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Ventilator-Induced Lung Injury and Acute Respiratory Distress Syndrome: A Basic Science Review

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Abstract

Acute respiratory distress syndrome is the most severe manifestation of acute lung injury and it is associated with high mortality rate. Despite better understanding of ARDS pathophysiology, its mechanism is still unclear. Mechanical ventilation is the main ARDS supportive treatment. However, mechanical ventilation is a non-physiologic process and complications are associated with its application. Mechanical ventilation may induce lung injury, referred to as ventilator-induced lung injury. Frequently, VILI is related to macroscopic injuries associated with alveolar rupture. The present article is a review of the literature on ventilator-induced lung injury in acute respiratory distress syndrome. Animal and human studies were reviewed. We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications.

Keywords: Ventilator-induced lung injury; Mechanical ventilation; Acute lung injury; Acute respiratory distress syndrome

Introduction

Acute respiratory distress syndrome (ARDS) is the most severe manifestation of acute lung injury (ALI) and is relatively common in the ICU setting [1-3]. Despite advances in our understanding of the pathophysiology and management of ALI/ARDS, it is still associated with high mortality rate [4-6]. Mechanical ventilation (MV) is the main ARDS supportive treatment [5]. It is intended to deliver air/oxygen at tidal volumes and frequencies sufficient to provide adequate alveolar ventilation to reduce the work of breathing and to improve oxygenation. However, MV is a non-physiologic process, and complications are associated with its application, including increased risk of pneumonia, impaired cardiac performance and lung injury. During MV, pressures, gas volumes, respiratory rates, and concentration of inspired oxygen are often applied at values that exceed those normally experienced by healthy lungs during spontaneous breathing [7]. Mechanical ventilation may induce lung injury, referred to as ventilator-induced lung injury (VILI). Frequently, VILI is related to macroscopic injuries associated with alveolar rupture. Clinical manifestations include interstitial emphysema, pneumothorax, pneumomediastinum, and pneumoperitonium [7]. It is generally accepted that alveolar stretch applied to the lung parenchyma, induced by either large inspired tidal volumes (volutrauma) or high ventilator pressures (barotrauma), to shear stresses occurring at the interface of open and closed lung regions (known as atelectrauma), and to cellular inflammatory response (biotrauma), play an important role in the genesis of ventilation induced lung injury, increasing vascular permeability, accumulation of lung fluid and inflammation induced by MV [8-10]. Ventilator-induced lung injury can be defined as a damage leading to acute lung injury that occurs in patients receiving mechanical ventilation. Importantly, it is an association between ALI and MV rather than a causal effect. The four mechanisms that lead to increased VILI are better described as follows:

Volutrauma

Alveolar stretch by large tidal volumes in animal models leads to rapid development of edema and death. Increase in extravascular edema is found more often in animals with previous lung injury. It has been thought that volutrauma appears from direct alveolar-capillary damage with rapid increase in capillary permeability. Increased protein content and edema affects the alveolar surfactant performance with consequent decrease in lung compliance.

Atelectrauma

Cyclical opening and closing in small airways or lung units may lead to local increased strain and stretch, which has been called atelectrauma. In theory, small airways can become occluded by exudates and overlapping the walls, thus the pressure required to restore them exceeds the normal airway pressure. Furthermore, the surfactant removed from the alveolar and the large strain required to open a collapsed lung unit leads to physical cells disruption and epithelial damage.

Barotrauma

Excessive pressure in the cells leads to alveolar epithelial damage, conducting the air into the interstitial space. Consequently, it has been thought that the use of high tidal volumes, which generates high inspiratory pressures in ARDS patients as well as lung damage in healthy areas, reproduces the anatomical and pathological ARDS damage, worsening hypoxemia and the outcome.

Biotrauma

The effects caused by lung inflammation and its mediators, which are produced in greater quantities when using more aggressive ventilator strategies with larger pulmonary stress, affecting organs at a distance. An increased interest for protective mechanical ventilation strategies has become an important concern in intensive care unit studies since the mid 1980's, when the idea of protecting the lung and reexpanding

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only the non-ventilated areas favored the development of independent lung ventilation by means of selective bronchial intubation. Later, in the 1990s the next step was to focus attention not only on reopening the lung but also on keeping it open during the whole breathing cycle, with the aim of preventing trauma originating from the pressure required to reopen the terminal bronchiole and overcome the shear forces which can favor the onset of lung damage [11]. An important review published by Parker et al. [12] in 1993 analyzing controlled experimental and clinical studies have shown that ventilation with high tidal volumes can increase vascular filtration pressures; produce stress fractures of capillary endothelium, epithelium, and basement membrane; and cause lung rupture. Mechanical damage leads to leakage of fluid, protein, and blood into tissue and air spaces or leakage of air into tissue spaces. This process is followed by an inflammatory response and possibly a reduced defense against infection. Predisposing factors for lung injury are high peak inspiratory volumes and pressures, a high mean airway pressure, structural immaturity of lung and chest wall, surfactant insufficiency or inactivation, and preexisting lung disease. Damage can be minimized by preventing overdistention of functional lung units during therapeutic ventilation. Based on these concepts, conventional protective ventilation has been introduced as a new approach to ventilatory support for ARDS patients. Reduction of the tidal volume delivered to mechanically ventilated patients, and thus of the stress applied to their lungs, clearly contributed to improve outcomes, as demonstrated by the ARDS network study, which showed a 22% higher survival in patients who received lower (6 mL/kg) than in those who received larger (12 mL/kg) tidal volumes. This method aims to protect the lung by limiting VT (6 mL/kg) and providing adequate positive end expiratory pressure (PEEP) with plateau pressure 30 cm H_2O [13,14]. High tidal volume is considered the major determinant to increase ventilator induced lung injury by overdistension and cyclic recruitment-derecruitment [15]. The use of PEEP can improve oxygenation indexes sufficiently to convert patients meeting the definition of acute respiratory distress syndrome to have acute lung injury, and can change the physiology in the lung such that the patient does not meet the criteria for acute lung injury or acute respiratory distress syndrome [4].

ARDS Definition, Etiology and Pathophysiology

Acute respiratory distress syndrome is a catastrophic form of acute respiratory failure characterized by nonhydrostatic pulmonary edema and severe hypoxemia, which results from alveolar-capillary damage caused by multiple factors. It is an important public health problem, more than 100,000 cases of ARDS occur in the United States annually, accounting for millions of days spent in hospitals and intensive care units. The mortality rate ranges from 30% to 60%, and those who survive have significant reductions in quality of life [16]. In 1994, an American-European Consensus Conference standardized the definition for ALI and ARDS on the basis of the following clinical parameters: acute onset of severe respiratory distress; bilateral infiltrates on frontal chest radiography; absence of left atrial hypertension, pulmonary capillary wedge pressure 18 mmHg, or no clinical signs of left heart failure; and severe hypoxemia (ALI, partial arterial pressure of oxygen/fraction of inspired oxygen ratio [PaO_2/FiO_2] ratio 300 mmHg; ARDS, PaO_2/FiO_2 ratio 200 mmHg), despite of using positive end expiratory pressure (PEEP) [17]. Acute lung injury and ARDS can be caused by direct lung injury (primary), as in aspiration, pulmonary infection, drowing, toxic inhalation, and pulmonary contusion, or by indirect aggression (secondary), as in sepsis, multiple trauma, massive transfusion of blood products, among others [18].

ARDS: A New Approach for Definition

It has been thought that the ARDS criteria defined by the American-European Consensus Conference should be revised due to the variability among ARDS patients inside the intensive care units and the definition should be applied using different degrees of lung injury. A study performed by Villar et al. [19] questioned whether an early assessment of oxygenation on specific ventilator settings would identify patients with established ARDS (persisting over 24 h). The authors studied one hundred and seventy patients meeting ARDS criteria. They found that the use of the American-European Consensus Conference definition for ARDS to enroll patients into clinical trials may result in the inclusion of patients with highly variable lung injury and mortalities. Recently, a review in the ARDS definition criteria has been proposed by the European Society of Intensive Care Medicine endorsed by the American Thoracic Society and the Society of Critical Care Medicine. Authors developed the Berlin Definition, focusing on feasibility, reliability, validity, and objective evaluation of its performance. It is based on the following criteria: Timing-within 1 week of a known clinical insult or new or worsening respiratory symptoms; Chest imaging- 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 (e.g. echocardiography) to exclude hydrostatic edema if no risk factor present; and Oxygenation-Mild 200 mmHg < PaO_2/FIO_2 300 mmHg with PEEP or CPAP 5 cm H_2O, Moderate 100 mmHg < PaO_2/FIO_2 200 mmHg with PEEP 5 cm H_2O, Severe $PaO_2/FIO_2 \leq$ 100 mmHg with PEEP 5 cm H_2O [20]. This new definition for ARDS addresses a number of limitations of the American-European Consensus Conference definition. It has concluded that the approach of combining consensus discussions with empirical evaluation may serve as a model to create more accurate, evidence-based, critical illness syndrome definitions and to better inform clinical care, research, and health services planning [20]. The aim of the present study was to review the Cochrane Library and MEDLINE (for entries up to March, 2012). We used the search terms: ventilator-induced lung injury (VILI), mechanical ventilation (MV), acute lung injury (ALI), and acute respiratory distress syndrome (ARDS). Animal and human studies were reviewed. We mainly selected publications in the past 5 years, but did not exclude commonly referenced and highly regarded older publications.

Clinical Studies

High tidal volume as harmful in ALI/ARDS

Bruhn et al. [15] have analyzed how high tidal volume increase cyclic recruitment-derecruitment in ARDS patients. Authors have established that VT=12 ml/kg increased cyclic recruitment-derecruitment compared to VT=6 mL/kg in ARDS patients with diffuse attenuations measured by dynamic computed tomography (CT). In addition, another study [21] assessing positron emission tomography to monitor regional inflammation, as reflected by local metabolic activity *in vivo,* has shown that patients with ALI were managed with relatively high end-expiratory pressure. Metabolic activity of aerated regions was correlated with both plateau pressure and regional VT normalized by end-expiratory lung gas volume, whereas no association was found between cyclic recruitment-derecruitment and increased metabolic activity. This correlation appeared to be due at least in part, to the effect of mechanical ventilation perse. Moreover, in patients with ARDS a focal distribution of loss of aeration in lung computed tomography predicts low potential for alveolar recruitment and susceptibility to alveolar hyperinflation with high levels of PEEP. In

a study performed by Grasso et al. [22], all patients had a lung stress index that revealed alveolar hyperinflation during application of the ARDS network strategy, and consequently, PEEP was significantly decreased to normalize the stress index value. Authors concluded that alveolar hyperinflation in patients with focal ARDS ventilated with the ARDS network protocol was attenuated by a physiologic approach to PEEP setting based on the stress index measurement. Patients with acute lung injury have impaired function of the lung surfactant system. In a prospective, blinded, randomized study of 843 patients [23], authors aimed to determine the clinical benefit of administering an rSP-C-based synthetic surfactant to patients with severe direct lung injury due to pneumonia or aspiration. They showed that delivery of a recombinant surfactant protein C-based surfactant provided no benefit to patients with severe direct lung injury. In a multicenter randomized controlled trial [24] of 767 adults with ALI conducted in 37 intensive care units, researchers compared the effect on outcome of a strategy for setting PEEP aimed at increasing alveolar recruitment while limiting hyperinflation to one aimed at minimizing alveolar distension in patients with ALI. Authors showed that a strategy for setting PEEP intended at increasing alveolar recruitment while limiting hyperinflation did not significantly reduce mortality. However, it did improve lung function and reduced the duration of mechanical ventilation and organ failure. In a recently published paper by Lellouche et al. [25] it was shown that after cardiac surgery, tidal volume above 10 mL/kg was a significant risk factor for organ failure, multiple organ failure, and prolonged stay in the intensive care unit. Another interesting finding from this study was that women and obese patients were at more risk of receiving injurious ventilation due to the exposure to high tidal volume. Lung injury caused by a ventilator results from nonphysiologic lung stress (transpulmonary pressure) and strain (inflated volume to functional residual capacity ratio). Chiumello et al. [26] aimed to determine whether plateau pressure and tidal volume are adequate surrogates for stress and strain, and to quantify the stress to strain relationship in patients and control subjects. Authors demonstrated that a given applied airway pressure produced largely variable stress due to the variability of the lung elastance to respiratory system elastance ratio, and low or high tidal volume, such as 6 and 12 ml/kg, respectively, could produce similar stress and strain. They concluded that plateau pressure and tidal volume are inadequate surrogates for lung stress and strain. Improvements in acute lung injury treatment, especially in mechanical ventilation methods have enhanced the survival rate. It has been pointed out that there are reports of recurrent acute lung injury. Authors [27] aimed to determine risk factors for development of recurrent acute lung injury. The results from this study showed that recurrent acute lung injury is not a rare phenomenon in the intensive care unit and may continue to increase with improvements in survival following acute lung injury. In addition, it has been shown that gastroesophageal reflux disease was identified as an important risk factor for recurrent acute lung injury and may suggest an important role of gastric aspiration in the development of this syndrome.

Experimental Studies

Ventilator-induced lung injury has been studied in several different animal models. VILI concept derived from animal studies has resulted in complete reconsideration of the use of mechanical ventilation for patients with acute lung diseases and it has changed mechanical ventilation treatment in the clinical practice. Experimental research in this area increased significantly in the past years, probably due to the possibility of using different strategies to reduce lung injury.

Positive end-expiratory pressure (PEEP)

Different protocols using high levels of PEEP in combination with low tidal volumes have been shown to reduce mortality in patients with severe acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). A PEEP above the lower inflection point of the pressure-volume curve has been thought necessary to maintain recruited lung volume in acute lung injury. Hua et al. [28] has used a strategy to identify the level of open-lung PEEP by detecting the maximum tidal compliance during a decremental PEEP trial. Authors concluded that setting values according to the open-lung PEEP identified by decremental PEEP trial is an effective method to attenuate lung injury and it was an indicator for optimal PEEP. In a study performed by Kostic et al. [29], authors aimed to evaluate if using respiratory system reactance for setting PEEP would improve lung mechanics and reduce lung injury compared to an oxygenation-based approach. They concluded that a PEEP optimization strategy based on maximizing respiratory system reactance attenuated the signs of ventilator induced lung injury. To evaluate whether PEEP affects intrapulmonary alveolar edema liquid movement and alveolar permeability to proteins during high volume ventilation, de Prost et al. [30] have studied a rat model of ALI induced by instillation of albumin solution in a distal airway to produce a zone of alveolar flooding. This study demonstrated that PEEP prevents the dispersion of alveolar edema liquid in the lungs and minimizes the increase in alveolar albumin permeability due to high volume ventilation. This effect of PEEP may account for the attenuation of sepsis and inflammation dissemination. Spontaneous breathing during assisted mechanical ventilation is an important determinant of total alveolar stretching. Based on this, Yoshida et al. [31] investigated whether potentially injurious transpulmonary pressure could be generated by strong spontaneous breathing and exacerbate lung injury. They found that even when plateau pressure is limited to 30 cm H_2O, combined with increased respiratory rate and tidal volume, high transpulmonary pressure generated by strong spontaneous breathing effort can worsen lung injury. When spontaneous breathing is preserved during mechanical ventilation, transpulmonary pressure and tidal volume should be strictly controlled to prevent further lung injury. Another important factor of lung injury involved in ALI and ARDS is the hyperoxia used in the treatment of these patients during mechanical ventilation. It can be due to damage induced in pulmonary epithelial cells through lung inflammation and apoptotic cell death. Hyperoxia has been shown to increase VILI, but the mechanisms regulating interaction between large tidal volume (VT) and hyperoxia are still unclear. Li et al. [32] hypothesized that the addition of hyperoxia to large tidal volume ventilation would increase neutrophil infiltration by upregulation of the cytokine macrophage inflammatory protein-2 (MIP-2) and would increase apoptosis via the mitogen-activated protein kinase pathways. Authors concluded that hyperoxia increased high-VT-induced apoptotic and non-apoptotic epithelial cell injury and resulted in increased lung neutrophil influx.

Adjunctives pharmacological treatment and ventilator-induced lung injury

The severity of ARDS has been the subject of great concern and the search for new therapies has been the objective of many studies, in an effort to reduce lung injury due to mechanical ventilation. Although several pharmacological therapies have been studied in ALI and ARDS, none of these pharmacological treatments have improved survival [33]. Terbutaline infusion reduced accumulation of plasma protein in the lungs of ARDS patients [34], which suggested that it might have lessened microvascular permeability alterations. Whether β2-adrenergic agonists may similarly lessen the increase in alveolar

permeability produced by mechanical stress is unknown. Based on this hypothesis, de Prost et al. [35] aimed to evaluate whether terbutaline may reduce acute alveolar-capillary barrier alterations during high-volume ventilation. Authors showed that terbutaline reduces edema formation, possibly by lowering microvascular permeability alterations, during an injurious, high-volume, ventilation modality, and decreases the rate of edema formation *in vivo*. The proinflammatory cytokine tumor necrosis factor (TNF) has been consistently implicated in the ALI pathogenesis. Also, it is upregulated in the alveolar space early in the course of ventilator-induced lung injury (VILI). Using a newly developed domain antibody, Bertok et al. [36] aimed to investigate the effects of selective inhibition of intra alveolar p55 TNF receptor on pulmonary edema and inflammation during ventilator induced lung injury. Authors have shown that specific and selective pharmacological inhibition of intra-alveolar TNF receptor p55 signaling by domain antibodies can ameliorate pulmonary edema and inflammation during VILI in mice, and may open new therapeutic approaches for ventilated patients with acute lung injury. The beneficial effects of statins have been attributed to properties other than their lipid-lowering actions, such as anti-inflammatory, antioxidant, and nitric oxide synthesis regulatory properties. Statins exhibits anti-inflammatory and endothelial barrier stabilizing properties *in vitro* and *in vivo* [37]. These effects can attenuate acute lung injury, including reduction of pulmonary microvascular leakage, limitation of pulmonary leukocyte infiltration, and attenuation of pulmonary and systemic hyperinflammation. Pulmonary and systemic hyperinflammation, leukocyte recruitment to the lungs, and the development of pulmonary microvascular leakage are crucial components of VILI [38,39]. Recently, Craig et al. [40] conducted a randomized, double-blinded, placebo controlled trial in 60 patients with ALI. Patients received 80 mg simvastatin or placebo until cessation of mechanical ventilation or up to 14 days. They demonstrated that treatment with simvastatin appears to be safe and may be associated with an improvement in organ dysfunction in ALI. These clinical effects may be mediated by a reduction in pulmonary and systemic inflammation. On the other hand, Kor et al. [41] in a retrospective cohort study evaluated the role of statin therapy in patients with ALI/ARDS. They concluded that statin use was not associated with improved outcome in patients with ALI/ARDS. Authors were unable to find evidence for protection against pulmonary or nonpulmonary organ dysfunction. In a study performed by Müller et al. [42], high-dose simvastatin attenuated VILI in mice by reducing mechanical ventilation-induced pulmonary inflammation and hyperpermeability. Siempos et al. [43] using an isolated rabbit lung model, treated animals with atorvastatin for 3 days before surgery. They showed that atorvastatin improved alveolar capillary permeability and hemodynamics and, thus, attenuated lung injury caused by high-stretch mechanical ventilation.

Inhaled nitric oxide to reduce mechanical ventilation aggressiveness

In the late 1980's, nitric oxide (NO) was identified as an endothelial-derived relaxing factor and its physiological effects were first presented in 1992. Nitric oxide is a 1:1 combination of the two most abundant gases in the atmosphere. It is synthesized from L-arginine by nitric oxide synthase in a variety of cells. When produced in vascular endothelial cells, NO diffuses to subjacent smooth muscle cells and activates soluble guanylate cyclase by binding to the heme moiety, which leads to increased production of cyclic guanosine 3,5'-monophosphate (cGMP). An increase in cGMP decreases intercellular calcium concentration resulting in smooth muscle relaxation and vasodilation. Inhaled nitric oxide (iNO) is a selective vasodilator of well-ventilated lung regions, thus reducing intrapulmonary shunt and improving arterial oxygenation. Furthermore, iNO has been shown to have a high affinity for hemoglobin, which thereby inactivates it and prevents systemic vasodilation. The rationale for its use in ARDS is that iNO-induced vasodilation of pulmonary vasculature adjacent to well-ventilated alveoli increases blood flow to these lung areas and preferentially shunts blood away from poorly ventilated regions, matching V/Q and reducing intrapulmonary shunt. This results in improved oxygenation and a reduction in both pulmonary vascular resistance and right ventricular after load. By improving V/Q matching, iNO may allow less aggressive mechanical ventilation, which in turn might minimize the risk of VILI and morbidity. Also, the local effects that iNO has on oxygenation, inflammation, pulmonary hypertension, edema, and capillary permeability make it suitable for use in ARDS.

In the early 90's, the beneficial effects of iNO on oxygenation, pulmonary hypertension, and cardiac index were described in both adults and children with ARDS. After this, many studies, while confirming those effects, were not able to demonstrate a sustained response to iNO therapy. However, Dobyns et al. [44], in a multicenter randomized controlled trial observed sustained response to iNO versus placebo therapy in pediatric patient subgroups (oxygenation index <25 and immunocompromised group). They explained that iNO therapy did not sustain improved oxygenation in all patients because they were enrolled in the study in the later stages of the disease.

The hypothesis that response to iNO therapy depends on its introduction time had already been tested in an experimental study with a mouse model of sepsis induced acute lung injury, demonstrating that early iNO exposure was associated with reduced pulmonary leukocyte infiltration and less oxidative injury. Following this idea of early administration and beneficial effects, Fioretto et al. [45] published a protocol in 2001 for early iNO introduction associated with conventional therapy in ARDS children. Authors demonstrated acute and sustained response of oxygenation indexes whilst using iNO as early as 12 hours after ARDS diagnosis, giving relevance to the idea that early iNO treatment may be more effective. Later in 2004, Fioretto et al. [46] compared early iNO administration plus conventional therapy against conventional therapy in two groups of ARDS children: iNO group (iNOG) composed of patients prospectively enrolled, and conventional therapy group (CTG) consisting of historical control patients. Our objective was to determine the acute and sustained effects of early iNO on some oxygenation indexes and ventilator settings, to analyze the weaning process, and to assess the safety of nitric oxide inhalation. Therapy with iNO was introduced as early as 1.5 hours after ARDS diagnosis, in optimally ventilated patients with appropriate PEEP levels (10 cm H_2O), leading to acute improvements in the PaO_2 /FiO_2 ratio and oxygenation index. Prolonged treatment was also associated with improved oxygenation, so that FiO_2 and peak inspiratory pressure could be quickly and significantly reduced. Mortality rate for iNO patients was lower (CTG: 10/21- 47.6%; iNOG: 3/18 - 16.6%, p<0.001). Median iNO treatment period was 2 days (1-6) and mean iNO dose was 4.03 ± 1.59 ppm. There were no serious adverse events during iNO administration: methemoglobin levels did not rise above 1% of total hemoglobin in any child, and maximum NO concentration was 1.5 ppm. Discontinuation of iNO caused a "rebound" of increased hypoxemia in two children. Reintroduction of iNO promptly corrected this, and therapy was successfully withdrawn 24 hours later. Authors concluded that early treatment with iNO causes acute and sustained improvement in oxygenation, with earlier reduction in ventilator setting that are associated with a high risk of VILI and oxygen toxicity (Pip and FiO_2); this might contribute to reducing the mortality rate in

children with ARDS. Length of stay in intensive care, and duration of mechanical ventilation were not changed. In a recent study performed from our group, Fioretto et al. [47] have shown that early use of low doses of inhaled nitric oxide associated with protective conventional mechanical ventilation attenuates oxidative stress, histopathological and inflammatory lung injury in a saline-lavaged rabbit model of acute lung injury.

High-frequency oscillatory ventilation as a tool to prevent VILI

High-frequency oscillatory ventilation (HFOV) is an attractive ventilatory method [48,49]. It uses a lower VT (1-3 mL/kg) with a frequency above normal physiological breathing (5-10 Hz), thus avoiding larger alveolar pressure and volume excursions, typical of conventional mechanical ventilation (CMV). In HFOV, a constant mean airway pressure (Paw) is applied to achieve and maintain alveolar recruitment even at end expiration [50-53]. The small tidal volumes that high-frequency oscillatory ventilation delivers are the key to its lung-protective potential. By delivering these small tidal volumes, HFOV produces minimal variation around the mean airway pressure and mean lung volume during tidal breathing, and this can clearly limit volutrauma. Additionally, because of this minimal tidal variation in airway pressure, clinicians can set higher mean airway pressures than can be safely applied with conventional mechanical ventilation. The lung recruitment that results from this higher mean airway pressure can directly reduce opening and closing injury (atelectrauma). Also, volutrauma may be reduced by increasing the size of the baby lung and reducing the tidal stretch that any individual alveolus has to accommodate [54]. In two recent publications from our group, HFOV showed substantial benefits against ventilator-induced lung injury in an animal model of acute lung injury. It improved oxygenation, reduced the inflammatory process and Histopathological damage, and attenuated oxidative lung injury compared to protective conventional mechanical ventilation [55,56]. Moreover, Jian et al. [57] comparing conventional mechanical ventilation and HFOV, showed reduced inflammatory responses measured by tumor necrosis factor alpha (TNF-α) production and neutrophil infiltration in bronchoalveolar lavage fluid in a rat model of ALI. In agreement, Allardet-Servent et al. [58] reported that HOFV ameliorates VILI in a rabbit model of ALI.

Conclusion

The reduction in ventilator-induced lung injury is still a challenge for researchers in intensive care unit. Mechanical ventilation is the most important treatment for acute lung injury and acute respiratory distress syndrome. Thus, there is a need to find a combination of different associated strategies of protective mechanical ventilation methods and new approaches to reduce lung injury and, most importantly, as a key to reduce the mortality rate in these patients.

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