

Is there any need for higher PEEP levels in ARDS patients?

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Abstract

Lung protective ventilation has been shown to reduce mortality in ARDS patients. Current guidelines are focussed on lowering tidal volumes and minimizing mean airway pressures. In this review we discuss possible future improvements to mechanical ven-

tilation; especially the open lung maneuver. We discuss the rationale for the use of higher PEEP levels in ARDS patients, using data from animal and human studies. Finally, guidelines for future strategies and/or investigations are presented.

Keywords: ARDS, mechanical ventilation, PEEP, open lung maneuver, recruitment, randomized controlled study.

Introduction

Every year, millions of patients worldwide receive ventilator support during surgery. Mechanical ventilation has become an important therapy in the treatment of patients with impaired pulmonary function and particularly in patients suffering from adult respiratory distress syndrome (ARDS). ARDS is caused by multiple factors and is characterized by respiratory dysfunction including hypoxemia and decreased lung compliance. It is known that the decrease in lung distensibility is due to a disturbed surfactant system with an elevated surface tension. This increase in surface tension leads to an increase in forces acting at the air-liquid interface, resulting finally in end-expiratory collapse, atelectasis, an increase in right-to-left shunt and a decrease in PaO₂.

Ventilator associated lung injury (VALI)

It has become clear, however, that mechanical ventilation itself can cause lung damage and may even be the primary factor in lung injury. The recent recognition that alveolar overdistension rather than high proximal airway

pressures is the primary determinant for lung injury (i.e. volutrauma instead of barotrauma) combined with shear stress evoked by repeated alveolar collapse and re-opening due to low end-expiratory volumes [1], has led to renewed interest in lung mechanics and ventilation. In the recent international consensus conference on ventilator-associated lung injury (VALI) in ARDS [2] the question was asked what nonpharmacological approaches are currently available for prevention of VALI?.

Clinical studies showed that a reduction of tidal volume, reduction of peak airway pressures combined with an increase in PEEP resulted in improved outcome of ARDS patients [3]. Furthermore by applying a lung protective strategy pro-inflammatory mediators both in the lung as well as those circulating can be reduced [4], and reducing the circulating levels of pro-inflammatory mediators reduces the development of multi-organ failure the major cause of mortality in ARDS patients [5].

Role of peak pressures, tidal volume and PEEP

Webb and Tierney in 1974 demonstrated the critical role that PEEP plays in preventing/reducing lung injury [6]. In rats ventilated with 10 cmH₂O of PEEP and a peak pressure of 45 cmH₂O no lung injury was present but using the same peak pressure and omitting PEEP severe pulmonary edema was formed within 20 min [6]. In a

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study by Verbrugge et al. the difference in pressure amplitude between these two groups also resulted in difference in tidal volume, i.e. 18 ml/kg and 45 ml/kg in the 45/10 and 45/0 group, respectively [1]. Dreyfuss and colleagues further explored the role of tidal volume and peak inspiratory pressures on lung injury [7]. In an animal model they applied high inspiratory pressures in combination with high volumes which resulted in increased alveolar permeability [7]. In a second group low pressure were combined with high volume (iron lung ventilation) again resulting in alveolar permeability [7]. In the third group the effect of high pressures combined with low volume was studied, by strapping the chest wall to reduce chest excursions; the permeability of this group (high-pressure low-volume group) did not differ from the control group [7]. Thus large tidal volume ventilation increases alveolar permeability, whereas peak inspiratory pressures do not seem to influence the development of this type of lung injury. Similar observations were made in rabbits ventilated with high peak pressures in which thorax excursions were limited by a plaster cast [8]. In injured lungs the effect of higher volumes only aggravated the permeability, as demonstrated in animals in which the surfactant system was inactivated and which were subsequently ventilated with high tidal volumes [9, 10].

Although Webb and Tierney already demonstrated that PEEP could ameliorate lung injury [6], the mechanism is still not clearly understood. PEEP can stent alveoli at end expiration and thus prevent repetitive collapse, reducing shear forces [11, 12]. The most important role of PEEP is to preserve surfactant function. Two basic mechanisms have been reported to explain the surfactant-preserving effect of PEEP during mechanical ventilation. The first mechanism is alteration of the surfactant film by surface area changes, already suggested in 1972 [13]. Wyszogrodski et al. demonstrated that PEEP could prevent collapse of the alveolar surface film due to low lung volumes in no-PEEP ventilation and thus prevent alteration of the endogenous surfactant, substantiated in this model by surface tension measurement and lung compliance [14]. Later it was shown that especially large area changes result in conversion of active surfactant (large aggregates LA) into inactive surfactant (small aggregates SA), believed to be the reason for the deterioration of surfactant function [1, 15, 16]. In the model first described by Webb and Tierney, 10 cmH₂O PEEP prevents a significant conversion of large aggregates into small aggregates compared with non-ventilated controls [1, 17]. A second mechanism explaining how PEEP preserves surfactant function is the prevention of loss of surfactant to the proximal airways. In 1976, an ex-vivo model

was used to show that ventilation caused movement of surfactant to the airways from the alveoli [18]. Preventing alveolar collapse and keeping the end-expiratory volume of alveoli at a higher level, prevents excessive loss of surfactant in the small airways by a squeeze-out mechanism during expiration [1, 18-20].

Accumulation of proteins in the lung due to influx of edema results in inactivation of surfactant [21-23]. PEEP can reduce this accumulation of protein in the lung and the subsequent inactivation of surfactant. Studying the effect of two PEEP levels Hartog and colleagues subjected rats to whole lung lavage to remove the endogenous surfactant [12]. In the first group PEEP was set to prevent hypoxemia (PEEP 8 cmH₂O) and in the other group PEEP was set to prevent collapse of alveoli (PEEP 15 cmH₂O) during the lavage procedure [12]. Although there was a similar amount of surfactant left in the lungs of both groups, there was a marked increase in alveolar protein levels in the low PEEP group, resulting in inactivation of surfactant as well as a deterioration of lung mechanics [12]. Reducing protein influx, minimizing deterioration of lung mechanics and other such protective effects by ventilating with higher levels of PEEP have been reported by others [24, 25]. Different animal models have shown that ventilation with PEEP at lower tidal volumes results in less edema than ventilation without PEEP and a higher tidal volume for the same peak or mean airway pressure [6, 7, 26, 27] and that, more specifically, PEEP prevents alveolar flooding [1, 6].

Why do we need higher PEEP?

When a lung is “open” it is characterized by an optimal gas exchange (28) and a low rate of intrapulmonary shunting (ideally less than 10%) corresponding with a PaO₂ of more than 450 mmHg on pure oxygen [29]. At the same time, airway pressures are at the minimum that ensure the required gas exchange; hemodynamic side-effects are thus minimized [28].

How can we open the lung?

To recruit the collapsed alveoli to improve gas exchange a high opening pressure is needed. The rationale behind the high opening pressure to recruit the lung and the need for lower pressures to keep the alveoli open can be deduced from the pressure-volume curve of an individual alveolus (**Figure 1**). The behavior of an alveolus is quantal in nature; it is either open or closed [30]. A critical opening pressure has to be reached before previously col-

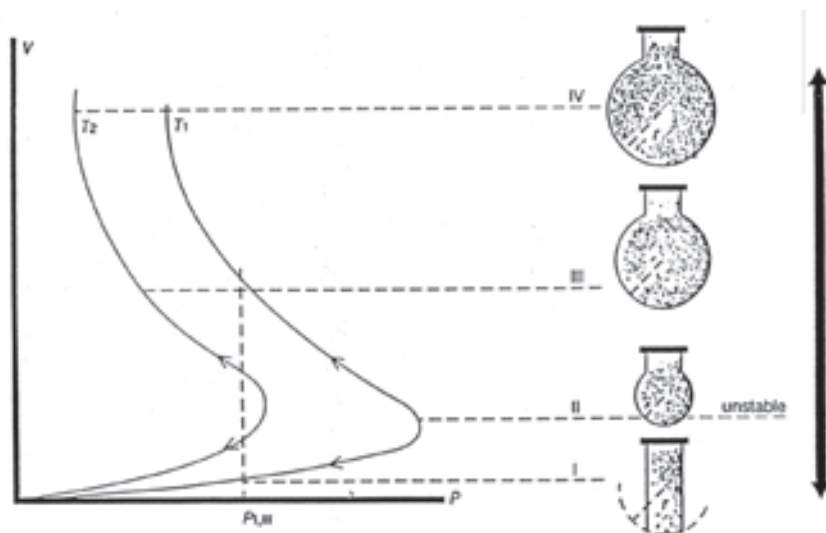


FIGURE 1. PHYSIOLOGICAL BEHAVIOUR OF THE ALVEOLUS. THE PRESSURE-VOLUME (P-V) RELATION IS SHOWN ON THE X-Y AXES. THE RIGHT SIDE SHOWS THE STATUS OF THE BRONCHO-ALVEOLAR UNIT: ITS RADIUS(R) REFLECTS THE P-V RELATION (I-IV). SURFACE TENSION IN PATHOLOGICAL (T1) AND NORMAL CONDITIONS (T2) IS SHOWN. THE ARROWS INDICATE THE DIRECTION FROM CLOSED (BOTTOM) TO OPEN (TOP) STATES AND VICE VERSA.

lapsed alveoli can be opened. Once open, alveoli remain open until the pressure drops below a critical level and immediate collapse occurs. Re-opening again requires the high recruiting pressure. Any state between open and closed is unstable and impossible to maintain. After opening of the alveoli, they should be kept open by using a ventilator setting which will keep the pressure above the critical closing pressure of the alveolus i.e. with a sufficient high PEEP level. Because the alveoli are open during the whole ventilation period no collapse of alveoli occurs, reducing shear forces to a minimal level.

In summary there are three steps to open the lung [31].

1. A critical opening pressure must be overcome during inspiration
2. This opening pressure must be maintained for a sufficiently long period of time
3. During expiration, no critical time that would allow closure of lung units should pass, by using auto or intrinsic PEEP or applying sufficiently high PEEP levels which prevent alveolar collapse.

Open lung management

“The open lung management” describes the steps and methods used to safely open the lung and how to keep it open. **Figure 2** shows the predetermined sequence of therapeutic phases, each with its specific treatment objective [28, 32]. As shown in **Figure 2**, the goal of the

initial increase in inspiratory pressure is to recruit collapsed alveoli and to determine the critical opening pressure. Then, the minimum pressures that prevent the lung from collapse are determined. Finally, after an active re-opening maneuver sufficient pressure is implemented to keep the lung open.

After opening the lung and finding the lowest pressure to keep it open, the resulting pressure amplitude is minimized and at the same time pulmonary gas exchange is maximized. A reduction of the total level of support is generally possible after a successful alveolar recruitment.

Should a renewed collapse of alveoli occur, often caused by intrapulmonary suction or disconnection, a fall in PaO_2 indicates that a re-opening maneuver has to be performed in the same way as previously described.

First results of the open lung management

In one of the first clinical, prospective controlled randomized studies with the “open lung approach”, Amato and co-workers showed that a ventilation strategy with permissive hypercapnia resulted in a higher weaning rate from mechanical ventilator, a lower rate of barotrauma, and an improved 28-day survival in ARDS patients, compared with conventional ventilation [3].

The NIH ARDS multi center, randomized trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 ml per kilogram with ventilation with a lower tidal volume of 6 ml per kilogram of

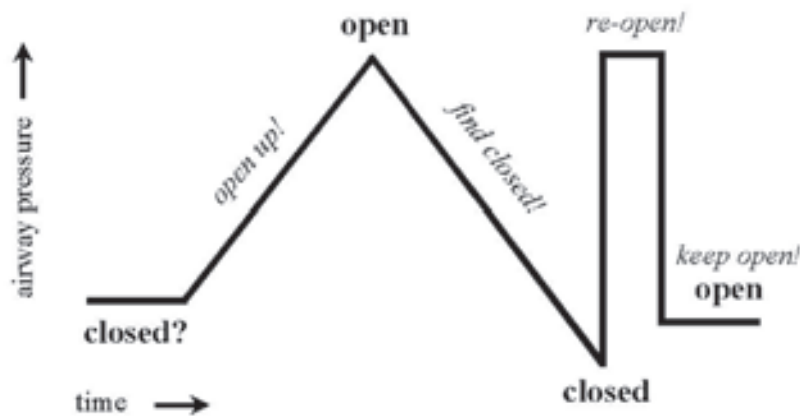


FIGURE 2. SCHEMATIC REPRESENTATION OF THE OPENING PROCEDURE FOR COLLAPSED LUNGS. NOTE: THE IMPERATIVES (!) MARK THE TREATMENT GOAL OF EACH SPECIFIC INTERVENTION. THE **BOLD** WORDS MARK THE ACHIEVED STATE OF THE LUNG. AT THE BEGINNING THE PRECISE AMOUNT OF COLLAPSED LUNG TISSUE IS NOT KNOWN.

predicted body. The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean (\pm SD), 12 ± 11 vs. 10 ± 11) [33].

Data from our group suggest that early application of the open lung management in animals suffering from ARDS prevents a decrease in pulmonary compliance compared with animals ventilated in settings that do not open the lung [12]. Therefore, application of “the open lung management” should be used in each patient needing mechanical ventilation and thus minimizing VALI in patients without compromising optimal ventilation therapy.

Recently Schreiter *et al.* ventilated 32 polytraumatized patients suffering from severe chest contusion according to the Open Lung Concept (OLC) [34]. Oxygenation improved significantly; $\text{PaO}_2/\text{FiO}_2$ rose from 134 mmHg before start of the OLC to 522mmHg after the recruitment procedure. For the recruitment procedure, a mean PIP of 65 mbar was required, and the recruited alveoli were kept open by a total-PEEP of 22 mbar [34]. After the recruitment procedure, PIP and FiO_2 could be reduced, resulting in tidal volumes of 3.5 ml per kg bodyweight. Only two patients (6.25%) died of extra pulmonary causes [34].

Schreiter *et al.* used a lung ventilation strategy which was described by Lachmann in 1992 [28]. 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 [35]. This results in low tidal volumes of 3.5 (3.0;3.9) ml per kg bodyweight [34]. 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 [36]. The recruitment reduced atelectatic areas from 604 ml to 106 ml and increased the normally aerated volume from 1742 ml to 2971 ml [36]. Furthermore, arterial oxygenation levels were stable after the recruitment procedure thus minimizing the cyclic opening and collapse which augments cytokine release [37-39].

Recommendations

To minimize the effects of ventilation-induced lung injury, practical guidelines must be followed:

1. Always use a pressure-controlled ventilator setting. When ventilating in a pressure-controlled mode the risk of overdistension of healthy parts of injured lung areas (as present in inhomogenous lung injury like ARDS) are prevented.
2. Use sufficiently high levels of PEEP to prevent end-expiratory collapse and the ensuing shear forces, which will further impair lung function. Also, sufficiently high levels of PEEP can help to prevent further loss of surfactant in still healthy alveoli, halting the further spread of the disease process. To minimize hemodynamic deterioration provide sufficient volume substitution.

3. Use as small as possible tidal volumes, again to prevent overdistension and shear forces.
 - Keep the lung open with PEEP levels above the closing pressures
 - Maintain optimal gas exchange at the smallest possible pressure amplitudes to optimize CO₂ removal.

Summary

The basic treatment principles are:

- Open up the whole lung with the required inspiratory pressures

With the strict application of these principles, a prophylactic treatment is available, that is aimed at preventing ventilator-associated lung injury and pulmonary complication without compromising optimal ventilation.

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