Hypoxemic Respiratory Failure. VILI

24

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Abstract

Acute hypoxemic respiratory failure (AHRF) is severe arterial hypoxemia that is refractory to supplemental oxygen and could be caused by pneumonia, cardiogenic pulmonary edema, ARDS, and chronic obstructive pulmonary disease (COPD). ARDS is an important syndrome of noncardiogenic edema in which the most common risk factors include pneumonia, nonpulmonary sepsis, and aspiration (Stefan et al., J Hosp Med, 8:79–82, 2013).

Ventilator-induced lung injury is the acute lung injury inflicted or aggravated by mechanical ventilation during treatment and has the potential to cause significant morbidity and mortality. The predominant mechanisms by which the ventilator-induced lung injury occurs include alveolar overdistention (volutrauma), barotrauma, atelectotrauma, and inflammation (biotrauma).

Keywords

Acute hypoxemic respiratory failure
Ventilator-induced lung injury · Volutrauma
Barotrauma · Atelectrauma · Biotrauma

Abbreviations

AHRF	Acute hypoxemic respiratory failure
ALI	Acute lung injury
APRV	Airway pressure release ventilation
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
CPAP	Continue positive airway pressure
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
HFOV	High-frequency oscillatory ventilation
HFPV	The high-frequency percussive ventilation
IPF	Idiopathic pulmonary fibrosis
P plat	Pressure of plateau
PE	Pulmonary embolism
PEEP	Positive end expiratory pressure
PFO	Patent foramen ovale
PP	Prone positioning
RCT	Randomized controlled study
VILI	Ventilator-induced lung injury

24.1 Introduction

Hypoxemia refers to low oxygen content in arterial blood, and there are several factors that impact this state: oxygen content of inspired gas,

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the matching of blood and alveolar gas, and amount of Hb in blood and its binding properties. Hypoxemia is defined as a partial pressure of oxygen of less than 80 mm Hg or arterial blood hemoglobin saturation of less than 95%.

The mechanisms of hypoxemia are as follows:

- Hypoventilation, as in narcotic overdose, head injury, airway obstruction, and neuromuscular weakness.
- Right-to-left shunt (anatomic or physiologic): PFO (patent foramen ovale), congenital cardiac disease, vascular malformations, atelectasis, pneumonia, and pulmonary edema.
- Ventilation/perfusion ratio mismatch: PE (pulmonary embolism) and COPD.
- Impaired diffusion: IPF (idiopathic pulmonary fibrosis).
- Low inspired oxygen: altitude.

24.1.1 VILI

Ventilator-induced lung injury (VILI) is an acute failure of pulmonary parenchyma caused by mechanical ventilation. It is characterized both by macroscopic damage that is pneumothorax and pneumomediastinum that represent the classic barotrauma and by microscopic injury like the alteration of alveolocapillary membrane, the degeneration of surfactant, and inflammatory modification very similar to the ones described in acute respiratory distress syndrome (ARDS).

The predominant mechanisms by which the ventilator-induced lung injury occurs include alveolar barotrauma, overdistention (volutrauma), atelectotrauma, and inflammation (biotrauma). Other mechanisms that are attributed include adverse heart-lung interactions, deflation related, and effort induced injuries. Related factors being studied in this context also include heterogeneous local lung mechanics, alveolar stress frequency, and stress failure of pulmonary capillaries. Variation in the expression of genetically determined inflammatory mediators has been known to affect VILI susceptibility [2].

Barotrauma is a pressure-related lung injury. It is defined as the presence of extraalveolar air in locations, where it is not normally found in patients receiving mechanical ventilation caused by high transpulmonary pressure. It may occur even at lower airway pressure if pleural pressure is very negative (e.g., forceful inspiratory effort). It includes pneumothorax and pneumomediastinum that can be found in lung X-ray in patients in high-pressure mechanical ventilation. Sometimes, there was also the presence of embolism above all in lower lung regions.

Volutrauma is lung injury caused by alveolar overdistension. It is caused by a ventilation based on high tidal volumes and high transpulmonary pressure.

Cyclical opening and closing of the atelectatic alveoli during the respiratory cycle could damage the adjacent non- atelectatic alveoli and airways by shear stress forces. This mechanism is called atelectotrauma. For atelectatic alveoli, high shear stress is generated during recruitment at the interface between the air bolus and collapsed airway, causing mechanical injury [3]. For flooded alveoli, formation and destruction of foam bubbles at the gas–liquid interface of flooded alveoli contribute additional local interfacial stress that disrupts plasma membrane–cytoskeletal adhesions and leads to lung injury [4]. The use of positive end expiratory pressure (PEEP) can prevent this damage because it avoids the continuous opening and collapse of alveolus, reducing also the inflammatory response associated with it. The application of optimal PEEP is important in the prevention of atelectrauma. Higher PEEP can cause alveolar overdistension, and lower PEEP may be inadequate to stabilize the alveoli and keep them open.

Biotrauma is the release of inflammatory mediators from the cells in the injured lungs in response to volutrauma and atelectotrauma. In ventilator-induced lung injury, the neutrophils, macrophages, and probably alveolar epithelial cells secrete various inflammatory mediators, including TNF-alpha, interleukins 6 & 8, transcription factor nuclear factor(NF)-kB, and matrix metalloproteinase-9. These cytokines could trigger detrimental effects locally and systemically, resulting in multiorgan failure.

24.2 Discussion and Analysis of the Main Topic

Given that mechanical ventilatory support with high volumes and pressures can cause preventable morbidity and mortality in critically ill patient, the first two mechanisms that were described at the basis of VILI were barotrauma and volutrauma. In fact, in 2000, the ARDS Network trial established that limiting tidal volume (6 vs. 12 ml/kg predicted body weight) and plateau airway pressure (</= 30 vs. </= 50 cmH_2O) brought a major survival in patients with ARDS.

The main cause of VILI is represented by transpulmonary pressure, which is the difference between alveolar pressure and pleural pressure, the difference between the pressure inside and the pressure outside the lung [3, 4].

There is a strong relation between transpulmonary pressure and tidal volume and a given lung volume produces a defined transpulmonary pressure. The alveoli are likened to balloon-like structures that stretch during insufflation of the tidal volume. In this phase, the alveolar walls seem to unfold so as to minimize this stretching up to the volume limit which corresponds to the total lung capacity. The stretching of the alveolar walls produces a rapid migration of lipids toward the plasma membranes so as to increase the cell surface and prevent its rupture [3, 5, 6].

When this inflammatory response is overwhelmed because a tidal volume greater than the total pulmonary capacity is insufflated, a systemic response and barrier damage with alveolar and interstitial edema, rupture of the joints and bubbles in the alveolar-capillary interstitium are triggered.

The other mechanism responsible for VILI is atelectrauma, which occurs through the cyclical opening and closing of the alveolar units. For atelectatic alveoli, shear forces that cause the mechanical damage come into play; in the edematous alveoli, on the other hand, air bubbles are formed and destroyed in the liquid–gas interface, which causes the destruction of the cellular junctions, at the basis of the microscopic lung damage. Low tidal volume ventilation may reduce the likelihood of atelectrauma because it avoids the exceeding of the critical opening pressure of the collapsed lung units. In addition, the role of PEEP is fundamental because of sustained recruitment and may prevent atelectrauma.

Finally, biotrauma is caused by an extensive biological response, including the activation of proinflammatory and proinjurious cytokine cascade that promote pulmonary and extrapulmonary organ injury. Epithelial surface area of adult lung is estimated to be 65–84 m^2; for this reason, the biological response undergoes an amplification mechanism as the entire volume of blood passes through the pulmonary filter with consequent damage at a systemic level and multiorgan failure syndrome.

Both the magnitude and frequency of peak alveolar stretch likely contribute to VILI in human studies, the use of infrequent high-volume breaths, like recruitment maneuvers, do not seem to cause lung injury, whereas the delivery of high tidal volumes with every breath worsens VILI and ARDS. For this reason, the right ventilation strategy of a patient with ARDS is to use low tidal volumes and high PEEPs.

There are risk scores that can be used to stratify the risk of developing a VILI: the lung injury prediction score (LIPS) and the early acute lung injury score. The first one is a score used to identify patients at risk for ARDS in the emergency department (ED). The second one is based on similar parameters:

- Oxygen requirement.
- Maximal respiratory rate.
- Baseline immune suppression.

These predictors accurately identify patients who can progress to acute lung injury requiring positive pressure ventilation (1 point for oxygen requirement >2–6 L/min or 2 points for >6 L/min; 1 point each for a respiratory rate ≥ 30 and immune suppression). An early acute lung injury score greater than or equal to 2 identified patients who progressed to acute lung injury with 89% sensitivity and 75% specificity.

Through these scores, patients at risk of developing lung damage from mechanical ventilation are identified but it is not possible to plan strategies to prevent the damage itself.

VILI prevention strategies in patients at risk include the following:

- Limitation of tidal volume (</ = 8 ml/kg PBW) in order to prevent volutrauma, decrease barotrauma, shear forces via smaller volume inflation of aerated alveoli adjacent to flooded/atelectatic alveoli and atelectrauma.
- Limitation of the inspiratory pressure to reduce the plateau pressure, the driving pressure or the transpulmonary pressure.
- Use a level of PEEP that maintains positive lung distending transpulmonary pressure at end-expiration leading to minimizing dependent collaps, but, at the same time, avoiding barotrauma.
- The use of prone position for at least 16 h to improve lung homogeneity and decrease shear forces.
- Respiratory rate limitation, to maintain either the lowest pH possible or the highest allowed $PaCO_2$. This strategy may require deep sedation, curarization, as well as extracorporeal CO_2 removal techniques.
- Limitation of respiratory effort through increased sedation and curarization to reduce expiratory effort and prevent cyclic derecruitment (atelectrauma).

The Berlin criteria categorize the severity of hypoxemia with a minimum positive end-expiratory pressure (PEEP) of 5 cmH_2O. On the basis of this definition, severe ARDS is defined as a PsO_2/FiO_2 </= 100 mmHg, moderate ARDS with a paO_2/FiO_2 between 100 mmHg and 200 mmHg, and mild ARDS with a PaO_2/FiO_2 >/= 200 mmHg. Several recent studies have focused on patients with ARDS in whom PaO_2/FiO_2 is <150 mmHg. This kind of ARDS is defined severe-moderate/severe ARDS, and it includes all patients most likely to respond to interventions such as prone positioning (PP) and neuromuscular blockade.

For patients suffering from severe respiratory failure volume-control and pressure-control modes are preferred, possibly associated with paralysis and deep sedation of the patient. The target tidal volume should be between 4 and 8 ml/kg predicted body weight and reduced to 4 ml/kg if the pressure of plateau (Pplat) exceeds 30 cmH_2O. In obese subjects, in abdominal hypertension, and in spinal deformities, conditions in which the chest wall exerts a collapsing effect on the lungs, it is safer to use a plateau pressure greater than 30 cmH_2O as long as an acceptable transpulmonary pressure is maintained. Gattinoni et al. [7] have suggested that the transpulmonary pressure should not exceed 22/23 cmH_2O since patients with ARDS suffer from a significant reduction of the lung parenchyma in which atelectatic areas are flanked by normally ventilated areas and, they can experience overdistension. For these reasons, patients with ARDS must receive protective mechanical ventilation with permissive hypercapnia. An important concept concerns the driving pressure mechanism which represents the difference between Pplat and PEEP.

Recent studies have correlated the driving pressure with patient outcome: the relative risk of death is >1 when the driving pressure > 15 cmH_2O.

24.2.1 Peep

The first step to optimize oxygenation and ventilation in patients with refractory hypoxemia is setting an optimal PEEP. In subjects with moderate and severe ARDS, hospital mortality was 34% with higher PEEPs and 39% with lower PEEPs. In subjects with mild ARDS, on the other hand, mortality was 27% with higher PEEP levels and 19% with lower levels. These data suggest that only patients with severe and moderate ARDS (P/F < 150 mmHg) benefit from higher end-expiratory pressures while those with mild ARDS do not derive any benefit from high PEEPs which can even be harmful.

Chiumello et al. [8] have shown that in the best PEEP trial, it is necessary to consider the changes in oxygenation reached after 5 min from the setting of a certain value of PEEP, while to evaluate the trend, it is necessary to wait 60 min or even more. The benefit of using PEEP in patients with refractory hypoxemia depends on the potential degree of alveolar recruitment. Gattinoni et al. [7] suggested that the same PEEP levels should be applied in patients with lungs with high and low recruitment potential and that choosing PEEP based on FiO_2 is the best choice. On the basis of the severity of

ARDS, the various levels of PEEP are set: 5–10 cmH_2O in mild ARDS, 10–15 cmH_2O in moderate ARDS, 15–20 cmH_2O in severe ARDS.

The choice of a PEEP suitable for the patient's respiratory mechanics is an essential aspect of proper ventilation. It is a balance between recruitment and overrelaxation. Goligher et al. [9] reported that an increase in P/F with an increase in PEEP is associated with a lower mortality, while a decrease in the P/F ratio after an increase in PEEP is associated with a higher mortality.

24.2.2 Recruitment Maneuvers

A recruitment maneuver is a transient increase in transpulmonary pressure in order to promote the reopening of collapsed alveoli, improving gas exchange and the distribution of volume in the lungs.

There are two possible approaches:

- Sustained high-pressure inflation using pressures of 30–40 cm H_2O for 30–40 s,
- A stepwise increase in PEEP with a constant Delta P or a fixed tidal volume.

Kenan et al., [10] suggested that stepwise recruitment maneuvers are more effective than abrupt applications of high peak pressure with less adverse hemodynamic effects.

One way to set the PEEP correctly is to perform a recruitment maneuver followed by a decreasing titration of the PEEP. The decremental titration is achieved by setting the positive pressure of finer expiration from 20 to 25 cmH_2O and then lowering it by 2 or 3 cmH_2O every 4/5 min. The correct level of PEEP is set to the value that can ensure good oxygenation and good compliance of the respiratory system.

There are also unconventional modes of ventilation used to treat refractory hypoxemic respiratory failure such as the high-frequency oscillatory ventilation (HFOV), the high-frequency percussive ventilation (HFPV), and airway pressure release ventilation (APRV).

HFOV delivers very low tidal volume (1–2 ml/kg) at high frequency (3–15 Hz/min). HFPV consists of pneumatically powered, pressure-limited, time-cycled, and flow-interrupted breaths with biphasic percussions. It generates pulses of subtidal volume that produce intrapulmonary percussive waves. These kinds of ventilation facilitate clearance of secretions, lung recruitment and reduce the need for sedation.

APRV applies CPAP (P high) for a prolonged time (T high) to maintain adequate lung volume and alveolar recruitment, with a time-cycled release phase to a lower set of pressure (P low) for a short period of time (T low) or (release time) where most of ventilation and CO_2 removal occurs.

24.2.3 ECMO

Extracorporeal membrane oxygenation, plays a crucial role in the management of acute hypoxemic respiratory failure. To perform standard respiratory ECMO, two vascular accesses are established, one for removal of venous blood and the other for infusion of oxygenated blood. Blood is drained from a major vein and pumped through a circuit that includes an oxygenator, which oxygenates the blood and removes carbon dioxide (CO_2), after which the oxygenated blood is returned via the other cannula. When blood is returned to the venous side of the circulation, the procedure is known as veno-venous ECMO (VV ECMO), which provides gas exchange but cannot give cardiac support. When blood is returned to the arterial side of the circulation, this is called veno-arterial ECMO (VA ECMO), and it can be employed for both gas exchange and cardiac support. Initiation of ECMO for adult ARDS should be considered when conventional therapy cannot maintain adequate oxygenation. Although there are no universally accepted criteria for ECMO initiation in ARDS, severe hypoxemia (PaO_2 to FiO_2 ratio < 80), uncompensated hypercapnia with acidemia (pH < 7.15), or excessively high end-inspiratory plateau pressures (>35–45 cm of water), despite standard of care ventilator management, have been proposed as reasonable indications for ECMO. ECMO can stabilize gas exchange and haemodynamic compromise, consequently preventing further hypoxic organ damage.

24.3 Conclusion Discussion

Treatment strategies for acute respiratory failure therefore include the use of a protective ventilation with low tidal volumes, high respiratory rates, and high PEEP values. This strategy allows to ventilate the hypoxemic patient by limiting the damage from pulmonary overdistension, which is responsible for barotrauma and volutrauma. The use of high positive pressure values at the end of expiration allows to recruit the alveoli, which would tend to collapse at the end of each respiratory cycle and to keep them open in order to avoid the formation of areas of atelectasis. The mode of ventilation that should preferably be used in these conditions is a mechanical ventilation with volume or pressure control that also limits the effort of the respiratory muscles. If the attempted controlled ventilation fails, additional strategies may be used including prone position, intermittent high-frequency ventilation, and ultimately, ECMO.

VILI is a pulmonary injury caused by mechanical ventilation. Its mechanisms are similar to those of ARDS because they recognize the same pathophysiology. In order to prevent barotrauma, atelectrauma, volutrauma and biotrauma, we use the same ventilatory strategy used for the treatment of ARDS. The goal of supportive therapy with artificial ventilation has changed over time, passing from normalization of plasma oxygenation and $PaCO_2$ values, at the cost of using high pressures or tidal volumes, to a ventilatory strategy based on the protection of the lung parenchyma in order to avoid alveolar overdistension and maintain its recruitment.

Key Major Recommendations

- VILI is a pulmonary damage caused by mechanical ventilation and multiple mechanisms have been described: barotrauma, volutrauma, atelectrauma, and biotrauma.
- VILI prevention strategies include limitation of tidal volume, use of PEEP, and limitation of the inspiratory pressure.
- PEEP is the first step to optimize oxygenation.
- Recruitment maneuvers consists of a transient increase in transpulmonary pressure that can reopen previously collapsed alveoli.
- ECMO provides an alternative to rescue patients with severe respiratory failure that conventional mechanical ventilation fails to maintain adequate gas exchange.

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