

# Opening Up to Lung Recruitment Pulmonary Contusion and Derecruitment - The Role of Inflammation

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## Abstract

**Purpose of review:** It was recently reported that a lung protective ventilation strategy resulted in no fatalities in 17 patients with ARDS secondary to lung contusion. Although the efficacy of a lung protective ventilation strategy to reduce mortality in ARDS patients has been demonstrated, the underlying mechanisms for this reduction remain unclear.

**Recent findings:** ARDS is characterized by an inflammatory state of the lung that can be aggravated by mechanical ventilation. Especially mechanical ventilation allowing cyclic opening and closing of unstable alveoli, enhances cytokine release and can even result in loss of compartmentalization. Disbalance in the cytokine response can promote bacterial colonization

and result in multiorgan failure. Recent clinical trials and experimental studies have demonstrated that recruitment of collapsed alveoli and stabilization of alveoli using sufficient levels of PEEP can reduce inflammation, bacterial colonization and the number of failing organs, thereby decreasing mortality.

**Summary:** Lung protective ventilation strategies minimizing this cyclic opening and closing by recruiting collapsed alveoli and subsequent stabilization with adequate levels of PEEP offer the clinician a tool to improve patient outcome in ARDS. This benefit is partly mediated by maintaining a 'natural' balance in the cytokine response. Future studies should explore this strategy in a randomized prospective study.

**Keywords:** ARDS, mechanical ventilation, blunt chest trauma, pulmonary contusion

## Introduction

Pulmonary contusion is a common lesion occurring in patients sustaining severe blunt chest trauma; 30 to 75% of blunt chest trauma incorporates pulmonary contusion. Although the specific effect of pulmonary contusion on mortality is difficult to assess, a mortality range of 10 to 25% has been suggested [1]. While most initial reports of pulmonary contusion were secondary to blast injury in war time, Johnson *et al.* reported that currently the most common mechanisms of injury are caused by motor vehicle accidents (65%), farming accidents (10%)

and falls (9%) [2]. Even flail chest after cardiopulmonary resuscitation has been linked to pulmonary contusion [3].

Alveolar hemorrhage and parenchymal destruction are maximal during the first 24 hours after injury and then usually resolve within 7 days. The diagnosis of traumatic lung injury is usually made clinically with confirmation by chest X-ray. The chest computed tomography scan is highly sensitive in identifying pulmonary contusion and may even help predict the need for mechanical ventilation [4]. Respiratory distress is common after lung trauma, with hypoxemia and hypercarbia greatest at about 72 hours. Although management of patients with pulmonary contusion is supportive, pneumonia and adult respiratory distress syndrome (ARDS) with long-term disability frequently occur [5].

In a large cohort study of blunt trauma patients an Injury Severity Score (ISS) >25 and pulmonary contusion were the main risk factors for the subsequent development of ARDS [6]. The incidence of acute lung injury (ALI) in the United States is estimated at 64.2 cases per

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100,000 persons/year, similar to levels in other developed countries; the estimated mortality is 40% [7]. According to a recent European epidemiological study, mortality of patients with ALI/ARDS secondary to lung contusion exceeds 20% [8].

In a recent retrospective analysis of patients with ARDS due to pulmonary contusion Schreier and co-workers showed that mechanical ventilation according to the open lung concept dramatically improved oxygenation and lung aeration [9]. No fatalities were observed in the patients studied, and the authors stated that: "these results indicate that the open lung concept is a reasonable mode of ventilation for patients with severe chest trauma" [9].

What can we learn from this study to improve the care and outcome of patients with ARDS due to lung contusion?

## Background

Mechanical ventilation in patients with respiratory failure is considered a trade off between preventing hypoxemia and too high mean airway pressures. Current clinical ventilation strategies demonstrate that implementation of a volume-limited strategy can reduce mortality in these patients [10]. However, the use of higher PEEP levels to prevent alveolar collapse and recruitment maneuvers to re-aerate collapsed lung areas remain controversial. The ARDS network trial (ALVEOLI) in which low tidal volume ventilation with higher PEEP values were compared with the PEEP levels used in their low tidal volume study [10] failed to demonstrate a significant benefit between either of the two strategies. In contrast, Amato *et al.* [11] and Ranieri *et al.* [12] showed a reduction in mortality through the application of higher PEEP levels. In contrast to the ARDS network study, the latter two studies [11,12] utilized a recruitment maneuver. Can current perceptions in mechanical ventilation research help us understand these conflicting results?.

## Cytokine release

In ARDS patients the inflammatory state of the lung is a substantial factor related to the underlying etiology of the disease. Especially in pulmonary ARDS, such as lung contusion, the alveolar epithelium is primarily injured, causing activation of alveolar macrophages, neutrophils and the inflammatory network, leading to intrapulmonary inflammation [13]. Although it remains unclear how inflammation progresses during ARDS, several studies have

shown that the outcome of ARDS patients correlates with bronchoalveolar lavage fluid and serum cytokine levels [14-17]. Persistent higher cytokine levels correlated with poor outcome and some studies even suggested that cytokine plasma levels had a stronger correlation with outcome than clinical criteria [16]. An inflammatory response is regulated by a careful balance between pro- and anti-inflammatory mediators, disbalance is associated with ARDS severity [18]. Recently, Meduri hypothesized that higher cytokines levels, as observed in ARDS, could increase the incidence of nosocomial infections [19]. He based this assumption on *in vivo* experiments demonstrating that lower concentrations of pro-inflammatory cytokines hampered bacterial growth, whereas high cytokine levels actually enhanced bacterial growth [20]. All these data support the current concept that outcome of ARDS is dependent on the inflammatory state of the lung and may be even more important the inflammatory state of the whole body. The inflammatory response is compartmentalized in the area of the body where it is produced, i.e. in the alveolar space or in the systemic circulation [21-24]. Loss of (especially pulmonary) compartmentalization could lead to the development and progression of multi-organ failure [25], the leading cause of mortality in ARDS patients [26].

## Role of mechanical ventilation in cytokine balance

We have demonstrated that injurious mechanical ventilation leads to loss of compartmentalization [27] causing an imbalance in the inflammatory response. These high levels of cytokines can cause severe organ dysfunction [28]. Experimental data show that low tidal volume ventilation which still allows repetitive opening and collapse of alveoli actually augments lung injury [29] and that such ventilator settings increase the levels of pro-inflammatory cytokines produced in the lung [30]. In the study by Ranieri *et al.* their lung protective ventilation strategy resulted in lower levels of these cytokines in both the lung and the systemic circulation [12]. A later report demonstrated that these lower cytokine levels correlate with decreased numbers of multiple-organ failure in the patients ventilated with higher PEEP levels and lung recruitment [31]. In pulmonary ARDS (such as lung contusion) higher levels of inflammatory mediators are already present in the alveolar compartment increasing the susceptibility for leakage of these cytokines to the systemic circulation [13]. Therefore, preventing an uncontrolled inflammatory response through higher PEEP levels and a recruitment maneuver may reduce mortality in

patients with severe lung disease. We therefore speculate that the benefit observed in the study by Schreiter *et al.* is due to preservation of a 'balanced' cytokine response by optimizing mechanical ventilation.

Although it has been proven that injurious ventilation settings increase cytokine release in injured lungs [30,32,33] an ongoing debate also reiterates that cytokines levels alone are not the only explanation for the observed effects of protective ventilation strategies [34]. As discussed by these authors, basic physiology should be used to improve outcome in ARDS independent of the effect on the cytokine response [34]. Furthermore, improving mechanical ventilation using these guidelines will help to preserve surfactant function in ARDS lungs and minimize the accumulation of cells and edema in the alveoli, which also modulates inflammation [35].

## Physiological rationale

Schreiter *et al.* used a lung ventilation strategy which was described by Lachmann in 1992 [36]. In this strategy lung volume is optimized by a recruitment maneuver and subsequently reducing mean airway pressure to a level above the airway pressure when lung collapse occurs, thereby preventing collapse of 'newly' recruited lung tissue [37]. This results in low tidal volumes of 3.5 (3.0;3.9) ml per kg bodyweight [38]. Schreiter *et al.* carefully monitored lung recruitment by both arterial oxygenation and thoracic helical computed tomography scans before and after ventilation with the open lung concept [9]. The recruitment reduced atelectatic areas from 604 ml to 106 ml and increased the normally aerated volume from 1742 ml to 2971 ml [9]. Furthermore, arterial oxygenation levels were stable after the recruitment procedure thus minimizing the cyclic opening and collapse which augments cytokine release [29,30,33].

Unfortunately they did not measure cytokines in this study, thus we can only speculate whether this ventilation strategy also resulted in lower cytokine levels. Data from other studies have confirmed the beneficial effect of lung protective ventilation on cytokine levels. Stüber and co-workers demonstrated in patients with ALI that a lung protective ventilation after previous injurious settings can dramatically reduce plasma cytokine levels within a few hours of ventilation [39]. In experimental studies the open lung strategy has been shown to reduce inflammation [40] and to even reduce bacterial colonization [41]. Finally, lower cytokine levels also corresponded with a decrease in mortality in the ARDS network trial [10].

The severity of the injury in the patients studied by Schreiter *et al.* is illustrated by the ISS and Acute Physiology and Chronic Health Evaluation II (APACHE II) of 38 (range, 14–75) and 23 (range, 11–26) points, respectively. The predicted mortality of the APACHE II score was 49.7%, and the adjusted APACHE II had a predicted mortality of 22.4%. These rates correspond with the respective mortality rate observed in ARDS patients (42%) [42] and in ARDS due to pulmonary contusion (20%) [8]. However, all patients in the study by Schreiter *et al.* survived and were alive up to of 14–60 months after treatment for ALI/ARDS [9].

## Limitations

A major limitation of the study by Schreiter and colleagues is the lack of a control group receiving standard care, and the retrospective analysis of the data [9]. Therefore, future studies should prospectively compare the open lung strategy with the current standard therapy in patients at risk for development of ALI/ARDS after chest trauma.

A possible explanation for the success of the ventilation strategy could be the early initiation of this treatment regimen. However, in the studied patients, lung contusion had already resulted in ARDS with a mean PaO<sub>2</sub>/FiO<sub>2</sub> ratio of 107 mmHg [9]. This was further corroborated by the high ISS (mean 38) and the presence of pulmonary contusion, both known to be the major risk factors for the development of ARDS [6].

## Clinical lessons

Current treatment guidelines for pulmonary contusion trauma patients should consist of minimizing tidal volumes in accordance with the ARDS network protocol [10]. However, this treatment strategy by itself resembles a non-active approach towards the patient's state, where ventilation is adjusted only after deterioration of the patient's vital parameters. Especially in suspected pulmonary contusion where the lung can deteriorate rapidly within the first hours after the occurrence of the blunt trauma, a pro-active approach towards mechanical ventilation could prevent this deterioration. The study by Schreiter *et al.* [9] and a recent study by Ferguson *et al.* show that a recruitment maneuver applied at an early state of severe lung injury can dramatically improve oxygenation, recruit lung tissue and maintain the newly recruited lung tissue. We therefore would include (mandatory) recruitment procedures as a part of the treatment of suspected lung contusion patients, thus obtaining and main-

taining oxygenation values above acute lung injury values, while minimizing further injury by applying low tidal volume ventilation at minimal mean airway pressures (for guidelines see [37]).

In conclusion, patients with chest trauma at risk for ARDS can benefit from ventilation strategies, which combine a recruitment maneuver to open up atelectatic lung areas and prevent derecruitment of these 'newly' aerated lung areas with a sufficient PEEP level combined with low volume ventilation. This physiological based ventilation strategy preserves lung function and minimizes

surfactant inactivation and edema formation. We believe that the benefit is partly mediated by maintaining a 'natural' balance in the cytokine response. This strategy should be explored in a randomized prospective study.

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