blood gas is obtained to evaluate for hypercarbia. For example, a patient who has a respiratory rate of 25 breaths/min and a tidal volume of 250 mL/breath has an RSBI of (25 breaths/min)/(.25

L) = 100 breaths/min/L. RSBI < 105 is associated with 80% wean success; RSBI ≥ 105 is associated with 95% wean failure.

- Prior to considering extubation, additional assessment includes the following: (a) does not require tracheal suctioning more than every 4 hours; (b) good spontaneous cough; (c) endotracheal tube cuff leak; (d) no recent upper airway obstruction or stridor; (e) no recent reintubation for bronchial hygiene
- If failure to wean and/or extubate persists despite maximal and repeated efforts to achieve these endpoints, other steps may be required prior to successfully liberating the patient from MV. Some patients require prolonged and more gradual ventilator weaning, which may be best facilitated by tracheostomy placement. In addition, data from observational studies shows that up to 60% of ventilator-dependent patients who are discharged from the ICU can be successfully weaned when they are transferred to specialized units dedicated to ventilator weaning.

X. TRACHEOSTOMY

- Previous studies suggested that tracheostomy was superior to prolonged intubation for VAP prevention. However, 2 recent, large, prospective, randomized, clinical trials have found no difference in VAP or any other outcomes measures in comparing early (6–8 days) with late (13–15 days) tracheostomy in 419 patients or comparing early (4 days) with late (after 10 days) tracheostomy in 909 patients in the TracMan trial. Early tracheostomy should not be performed for VAP prevention but may be considered for other reasons, such as difficult airway and difficult-to-wean patients, particularly for patient comfort.

- Some patients benefit from early tracheostomy, including those with traumatic brain injury and acute respiratory failure for airway protection, and those who will require prolonged mechanical ventilation (i.e. ARDS patients) for patient comfort.

Eight (8) Axioms:

1. Acute respiratory failure (ARF) is classified as either hypoxemic (Type I) or hypercapneic (Type II).

2. Severe hypoxemic ARF should raise concern for possible ARDS (PaO_2/FiO_2 ratio < 300).

3. Noninvasive ventilation should be considered for patients with ARF due to COPD or pulmonary edema, since it is associated with improved outcomes.

4. Following intubation for ARF, all strategies for prevention of ventilator-associated pneumonia should be initiated.

5. The initial strategy for management of ARDS should include the use of low tidal volume ventilation (6 ml/kg) with adequate PEEP.

6. Adjuncts to mechanical ventilation in severe hypoxemia and ARDS include recruitment maneuvers, diuretic therapy, neuromuscular blockade, inhaled nitric oxide, prone position, and ECMO.

7. Weaning of mechanical ventilation should be initiated to allow spontaneous breathing as soon possible. A paired daily Spontaneous Awakening Trial (SAT) and Spontaneous Breathing Trial (SBT) should be performed in all patients on MV since it is associated with improved outcomes with reduced mortality, increased ventilator-free days and reduced ICU and hospital length of stay.

8. Early tracheostomy should not be performed for VAP prevention, but may be considered for other reasons, such as difficult airway, severe traumatic brain injury for airway protection and difficult-to-wean patients.

Figure 1. Pathophysiology of the acute respiratory distress syndrome.

(From: Ware LB and Matthay MA, N Engl J Med 2000 May;342 (18):1334)

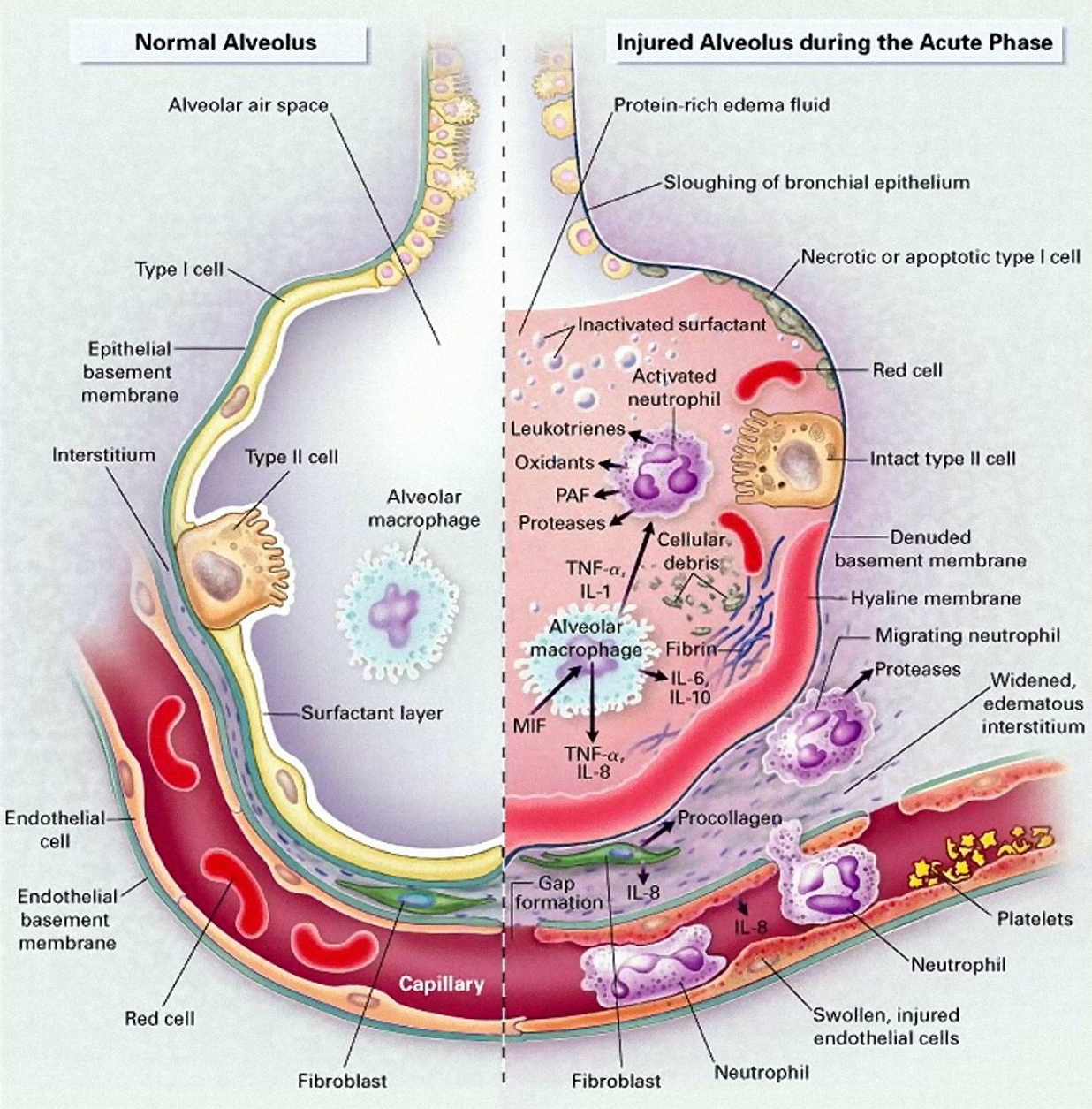


Figure 2. Pathogenesis of Ventilator-Associated and Ventilator-Induced Lung Injury.

(From: Belperio JA, Keane MP, Lynch JP 3rd, Strieter RM. The role of cytokines during the pathogenesis of ventilator-associated and ventilator-induced lung injury. Semin Respir Crit Care Med. 2006 Aug;27(4):350-64)

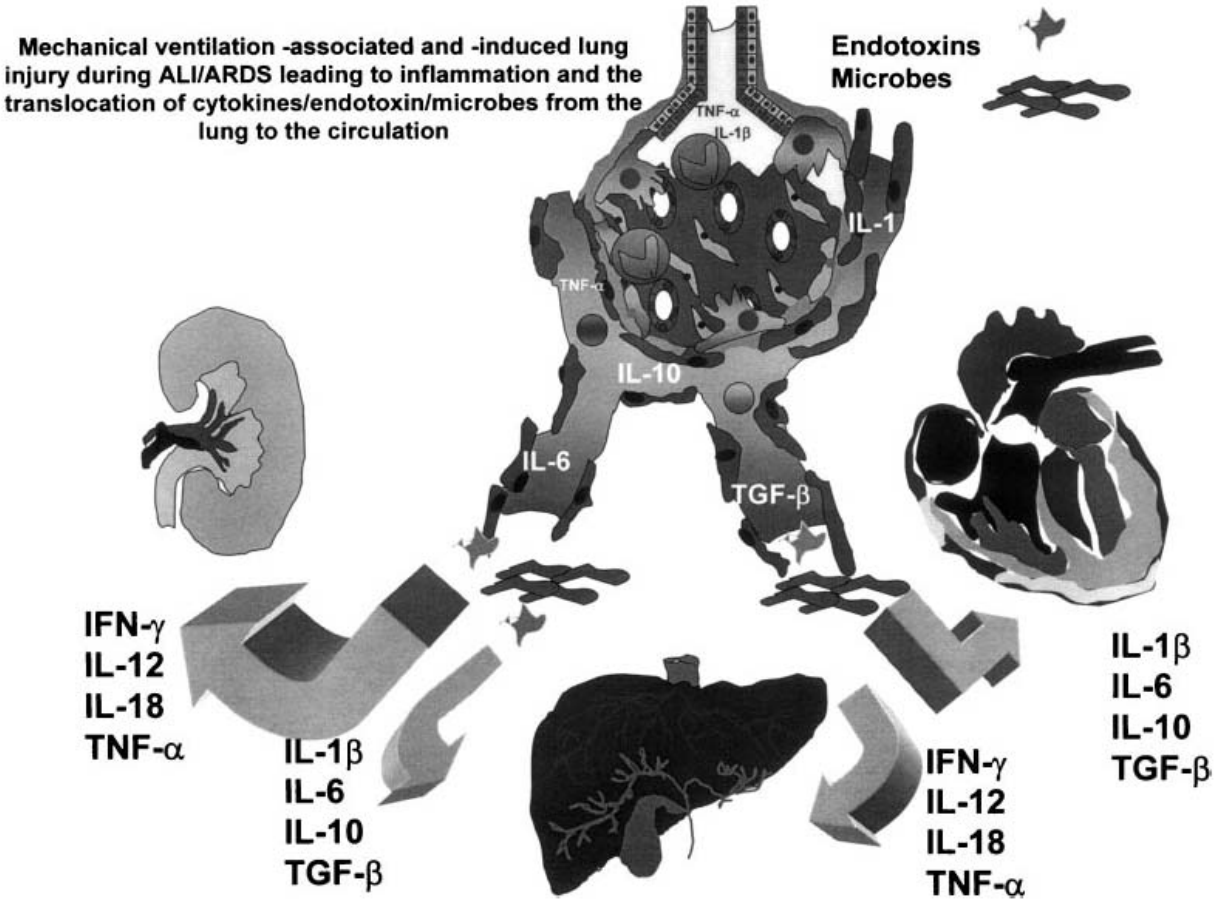
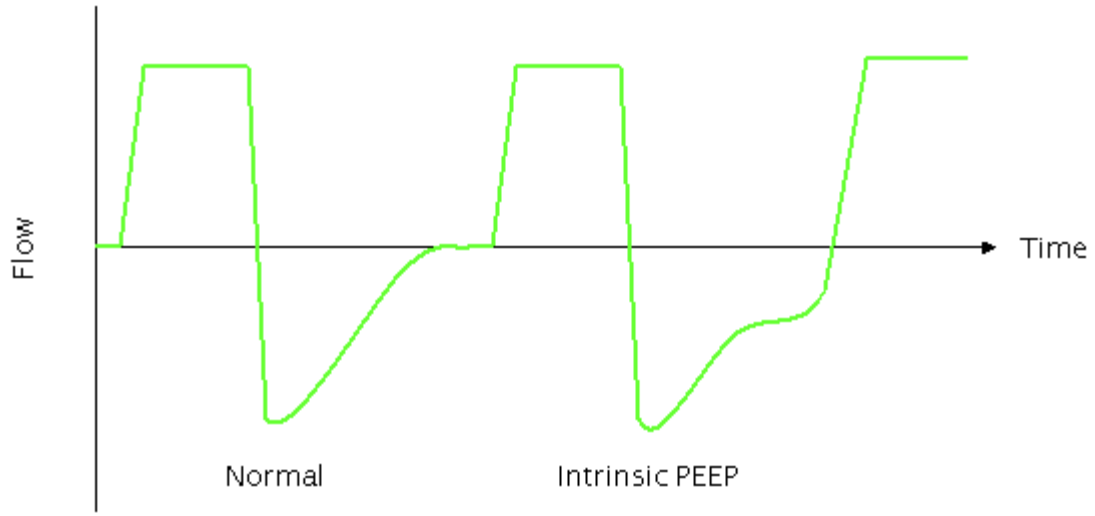


Figure 2 Cytokine, endotoxin, and microbial agents released from the acute lung injury/acute respiratory distress syndrome (ALI/ARDS) lung during injurious mechanical ventilation. Mechanical ventilation–associated and –induced lung injury causes impairment of the integrity of the alveolar–capillary membrane and results in augmented cytokine release leading to translocation of cytokines/endotoxin/microbial agents from the lung to the circulation, contributing to systemic inflammation and multiorgan dysfunction syndrome.

Figure 3. Intrinsic- or Auto- PEEP.

Examination of the flow-time curve from the ventilator gives an indication that there is intrinsic PEEP but does not give an indication of the magnitude. The patient does not need to be apneic.



A quantitative measurement of intrinsic PEEP can be obtained in an apneic patient by using the expiratory pause hold control on the ventilator. This allows equilibration of pressures between the alveoli and the ventilator allowing the total PEEP to be measured. The value for total PEEP can be read from the PEEP display. Intrinsic PEEP = Total PEEP – Set PEEP.

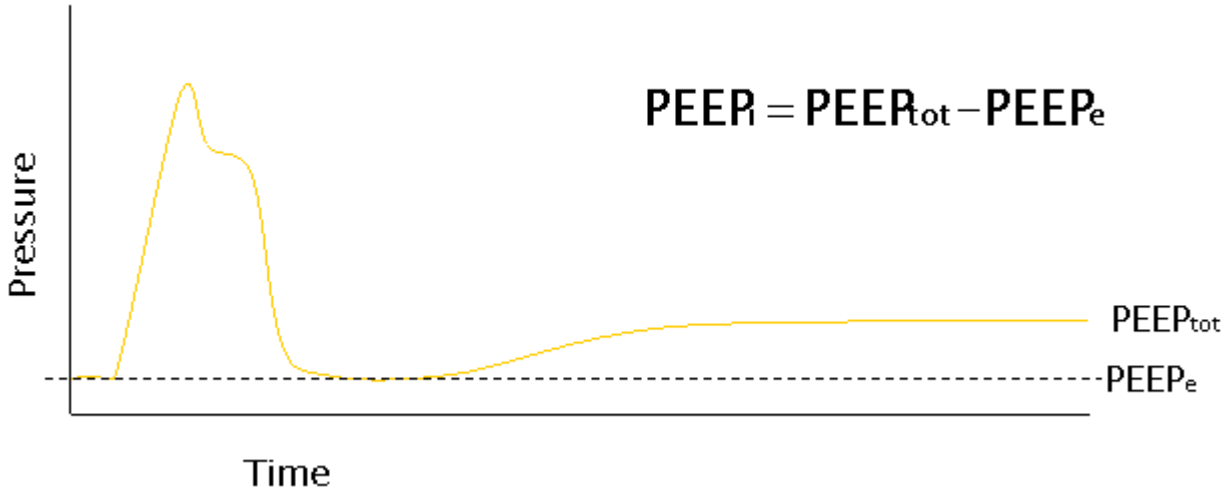


Figure 4. BiLevel Ventilation.

Bilevel ventilation uses 2 pressure levels (PEEP-low and PEEP-high) for 2 time periods (Time-low and Time-high), with spontaneous breathing at PEEP-low or PEEP-high.

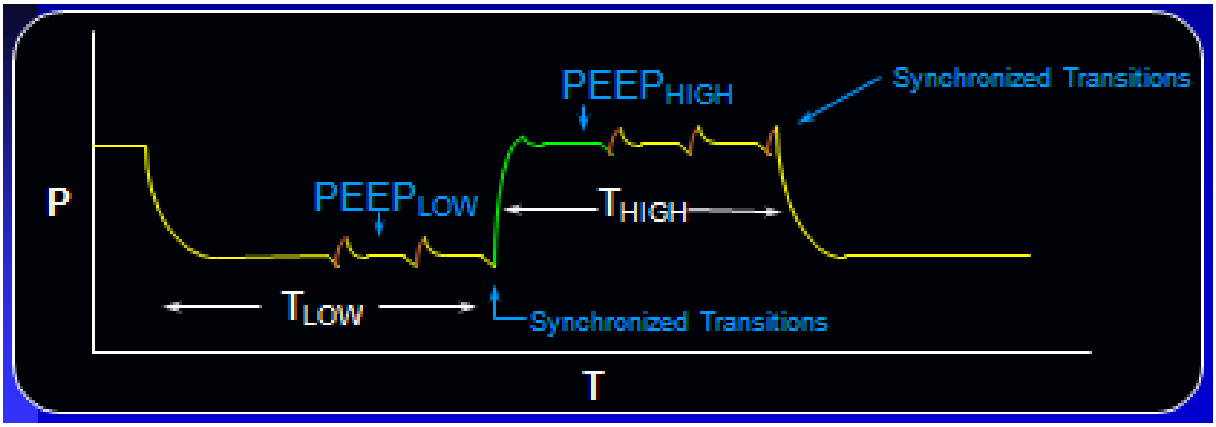


Figure 5. Open Lung Ventilation: pressure-volume curve during mechanical ventilation.

Two hazard zones exist: overdistention and derecruitment/atelectasis. Higher end-expiratory pressures and small tidal volumes are needed to stay in the "Safe" window. High-frequency oscillatory ventilation may have a larger margin of safety in keeping the lung open within the desired target range and avoiding alveolar overdistention.

[Reprinted with permission from: Imai Y, Slutsky AS: High-frequency oscillatory ventilation and ventilator-induced lung injury. *Crit Care Med* 2005; 33(3 Suppl):S129–S134)]

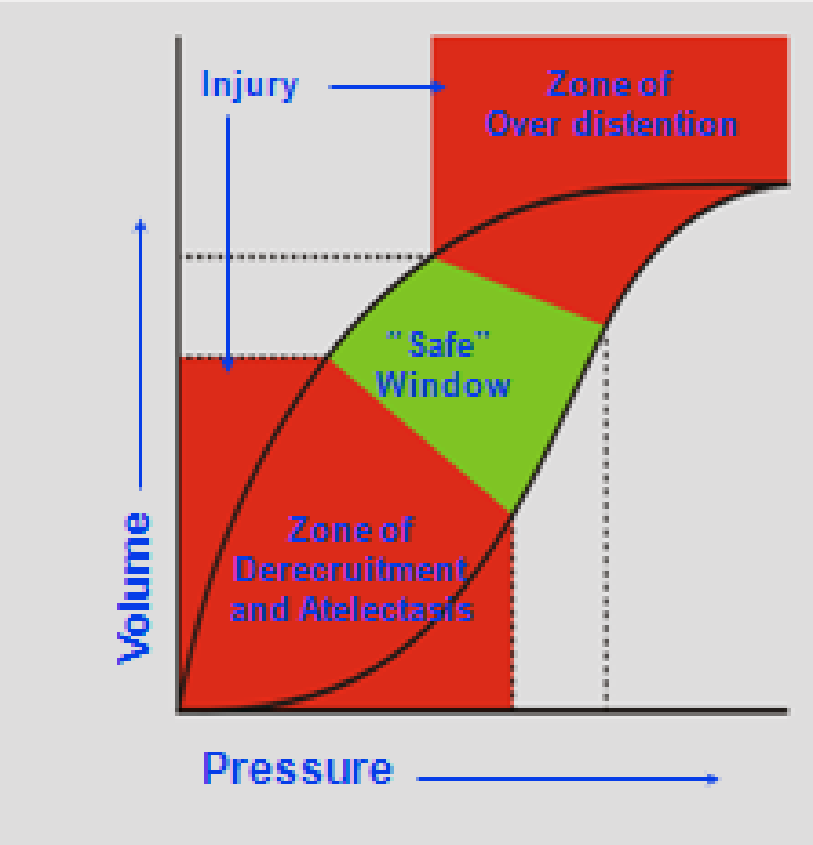


Figure 6. Relationship between mortality and Day 1 plateau pressures.

[Reprinted with permission from Hager et al: Tidal volume reduction in patients with acute lung injury when plateau pressures are not high. Am J Respir Crit Care Med. 2005 Nov 15;172(10):1241-5..]

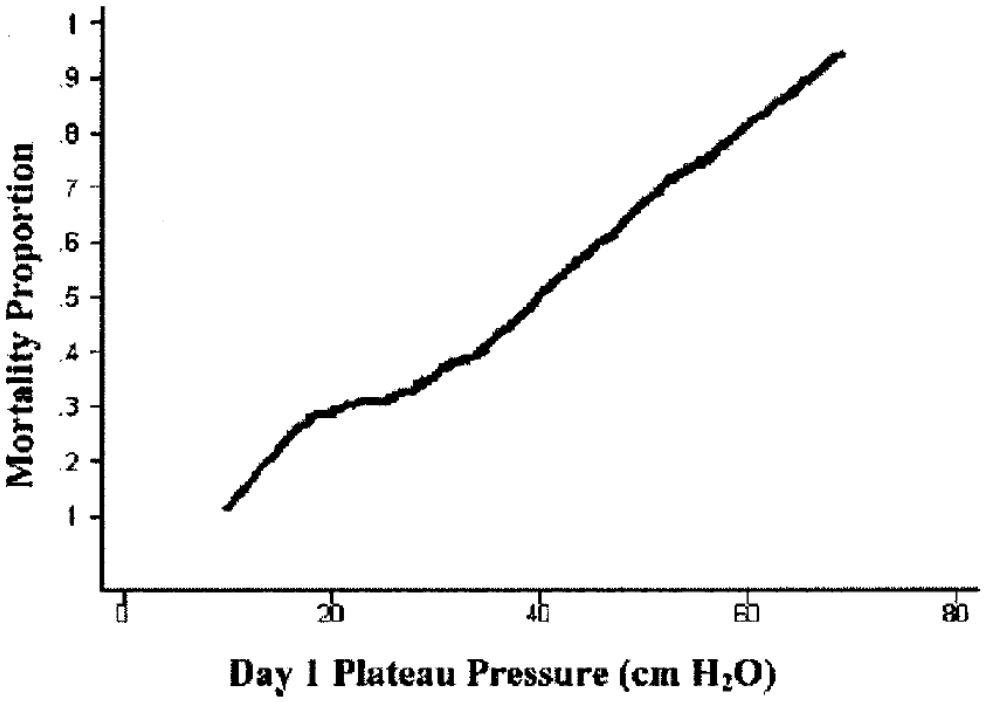
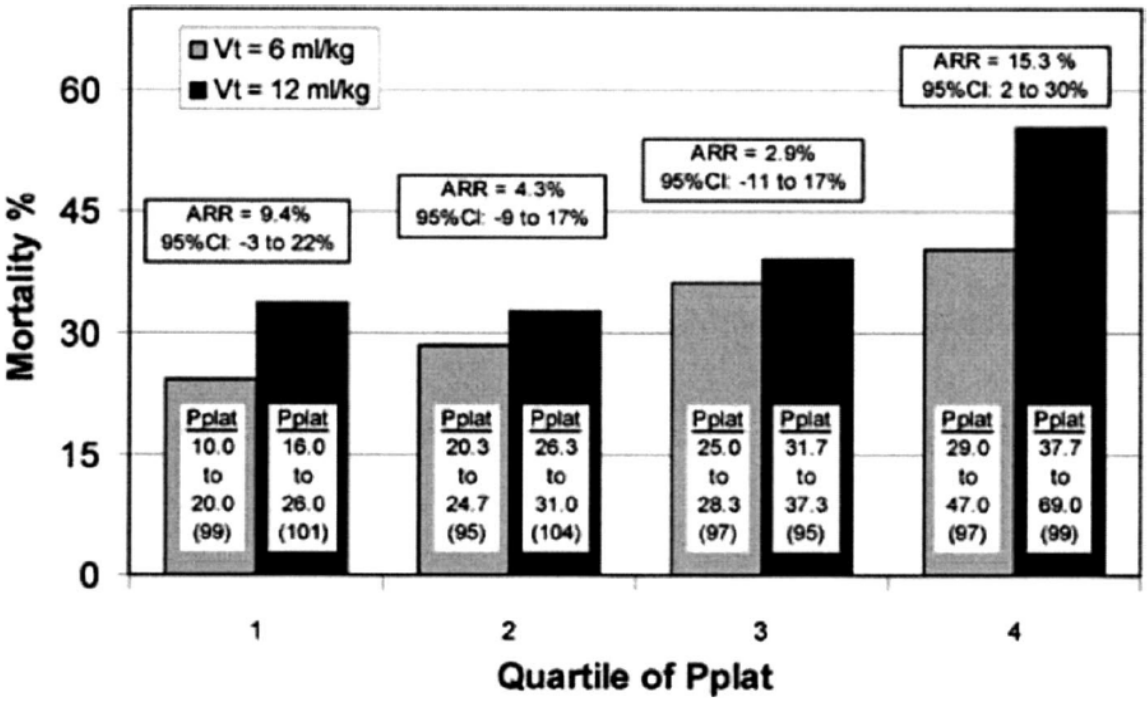


Figure 7. Mortality differences based on Day 1 plateau airway pressures.

[Reprinted with permission from Hager et al (27)]



Vt, tidal volume; *ARR*, absolute risk reduction; *CI*, confidence interval; *Pplat*, plateau pressure.

Figure 8. HFOV and ARDS Mortality.

Overall HFOV mortality in combined series was 39%

(From Sud et al. BMJ 2010;340:c2327)

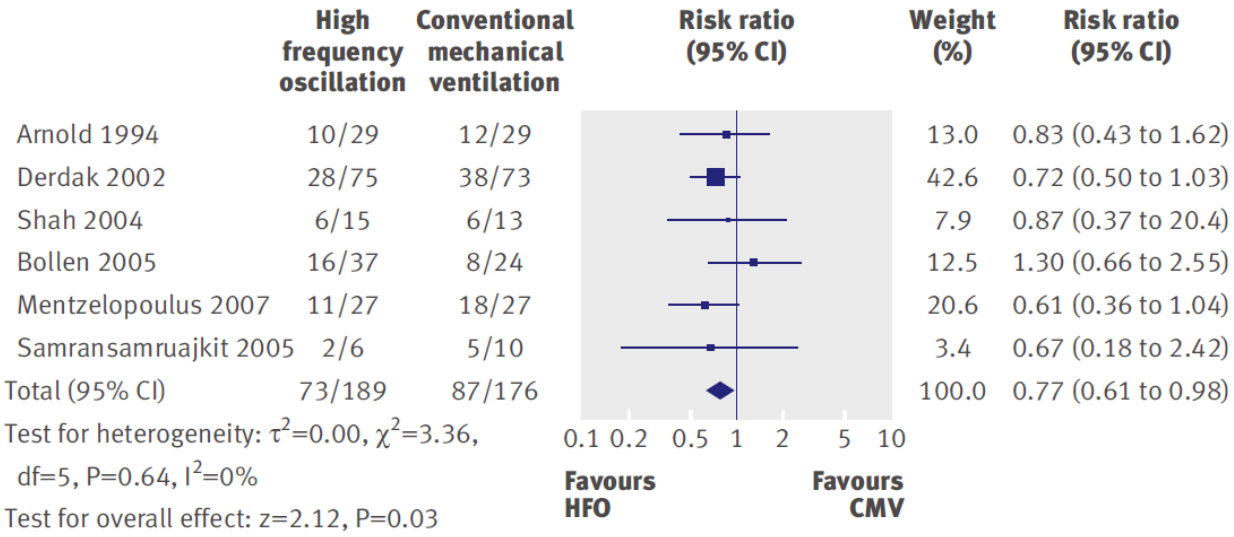


Fig 2 | Hospital or 30 day mortality in patients with acute lung injury/acute respiratory distress syndrome allocated to high frequency oscillation or conventional mechanical ventilation

Figure 9. ARDS Mechanical Ventilation Algorithm, including Rescue Strategies, University of Michigan.

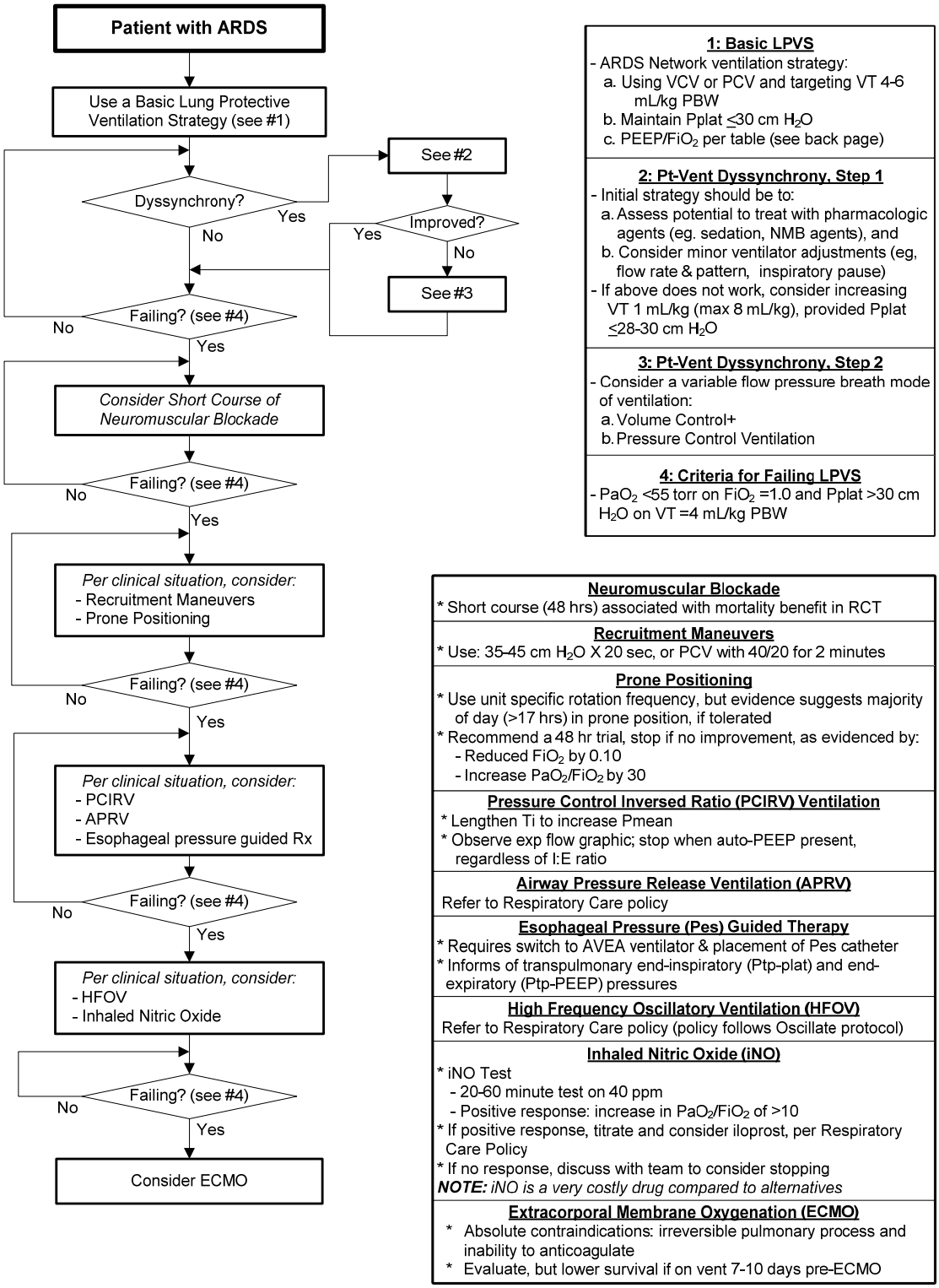


Figure 10. Increasing Intensity of Treatment Intervention for Increasing Severity of ARDS, with all Treatment Strategies available at ARDS Referral Center,

(From: Thompson, T. ARDS trials: Time for more splitting and less lumping. Critical Care Canada Forum 2011. Available at: http://www.criticalcarecanada.com/presentations/2011/ards_trials_time_for_more_splitting_and_less_lumping.pdf)

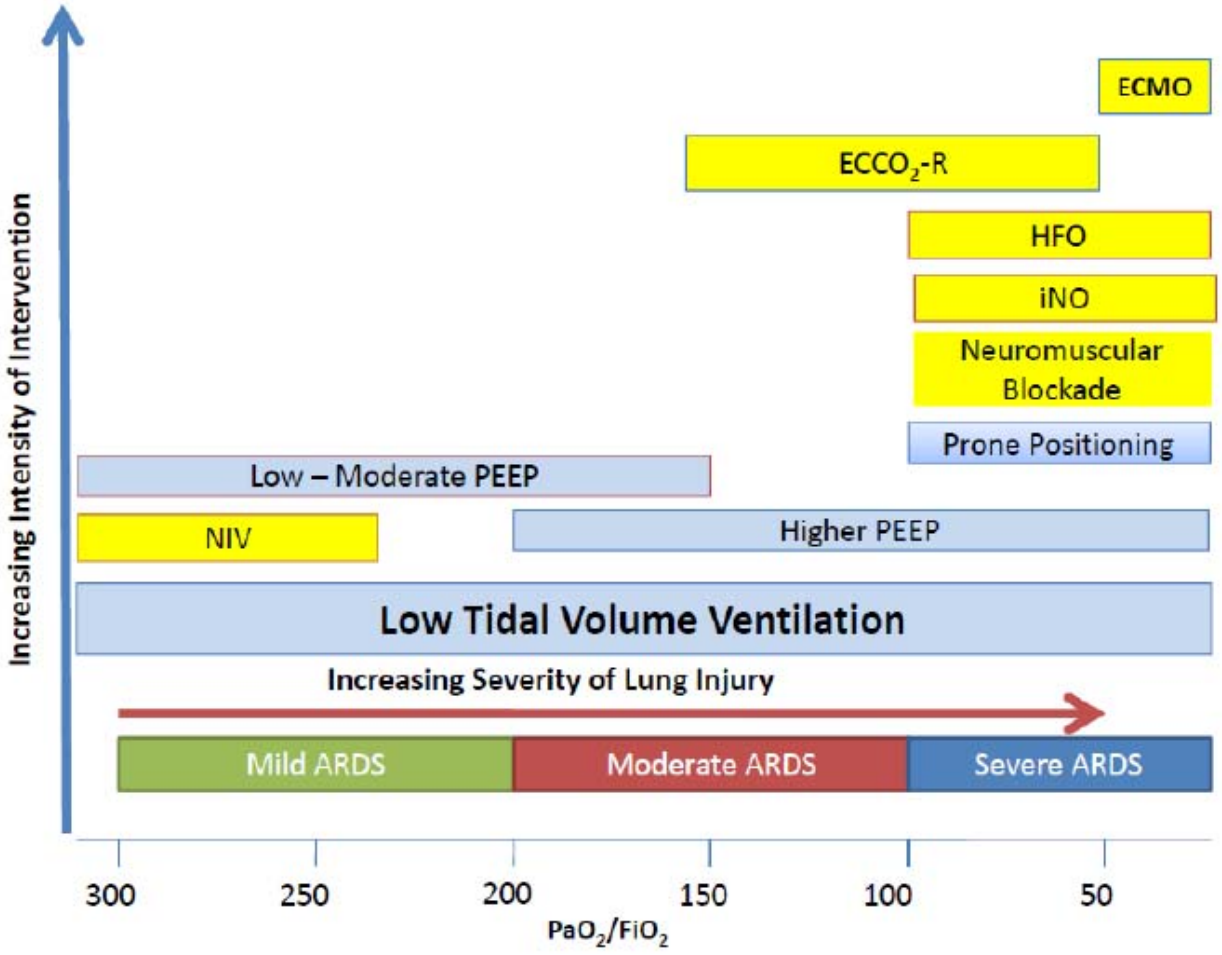


Table 1. Common Etiologies of Acute Respiratory Failure and Indications for Mechanical Ventilation

Etiologies of Respiratory Failure	Indications for Mechanical Ventilation
• Exacerbation of chronic obstructive pulmonary disease • Respiratory muscle fatigue • Neuromuscular diseases • Obtundation or coma • Pneumonia • Sepsis • Acute respiratory distress syndrome (ARDS)	• Apnea or respiratory arrest • Tachypnea (respiratory rate > 30 breaths per minute) or bradypnea • Vital capacity < 15 mL/kg, < 1.0 L or < 30% predicted • Minute ventilation > 10 L/min • Hypoxemia • Hypercarbia

Table 2. Definition of ARDS

The American-European Consensus Conference (AECC), 1994

ALI Criteria	Timing: Acute onset Oxygenation: $PaO_2/FiO_2 \leq 300$ mm Hg (regardless of positive end-expiratory pressure [PEEP] level) Chest radiograph: Bilateral infiltrates seen on frontal chest radiograph Pulmonary artery wedge: ≤ 18 mm Hg when measured or no clinical evidence of left atrial hypertension
ARDS Criteria	Same as ALI except: Oxygenation: $PaO_2/FiO_2 \leq 200$ mm Hg (regardless of positive end-expiratory pressure [PEEP] level)

New Proposed ARDS Definition – "Berlin" Definition, 2012

(From The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition JAMA. 2012;307(23):doi:10.1001/jama.2012.5669)

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < PaO_2/FIO_2 ≤ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < PaO_2/FIO_2 ≤ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	PaO_2/FIO_2 ≤ 100 mm Hg with PEEP ≥5 cm H_2O

Abbreviations: CPAP, continuous positive airway pressure; FIO_2, fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; PEEP, positive end-expiratory pressure.

[a] Chest radiograph or computed tomography scan.

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [$PaO_2/FIO_2 \times$ (barometric pressure/760)].

[c] This may be delivered noninvasively in the mild acute respiratory distress syndrome group.

Table 3. Clinical Disorders associated with the Development of ARDS.

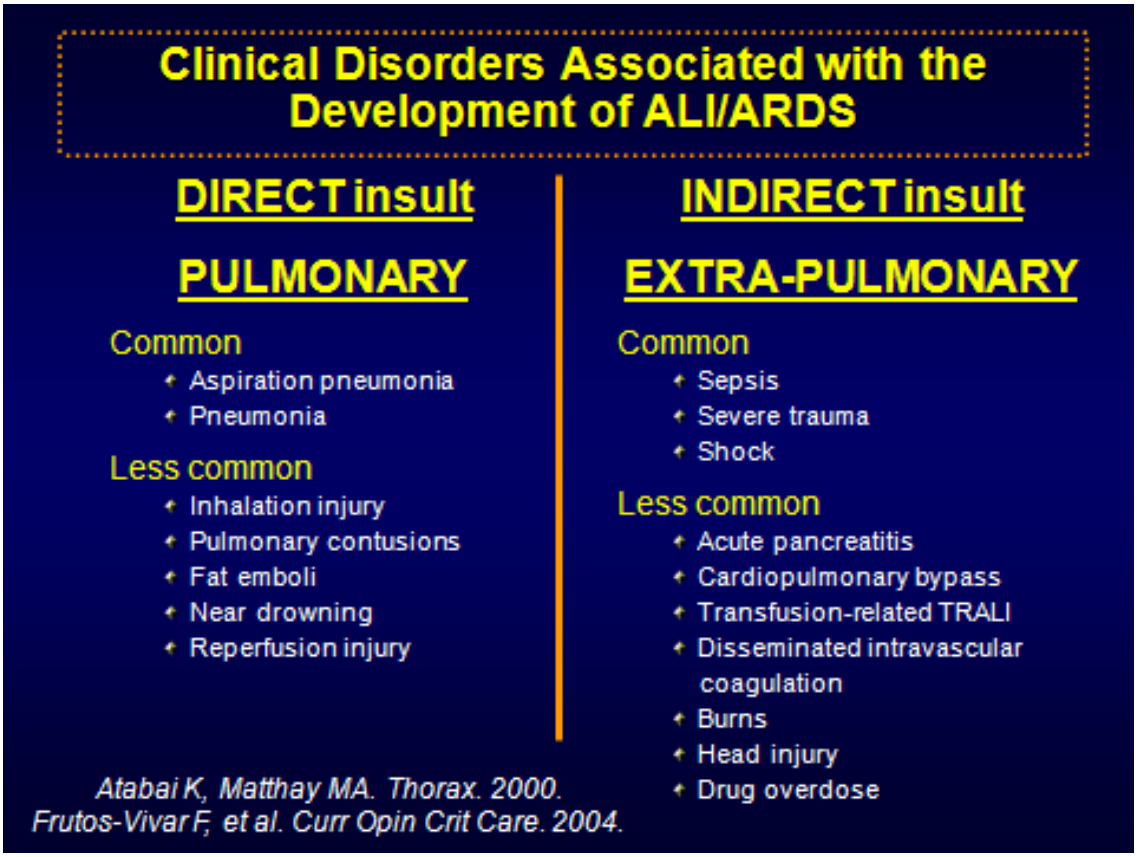


Table 4. Pocket card summary of mechanical ventilation of the trauma patient.

(From: Nathens AB, et al; Inflammation and the Host Response to Injury Investigators. Inflammation and the Host Response to Injury, a large-scale collaborative project: Patient-Oriented Research Core--standard operating procedures for clinical care. I. Guidelines for mechanical ventilation of the trauma patient. J Trauma. 2005 Sep;59(3):764-9.)

Mechanical Ventilation Protocol-Inflammation and the Host Response to Injury

In patients with ALI or established ARDS ($PaO_2/FiO_2 \leq 300$ or $PaO_2/FiO_2 \leq 200$, respectively, with bilateral pulmonary infiltrates) aim for the following within 24 hours of meeting criteria:

(1) Initial tidal volumes may be set at 8 mL/kg predicted body weight (PBW); tidal volumes should be reduced by 1 mL/kg at intervals of < 2 hours until the tidal volume = 6 mL/kg. Tidal volume calculations are based on predicted body weight as follows:
For Males: PBW (kg) = 50+ 2.3 {height (inches)-60}
For Females: PBW (kg)= 45.5 + 2.3 {height (inches)-60}

(2) PaO_2 55-80 mm Hg or SpO2 88%-95% FiO_2/PEEP ratio should be ≤ 5 and PEEP must be ≤ 35 cm H_20

(3) Arterial pH 7.25-7.45 with RR < 35 and $PaCO_2 \geq 25$. HCO_3 infusion may be given if necessary. If pH < 7.15 then Vt may be increased by 1 mL/kg to pH ≥ 7.15 and target plateau pressures (see below) may be exceeded.

(4) Plateau pressures (PP) ≤ 30 cm H_2O Reduce Vt to no less than 4 mL/kg. If Vt < 6 mL/kg and PP <25 then increase Vt until PP = 25-30 or Vt = 6 mL/kg.

Patients not meeting ALI/ARDS criteria can be ventilated using the mode, rate and tidal volume chosen at the treating physician's discretion.

Patients should undergo a daily assessment of their readiness for a spontaneous breathing trial (SBT):

(a) resolution or stabilization of the underlying disease process; (b) no residual effects of neuromuscular blockade; (c) exhibiting respiratory efforts; (d) hemodynamically stable; (e) FiO_2 ≤ 0.5 and PEEP ≤ 8 cm H_2O; (f) PaO2 > 70 mm Hg; (g) Ve<15 L/min; (h) Arterial pH between 7.30-7.50; (i) ICP < 20 cm H_2O. If not ready for an SBT, then return to a comfortable, nonfatiguing mode of ventilator support and reassess daily.

If ready, then the patient should receive **a trial of spontaneous breathing (SBT) on CPAP for 30-90 minutes. Criteria for failure of a SBT:**

(a) RR > 35 for ≥ 5 min; (b) SpO_2 < 90% for ≥ 30 seconds; (c) HR > 140 or increase or decrease of 20% from baseline; (d) SBP >180 mm Hg or < 90 mm Hg; (e) Sustained evidence of respiratory distress; (f) Cardiac instability or dysrhythmias; (g) Arterial pH ≤ 7.32; (h) ICP ≥ 20 cm H_2O. If any criteria are met, the CPAP trial is terminated and patient returned to a nonfatiguing mode of support and rested overnight. Repeat CPAP in the morning.

If patient completes CPAP trial, the following criteria should be assessed to determine readiness for extubation and patient extubated if possible:

(a) does not require suctioning more than Q 4 hours; (b) good spontaneous cough; (c) endotracheal tube cuff leak; (d) no recent upper airway obstruction or stridor; (e) no recent reintubation for bronchial hygiene

References:

[1] Raghavendran K, Napolitano LM. ALI and ARDS: Challenges and Advances. Crit Care Clin. 2011 Jul;27(3):xiii-xiv.

[2] Raghavendran K, Napolitano LM. Definition of ALI/ARDS. Crit Care Clin 2011 Jul;27(3):429-37.

[3] The ARDS Definition Task Force. Acute Respiratory Distress Syndrome: The Berlin Definition JAMA. 2012;307(23):doi:10.1001/jama.2012.5669

[4] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, Stern EJ, Hudson LD. Incidence and outcomes of acute lung injury. N Engl J Med. 2005 Oct 20;353(16):1685-93.

[5] Martin M, Salim A, Murray J, Demetriades D, Belzberg H, Rhee P. The decreasing incidence and mortality of acute respiratory distress syndrome after injury: a 5-year observational study. J Trauma. 2005 Nov;59(5):1107-13.

[6] Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med. 2000 May ;342(18):1334-49.

[7] Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2004;(3):CD004104.

[8] Vital FM, Saconato H, Ladeira MT, Sen A, Hawkes CA, Soares B, Burns KE, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary edema. Cochrane Database Syst Rev. 2008 Jul 16;(3):CD005351.

[9] Burns KE, Adhikari NK, Keenan SP, Meade MO. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. Cochrane Database Syst Rev. 2010 Aug 4;(8):CD004127.

[10] Ram FS, Wellington S, Rowe B, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD004360.

[11] Boldrini R, Fasano L, Nava S. Noninvasive mechanical ventilation. Curr Opin Crit Care. 2011 Dec 18. [Epub ahead of print]

[12] Muscedere J, Dodek P, Keenan S, Fowler R, Cook D, Heyland D; VAP Guidelines Committee and the Canadian Critical Care Trials Group. Comprehensive evidence-based clinical practice guidelines for ventilator-associated pneumonia: prevention. J Crit Care. 2008 Mar;23(1):126-37.

[13] Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intensive Care Med. 2006 Jan;32(1):24-33.

[14] dos Santos CC, Slutsky AS. The contribution of biophysical lung injury to the development of biotrauma. Annu Rev Physiol. 2006;68:585-618.

[15] Singer BD, Corbridge TC. Basic invasive mechanical ventilation. South Med J. 2009 Dec;102(12):1238-45.

[16] Singer BD, Corbridge TC. Pressure modes of invasive mechanical ventilation. South Med J. 2011 Oct;104(10):701-9.

[17] Lellouche F, Brochard L. Advanced closed loops during mechanical ventilation (PAV, NAVA, ASV, SmartCare). Best Pract Res Clin Anaesthesiol. 2009 Mar;23(1):81-93.

[18] Lellouche F, Mancebo J, Jolliet P et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. American Journal of Respiratory and Critical Care Medicine 2006 Oct 15; 174(8): 894–900.

[19] Hemmila MR, Napolitano LM. Severe respiratory failure: Advanced treatment options. Crit Care Med 2006;34 Suppl(9):S278-290.

[20] The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342:1301-1308.

[21] Nathens AB, Johnson JL, Minei JP, Moore EE, Shapiro M, Bankey P, Freeman B, Harbrecht BG, Lowry SF, McKinley B, Moore F, West M, Maier RV; Inflammation and the Host Response to Injury Investigators. Inflammation and the Host Response to Injury, a large-scale collaborative project: Patient-Oriented Research Core--standard operating procedures for clinical care. I. Guidelines for mechanical ventilation of the trauma patient. J Trauma. 2005 Sep;59(3):764-9.

[22] Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. N Engl J Med 2008;359:2095-104

[23] Briel M, Meade M, Mercat A, Brower RG, Talmor D, Walter SD, Slutsky AS, Pullenayegum E, Zhou Q, Cook D, Brochard L, Richard JC, Lamontagne F, Bhatnagar N, Stewart TE, Guyatt G. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA. 2010 Mar 3;303(9):865-73.

[24] Fort P, Farmer C, Westerman J, et al: High frequency oscillatory ventilation for adult respiratory distress syndrome: A pilot study. Crit Care Med 1997; 25:937–947

[25] Mehta S, Lapinsky SE, Hallett DC, et al: Prospective trial of high-frequency oscillation in adults with acute respiratory distress syndrome. Crit Care Med 2001; 29:1360–1369

[26] Sud S, Sud M, Friedrich JO, Meade MO, Ferguson ND, Wunsch H, Adhikari NK. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. BMJ. 2010 May 18;340:c2327.

[27] Ali S, Ferguson ND. High-frequency oscillatory ventilation in ALI/ARDS. Crit Care Clin. 2011 Jul;27(3):487-99.

[28] Imai Y, Slutsky AS: High-frequency oscillatory ventilation and ventilator-induced lung injury. Crit Care Med 2005; 33(3 Suppl):S129–S134

[29] http://www.oscillatetrial.com/

[30] http://www.oscar-trial.org/

[31] Higgins J, Estetter B, Holland D, et al: High-frequency oscillatory ventilation in adults: Respiratory therapy issues. Crit Care Med 2005; 33(Suppl):S196–S203

[32] Napolitano LM, Park PK, Raghavendran K, Bartlett RH. Nonventilatory strategies for patients with life-threatening 2009 H1N1 influenza and severe respiratory failure. Crit Care Med. 2010 Apr;38(4 Suppl):e74-90. Review.

[33] Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. JAMA. 2010 Dec 8;304(22):2521-7.

[34] Fan E, Wilcox ME, Brower RG, Stewart TE, Mehta S, Lapinsky SE, Meade MO, Ferguson ND. Recruitment maneuvers for acute lung injury: a systematic review. Am J Respir Crit Care Med. 2008 Dec 1;178(11):1156-63.

[35] National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006 Jun 15;354(24):2564-75.

[36] Papazian L, Forel JM, Gacouin A, Penot-Ragon C, Perrin G, Loundou A, Jaber S, Arnal JM, Perez D, Seghboyan JM, Constantin JM, Courant P, Lefrant JY, Guérin C, Prat G, Morange S, Roch A; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med. 2010 Sep 16;363(12):1107-16.

[37] Adhikari NK, Burns KE, Friedrich JO, Granton JT, Cook DJ, Meade MO. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ 2007 Apr 14;334(7597):779.

[38] Dickinson S, Park PK, Napolitano LM. Prone-positioning therapy in ARDS.Crit Care Clin 2011 Jul;27(3):511-23.

[39] Abroug F, et al. Crit Care 2011;15(1):R6

[40] Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol. 2010 Jun;76(6):448-54.

[41] Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NK, Latini R, Pesenti A, Guérin C, Mancebo J, Curley MA, Fernandez R, Chan MC, Beuret P, Voggenreiter G, Sud M, Tognoni G, Gattinoni L. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Med. 2010 Apr;36(4):585-99.

[42] Park PK, Napolitano LM, Bartlett RH. Extracorporeal membrane oxygenation in adult acute respiratory distress syndrome. Crit Care Clin. 2011 Jul;27(3):627-46.

[43] Brogan TV, Thiagarajan RR, Rycus PT, Bartlett RH, Bratton SL. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multi-center database. Intensive Care Med 2009 Dec;35(12):2105-14.

[44] http://clinicaltrials.gov/ct2/show/NCT01470703

[45] Medoff BD, Shepard JO, Smith RN, et al: Case 17-2005: A 22-year-old woman with back and leg pain and respiratory failure. N Engl J Med 2005; 352:2425–2434

[46] Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA, Jackson JC, Canonico AE, Light RW, Shintani AK, Thompson JL, Gordon SM, Hall JB, Dittus RS, Bernard GR, Ely EW. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet. 2008 Jan 12;371(9607):126-34.