Chapter 29

MECHANICAL VENTILATION OF THE TRAUMA PATIENT IN THE FIRST 24 HOURS

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INTRODUCTION

Trauma presents an immense global problem to both military and civilian populations. It is the most common cause of death in the first 3 decades of life and the third most common cause of death overall in the civilian population. Injury to the chest contributes to 30% of all combat-related deaths in the current military conflict in Afghanistan and 56% of lethal civilian trauma.1

Trauma to the chest can be classified according to whether the mechanism of injury is penetrating or blunt. Conditions common to both mechanisms of injury include hemothorax, cardiac tamponade, pneumothorax, rib fractures, and flail chest.2 Pulmonary contusion is common in blunt chest trauma, but may also occur in association with high-velocity penetrating injuries. The passage of a shock wave through the pulmonary tissue leads to microscopic disruption at the alveolar-air interface.3 This results in alveolar hemorrhage and parenchymal damage, which becomes maximal at 24 hours. Blast lung injury is an extreme form of pulmonary contusion and should be borne in mind when lung function deteriorates in the absence of signs of external thoracic injury. As the blast wave passes, there is a rapid expansion of the gas-filled alveoli, leading to secondary explosions within the lung.

Regardless of the mechanism of direct injury to the lung, the pathophysiology consists of an initial injury to the parenchyma followed by damage to the alveolar-capillary barrier due to inflammation. Inflammatory infiltrates, capillary leak, atelectasis, and later fibrosis all combine to cause a loss of compliance.4 Injury to the lung can also be incurred by a variety of extrapulmonary insults, including sepsis, aspiration pneumonia, multiple trauma, and massive transfusion.5,6 The relationship between severe injury to the lung and other organ failures in polytrauma is even more complicated. It has been suggested that lung injury can be both the consequence and cause of multiple organ failures.7

The terms acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) have been developed to represent the severity of lung dysfunction without specifying the etiology. The American-European Consensus Conference on ARDS standardized the definition of both terms on the basis of the following: (1) acute onset of respiratory distress; (2) bilateral infiltrates on frontal chest radiograph; (3) absence of left atrial hypertension; (4) a pulmonary capillary wedge pressure of 18 mm Hg or less; (5) severe hypoxemia, which is defined as a PaO2 to fraction of inspired oxygen (FiO2) ratio up to 300 mm Hg in ALI and up to 200 mm Hg in ARDS.8

The wide range of severity in lung injury makes a robust system for concomitant escalation of ventilatory support necessary. This chapter will describe how mechanical ventilation can be safely initiated and appropriately adjusted in the military environment.

PRINCIPLES OF SAFE VENTILATION

The mainstay of managing lung injuries is mechanical ventilation, which replaces or assists the function of the respiratory system. Mechanical ventilation may in itself exacerbate the initial injury by direct mechanical damage, induction of surfactant failure, or stimulation of pulmonary and systemic inflammatory cytokines.9 Improved understanding of the pathophysiology of ARDS has led to the development of safer ventilatory practices.

Tidal Volume

Traditionally, the primary aim of mechanical ventilation was to ensure oxygenation and control arterial carbon dioxide levels. To this end, tidal volumes of up to 15 mL/kg of ideal body weight were employed.10 A large clinical study by the ARDS Network demonstrated that conservative ventilation using tidal volumes up to 6 mL/kg together with a limit of maximum plateau pressure to 30 cm H2O conferred a highly significant improvement in 28-day mortality when compared with traditional ventilation strategies.11 This ventilation strategy is now widely employed to prevent adjuvant ventilator-induced lung injury (VILI), but the strategy’s main drawback is hypoxemia. The degree of hypoxemia that can be safely tolerated remains contentious, but it is clear that a more aggressive oxygenation strategy is necessary in the presence of significant tissue hypoxia manifesting as hemodynamic instability, lactic acidosis, and organ dysfunction.

Monitoring and Optimizing Ventilation

Modern microprocessor technology incorporated into ventilators provides a wide range of monitoring software to optimize interaction between the patient and the ventilator. Clinically useful options include pressure-volume loops, real-time inspiratory and expiratory flow profiles, measurement of intrinsic positive end-expiratory pressure (PEEP), and expiratory capnography. As discussed above, the plateau pressure is a prime target in the strategy of protective
ventilation. However, it should be remembered that the plateau pressure value depends on PEEP and respiratory system compliance. Dynamic flow-volume and flow-pressure loops have become increasingly popular, but they are inferior to static assessments and may underestimate the lung volume at which the upper inflection point is reached.

Positive End-Expiratory Pressure

Increasing PEEP may lead to recruitment of collapsed alveoli and improve the shunt fraction and PaO₂. If the recruitment potential is low, an increase in PEEP may not only have a marginal effect on the shunt fraction, but may also contribute to over-distension of open alveoli and increase the risk of VILI. The potential for recruitment can be identified by the following methods:

1. After a 30-minute trial of increased PEEP, minimal potential for recruitment is identified by minimal change or worsening PaO₂, increased dead space, and worsening compliance.
2. Assessing the shape of the pressure-time curve during delivery of a constant flow inflation can allow estimation of compliance. Worsening compliance is depicted by an upward concavity of the curve, and improved compliance is depicted by a downward concavity. Improving compliance during inflation suggests that the potential for recruitment is high and that an increase in PEEP may be efficacious.
3. Assessing the pressure-volume curve during inflation will yield the pressure at which the lung begins to inflate. Maintenance of PEEP above this lower inflection point will keep recruitable alveoli open at the end of expiration and prevent repetitive recruitment and de-recruitment during the ventilation cycle.
4. Assessing the intrapleural pressure with an esophageal balloon may allow a more precise setting of PEEP above the intrapleural pressure and prevent alveolar collapse. However, the constraints with this measurement technique include artifact or noise from cardiac contractions, compression of the esophagus by mediastinal contents in the supine patient, and nonuniformity in the distribution of pleural pressure; any of these occurrences renders the single site of pressure measurement in the esophagus highly inaccurate.

The optimum level of PEEP and how to determine it remain controversial. Three randomized controlled trials have evaluated modest versus high levels of PEEP in patients with ALI and ARDS.12–14 There was no survival advantage for a higher level of PEEP, but there were lower rates of refractory hypoxemia and use of rescue therapies. Post hoc analysis of this combined data showed that high PEEP levels conferred less benefit and more adverse effects to patients with mild lung injury when compared to patients with ARDS. This finding highlights the importance of making a comprehensive assessment of the potential benefits and risks of high PEEP on an individual basis.

MODE OF VENTILATION

The choice of mode of ventilation primarily depends on local factors, such as the technology available and experience of the physician. A mechanical ventilator employs a flow or pressure generator to deliver an inspiratory volume. Termination of inspiration occurs when inspiratory time, airway pressure, or tidal volume is achieved. Expiration is passive. Cycling to the inspiratory phase usually depends on time but may be triggered by the patient.

Volume-Preset Ventilation

The guarantee of a tidal volume in this mode is attractive, but it is the least forgiving mode and may lead to high airway pressures, gas trapping, and cardiovascular compromise. Additionally, there is no added flow reserve to compensate for leaks. The relatively low rates of flow generated at standard settings may result in homogenous ventilation and perpetuate any existing mismatch of perfusion and ventilation. Modifying this system by adding a pressure limit and increasing the maximum inspiratory flow to over 100 L/min results in a safer and more flexible variant, but it is essentially analogous to pressure-control ventilation. Pressure-regulated volume control is a hybrid mode in which peak inspiratory pressure is minimized for a given preset tidal volume. This mode confers additional safety but has limited ability to compensate for large or variable leaks.

Pressure-Preset Ventilation

The pressure generator system delivers a constant pressure, but flow decreases during the inspiratory
phase. The high initial inspiratory flow rates allow distribution of gas according to local expiratory time constants. Lung units with low levels of intrinsic PEEP are preferentially ventilated early in inspiration, and those with higher levels receive later and overall less ventilation. Together with the intrinsic pressure limit, a protective ventilation strategy is employed with improved matching of ventilation to perfusion. Commonly used pressure-preset modes include pressure-control ventilation and spontaneous variants, such as airway pressure-release ventilation (APRV) and biphasic positive airway pressure ventilation (BIPAP).

Modern ventilators permit a descending ramp of flow with volume-preset modes, which produces a result similar to the pressure-preset modes. The differences between pressure- and volume-preset modes are now relatively minor, and more emphasis is placed on ensuring that the following are tailored to each patient: tidal volume, plateau airway pressure as an estimator of average alveolar pressure at the end of inspiration, PEEP, and inspiratory time.

**Inverse-Ratio Ventilation**

This mode allows a period of inspiration of up to three times greater than the period of expiration. Additional recruitment of alveoli occurs due to the elevation of mean airway pressure and intrinsic PEEP. However, a number of controlled clinical studies have reported minimal or no benefit in patients with ARDS using this mode when compared to conventional ventilation strategies. In fact, inverse-ratio ventilation may confer a significant risk of hemodynamic compromise.

**Spontaneous Ventilation**

In minor cases of pulmonary contusion, supplemental oxygen by mask coupled with good analgesia and chest physiotherapy may be sufficient to prevent hypoxemia. Noninvasive positive pressure ventilation has been described for trauma patients, but there are a number of criteria that preclude its use in this group (Exhibit 29-1). Noninvasive positive pressure ventilation can be applied via a tightly fitting facial mask or nasal pillows. The two modes available apply either a continuous level of positive airway pressure (CPAP) or alternate between two levels of positive pressure during the respiratory cycle (BIPAP).

Modern mechanical ventilators can also permit spontaneous ventilation as part of invasive ventilatory support. A wide range of modes are available to facilitate spontaneous ventilation, but those in most common use are BIPAP and APRV. APRV is a system that intermittently varies two levels of CPAP with a very short expiratory time. The high airway pressure maintains adequate alveolar recruitment and together with the $\text{Fi}_2$ determines oxygenation. Alveolar ventilation is determined by the timing and duration of the pressure release together with the fraction of the cycle dedicated to low airway pressure. An active exhalation valve allows the patient to breathe spontaneously throughout the ventilator cycle. A time ratio for high to low airway pressures of up to 9:1 can be used, which maximizes recruitment. However, if too little time is allocated to low airway pressures, expiration may be incomplete. Crossover studies reported lower inflation pressures, improved oxygenation, and lower sedation requirements when this mode was compared with a pressure-preset mode. Two small randomized clinical trials suggested APRV was superior to conventional ventilation. However, this finding may not be relevant to current clinical practice because the definition of conventional ventilation is now markedly different.

Invasive BIPAP ventilation can be used along a spectrum from total mandatory ventilation to a single level of CPAP, through various intermittent mandatory and patient-triggered options. The benefits of this mode include an inherent pressure limit, reduction in shearing forces attributed to a half-sinusoid inspiratory flow pattern in spontaneous modes, additional recruitment of alveoli afforded by spontaneous variation in the depth of breathing, compensation for leaks, a pressure-generator gas distribution profile, and lower sedation requirements.

**Independent Lung Ventilation**

Independent lung ventilation (ILV) allows independent management of the lungs in the presence of the asymmetrical pulmonary pathologies listed in Exhibit 29-2. It is an obvious extension to the practice of one-
lungs of up to 80 mm Hg can be generated if the cuff is designed to contain a high volume and confer low pressures. However, high pressures of up to 80 mm Hg can be generated if the cuff is inflated beyond the sealing pressure. The potential for displacement of the DLT during prolonged management is well recognized and a major drawback to its widespread application. Left-sided tubes should be placed when possible because the right upper lobe bronchus is relatively easily occluded with small displacements of a right-sided DLT.

ILV can involve either one or two lungs. The former involves blocking one of the lungs to control and contain the spread of harmful fluid and secretions while the other lung is ventilated. The latter involves administration of different modes of ventilation to each lung using independent ventilator circuits. Initial ventilator settings should correspond to the practice of safe ventilation, but with adjustment for lung volumes of 55% on the right and 45% on the left. The lungs can be inflated synchronously or asynchronously. In theory, synchronization may prevent unfavorable mediastinal shift, but there is no evidence that this is a significant problem in clinical practice. Synchronization with the cardiac cycle has also been proposed, but this is of physiological interest rather than clinical importance.

In practice, effective ILV mainly involves asynchronous ventilation because of the heterogeneous nature of the majority of lung injuries. Meticulous attention to monitoring the airway pressures of each lung is required to prevent barotrauma to the less diseased lung. PEEP is applied in amounts inversely proportional to the compliance of the lung with the aim of equalizing the functional residual capacities. Equalization of the tidal volumes and end tidal CO₂ is one of many possible criteria that may indicate suitability for conversion to conventional ventilation. Although there are reports of successful use of ILV in the setting of ARDS and other bilateral lung injuries, it remains controversial.28-30

**High-Frequency Ventilation**

High-frequency technology has been utilized in thoracic and airway surgery since the early 1970s, but its role in the critical care setting is yet to be defined. Implementation of high-frequency jet ventilation and high-frequency percussive ventilation has been associated with reduced VILI31,32 and improved oxygenation,33-35 respectively. However, use of these devices requires a high level of technical expertise that is currently available only in thoracic centers.

High-frequency oscillatory ventilation (HFOV) is currently available at United Kingdom (UK) Role 4 facilities and has been used in cases that are refractory to conventional ventilation. The oscillators can operate at frequencies up to 3,000 breaths per minute because an active expiratory phase is incorporated. A high mean airway pressure is employed, and the ventilator oscillates the gas delivered to pressures above and below this pressure. Oxygenation depends on the mean airway pressure and FIO₂ whereas elimination of CO₂ depends on the frequency and amplitude of the oscillating pressure. Small tidal volumes are delivered because a large proportion of pressure is dissipated in the proximal airways. Lower volume delivery coupled with high mean airway pressure facilitates alveolar recruitment without the risk of over-distension. The following ventilator settings should be applied initially and then titrated according to requirements: FIO₂ of 1.0, frequency of 10 Hz, mean airway pressure of 5 cm H₂O above the current ventilator settings, cycle volume of 100 mL, and a base flow of 20 L/min.

Small observational studies have shown that HFOV is both effective and safe in the management of adult patients with severe ARDS.38-39 A systematic review of randomized controlled trials comparing HFOV to conventional ventilation in adults and children with ALI or ARDS has shown improved oxygenation with a concomitant decrease in mortality.40 Separate assessment of the data from the adult trials demonstrates an improvement in oxygenation with HFOV without a benefit to mortality. This ambiguity prompted the initiation of two large multicenter randomized controlled trials designed to compare HFOV with conventional positive pressure ventilation.41,42 Both trials recruited a broadly similar set of patients with moderate to se-

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**EXHIBIT 29-2**

**ASYMMETRICAL PULMONARY PATHOLOGIES**

- Airway protection in massive hemoptyisis or purulent disease
- Unilateral lung disease with marked mismatching of ventilation to perfusion, including:
  - Acute respiratory distress syndrome
  - Pneumonia
  - Pulmonary contusion
  - Pulmonary hemorrhage
- Bronchopleural fistula
- Severe unilateral airway obstruction

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"Mechanical Ventilation of the Trauma Patient in the First 24 Hours"
vere ARDS. The High Frequency OSCillation in ARDS (OSCAR) Trial demonstrated no difference in mortality at 30 days for patients treated with HFOV compared to those treated with conventional ventilation. The Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) trial was stopped after 548 of the planned 1,200 patients had undergone randomization to HFOV or conventional ventilation because there was an excess mortality of 12% in the former treatment group.

On further analysis, patients managed with HFOV had a higher requirement for inotropic agents when compared to those treated with conventional ventilation. This may be a consequence of an increase in after-load for the right ventricle by virtue of high intrathoracic pressures during HFOV. It may be significant that the OSCAR trial used lower airway pressures during HFOV and did not demonstrate this excess in mortality or a high requirement for inotropic agents. Although the OSCILLATE trial suggests that HFOV is injurious, there are many confounding factors. In particular, the mortality rate in the group managed with conventional ventilation is very low. It is possible that the conventional ventilation strategy of high PEEP and low lung volumes is particularly effective. As a consequence, the authors of both trials do not recommend HFOV for the routine care of patients with ARDS. In accordance with this recommendation, the ventilator is not currently used in the deployed military hospitals.

**ADJUNCTS TO MECHANICAL VENTILATION**

**Neuromuscular Blocking Agents**

Administration of neuromuscular blocking agents (NMBAs) has been shown to improve oxygenation in patients receiving a protective ventilation strategy for ALI or ARDS. It is postulated that this effect may be attributed to improved synchronization with the ventilator, thereby facilitating accurate adjustment of tidal volume and pressure levels. A concurrent reduction in pro-inflammatory cytokines has also been seen in this setting. The suggestion that NMBAs may modulate inflammation requires more research. A recent multi-center trial has reported that the use of NMBAs improves oxygenation and decreases mortality at 90 days, increases number of days outside the critical care unit, and increases number of days without mechanical ventilation. Despite these promising findings, it should be appreciated that the use of NMBAs in the critical care setting confers the risk of prolonged weakness from myopathy, especially if high-dose corticosteroids are concurrently administered.

**Recruitment Maneuvers**

A variety of techniques have been described to achieve a transient increase in transpulmonary pressure and thus recruit collapsed alveoli. There are many reports of an initial improvement in oxygenation followed by rapid resolution of this beneficial effect within 20 minutes of the maneuver. However, application of higher levels of PEEP after the recruitment maneuver may sustain the effect. The potential for recruitment of alveoli varies widely among patients, and there is no formula for the duration, pressure, or frequency of recruitment maneuvers. The most common complications are hypotension and desaturation. Barotrauma and induction of arrhythmias are relatively rare events.

**Prone Positioning**

A number of trials have demonstrated an improvement in oxygenation when patients with ALI or ARDS are placed in the prone position. This effect has not been translated into a definite improvement in mortality. However, a subsequent metaanalysis showed that the method conferred a benefit to mortality in patients with severe ARDS. The possible mechanisms involved in the improvement in oxygenation are recruitment of collapsed alveoli; redistribution of ventilation toward the dorsal regions in an attempt to match perfusion; and elimination of compression of the lungs by the heart. The problems associated with prone positioning include dislodgment of tracheal tubes and intravascular catheters, increased intraabdominal pressure, facial edema, and ophthalmic injury. However, the technique has been safely applied to trauma patients.

**Nitric Oxide**

Inhaled nitric oxide causes selective vasodilation of the pulmonary blood vessels in ventilated lung units and may improve matching of perfusion to ventilation. Although the therapy has been shown to improve oxygenation, it has not been translated into clinically beneficial outcomes. It is not available in the deployed setting.

**Conservative Fluid Management**

Alveolar-capillary injury in ARDS is particularly
characterized by pulmonary edema. The edema has a negative impact on the mechanics of ventilation. Patients with ARDS typically accumulate one liter of fluid per day when managed with a conventional strategy of fluid administration. Although several randomized controlled trials have indicated that a more conservative approach to fluid management may confer clinical benefit, a recent large multicenter trial has reported only a modest improvement in oxygenation. There is evidence that more efficacious fluid removal using diuretics, with concomitant colloid infusion, confers an improvement in oxygenation during the early phase of ventilatory management. However, an ideal strategy has yet to be elucidated and current emphasis remains on balancing the ventilatory benefits with hemodynamic requirements.

EXTRACORPOREAL MEMBRANE OXYGENATION

The goal of extracorporeal membrane oxygenation (ECMO) is to support gas exchange while allowing a reduction in the intensity of mechanical ventilation. A veno-venous or veno-arterial catheter is utilized to remove blood from the patient and circulate it through an artificial lung back to the patient. In 1972, Hill and colleagues first successfully applied the system for managing pulmonary failure secondary to trauma. Subsequently, trials have failed to demonstrate any benefit to survival when compared to mechanical ventilation. Although the most recent trial demonstrated that management with ECMO improved survival of patients with severe ARDS, the lack of standardized management of the control group makes definite conclusions difficult. Coupled with the significant risk of complications, the ECMO’s role in treating patients with refractory hypoxemia is likely to remain controversial in the UK.

Only a few facilities around the world have the capability of providing this therapy. In the military environment, the United States has the capability to deploy adult ECMO support teams. However, recent technological advances have yielded devices that could be more readily used in the military environment. The Lifebridge (Ampfing, Germany) B2T “Bridge to Therapy” system is a miniaturized ECMO system weighing only 18 kg that can deliver flows of 6 L/min. The Novalung (Heilbronn, Germany) system uses arterial pressure to drive blood across a membrane to remove CO2 only. Although it offers fewer treatment options than ECMO, it is easier to manage and is compact, weighing only 653 g.

TRANSFER VENTILATORS AND THEIR LIMITATIONS

Intubated patients require continued airway protection and ventilation during transfer. Transfer ventilators (also commonly referred to as transport ventilators) are usually specially designed for this purpose. Although a manually ventilated patient, using a bag and simple oxygen tubing, could be safely transferred for a very short period of time, the safer and more conventional method is to use a mechanical ventilator. This becomes essential, for example, in head-injured patients who require more accurate and stable ventilatory control. Transfer ventilators vary greatly in design and complexity from a simple intermittent blower to a ventilator with more advanced ventilatory modes; some are even able to support noninvasive ventilation. Many designs are in use by aeromedical evacuation teams around the world.

Transfer ventilators are expected to be operated in different and changing environments, whereas normal intensive care unit ventilators are set up and operated in a stable situation. A transfer ventilator may be moved with the patient three or four times. In the modern military environment this may entail exposure to extremes of temperature, humidity, and barometric pressure. In addition, equipment must be robustly built to withstand austere environments without being physically damaged. Transfer ventilators must be securely mounted for tactical flight maneuvers.

Oxygen delivered to the patient is usually expressed as an inspired concentration (FiO2), which stays the same with changes in altitude, if nothing else changes. The partial pressure of the inspired oxygen (Pao2) will decrease with an increase in altitude. If a ventilator does not compensate for altitude change, the medical team will have to increase FiO2. For example, on ascent from sea level to 7,000 feet, with a starting FiO2 of 0.4, FiO2 decreases from about 300 mm Hg (40 kPa) to 234 mm Hg (31 kPa). FiO2 would have to be increased from 0.4 to 0.52 to compensate. Airway pressures and delivered volumes may also change with altitude changes unless the ventilator compensates. In recognition of this potential hazard, each ventilator used for military aeromedical transfer is assessed in the controlled circumstances of a hypobaric chamber. The ventilator also undergoes tests to ensure that it is compatible and safe for use in a military aircraft.

Alarms in intensive care unit ventilators are visual and audible. In the aircraft environment, particularly in helicopters, audible alarms might not be heard,
and greater reliance is placed on visual alarms. Visual alarms on the ventilator should be in addition to visual capnography and pulse oximetry alarms on a separate monitor. The alarm system should be able to warn of the common and potentially dangerous situations of breathing circuit disconnection or endotracheal tube dislodgment during patient transfers in dark and noisy environments. Alarm lighting should not interfere with aircrew night vision equipment in a combat situation.

The requirements for adequate oxygen and electricity supplies for the ventilator are no different for ground or air transfers and are usually ensured by carrying spare oxygen cylinders and batteries. For longer transfers, the ability to use aircraft oxygen and electricity is an obvious advantage, but must be part of the larger process of equipment/aircraft integration. If high-pressure oxygen supply and batteries fail, there should be provision for manual ventilation with low-pressure oxygen, or air as a last resort. Decreasing cabin altitude might be necessary to maintain adequate oxygenation.

An ideal transfer ventilator would have the following characteristics:

- small size and low weight;
- wide range of operating temperatures and altitudes appropriate for proposed environments;
- ability to compensate for altitude changes with oxygen concentration, airway pressure, and delivered volumes;
- ability to ventilate complex patients (a number of different modes);
- long battery life and ability to use aircraft electricity supplies;
- fail-safe mode (ability to maintain operation when electricity supply fails);
- ability to use aircraft oxygen supplies and oxygen from different sources and connectors;
- controls and displays that are visible at night and are compatible with aircraft operations;
- alarms that are noticeable in a noisy environment; and
- ability to be mounted securely with the patient.

Although the ideal ventilator for all conditions does not yet exist, transfer ventilators have been used successfully for thousands of critical care air transfers despite their limitations. Only in exceptional circumstances should the deployed physician use a ventilator other than one designed for transfer, particularly in an aeromedical setting. Each user should be appropriately trained to understand the limitations of the ventilator, in particular the longevity of its power source. Alternate means of ventilation should be immediately available.

CONCLUSION

Patients with severe lung injury can present significant challenges to the military intensivist. The primary aim is to employ a ventilatory strategy that minimizes further injury to the lung. Rescue therapies may be considered in patients who develop refractory hypoxemia, but because of the lack of conclusive evidence and definitive guidelines, physicians must have a comprehensive understanding of the capabilities and drawbacks of each therapy.

REFERENCES


