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Does high PEEP prevent alveolar cycling?

Introduction

Acute respiratory distress syndrome (ARDS) is characterized by widespread lung inflammation with permeability alteration of the lung microvasculature and edema involving the whole lung parenchyma [2, 31, 38]. No etiologic treatment is available and supportive treatment with mechanical ventilation is associated with a mortality rate of up to 43% in severe ARDS [3]. The causes of mortality in ARDS patients are still debated, but hypoxemia is the leading cause of death in a minority of cases [37]. In most patients with unfavorable outcome the lung does not heal, but the persistence of the inflammatory process leads to widespread lung fibrosis [29] and the patient cannot be weaned from the ventilator. Some authors have shown that the inflamed lung releases cytokines into the blood stream, possibly leading to multi-organ failure [7, 34]. There is extensive experimental evidence that mechanical ventilation itself can damage healthy lungs [15, 19, 26]. Several theories to explain the possible mechanisms of lung damage in healthy and diseased lungs have been proposed over the years [17, 19]. Most of the literature accepts that excessive stress and strain (barotrauma and volutrauma) in healthy lungs [8] lead to mechanical rupture of lung parenchyma and activation of inflammatory cascade [7]. In contrast, a diseased lung is non-homogeneous on the small scale, presenting lung regions with different inflation statuses.

Consequently, in the ARDS lung, two additional disease mechanisms apply: pressure multiplication at the interface between lung regions with different inflation statuses [13, 15, 27] and intratidal collapse/decollapse [32]. Mead showed that the applied pressure is regionally multiplied at the interface between lung regions with different inflation statuses [7, 13]. A second possible mechanism of ventilator-induced lung injury (VILI) in a diseased lung is intratidal collapse and decollapse of lung units (atelectrauma) [32, 38], which may be seen both as an extension of the Mead model or a different disease mechanism. Lung damage may occur at the small airway level where the applied pressure acts on the

fluid meniscus, accelerating it towards the alveoli and damaging the epithelium [23]. A series of rat experiments showed that when the lungs were allowed to cyclically collapse and re-inflate, serious histological lung damage occurred [32], associated with cytokine release [7].

High PEEP mechanisms

Intratidal collapse and decollapse is almost unavoidable in ARDS, as it is related to the pathophysiology of the disease and, in particular, to the mechanism of lung collapse. The edematous lung becomes heavy and collapses under its own weight [14, 33]. The dependent (vertebral) lung regions become gasless, while the non-

Fig. 1 ▲ Effects of plateau pressure—no PEEP (positive end-expiratory pressure). The effects of different plateau pressures/tidal volumes on intratidal collapse and decollapse on a near completely collapsed ARDS lung. As shown, while increasing the plateau pressure/tidal volume the amount of tissue undergoing collapse/decollapse (light blue) increases

Fig. 2 ▲ Effect of PEEP. **a** The effect of adding a low PEEP level to the lung model shown in **Fig. 1**. As shown, part of the lung parenchyma would always be kept open through the respiratory cycle (gray), while the lung region undergoing intratidal opening and closing (light blue) should be reduced. **b** The putative effect of adding a higher PEEP level to the lung model shown in **Fig. 1**. As shown, a greater part of the lung parenchyma would be always kept open through the respiratory cycle compared to a lower PEEP model (gray), while the lung region undergoing intra-tidal opening and closing (light blue) should be reduced

dependent ones (sternal), even if they are edematous, remain inflated [33]. If the patient is positioned prone, the vertebral lung regions become non-dependent and re-inflate, while the sternal ones become dependent and collapse [20]. PEEP (positive end-expiratory pressure) works by overcoming the superimposed pressure and keeping open whatever lung region had been opened during the previous inspiration [21].

When a tidal volume/plateau pressure are applied, they overcome the surface forces at the level of the small airways

and open up the previously collapsed lung units [18]. **Fig. 1** shows the effect of different tidal volumes, and consequently opening pressures on a collapsed ARDS lung ventilated at zero end-expiratory pressure (ZEEP). The amount of collapsed lung tissue that regains inflation depends on the plateau pressure/ tidal volume applied, and the greater the applied plateau pressure, the greater the amount of lung tissue undergoing intratidal collapse and decollapse [18].

PEEP mechanism

PEEP acts on the closing pressures of the lung: at the end of inspiration the lung tissue collapses under its own weight. If an external counter-pressure is applied from the airways, the lung and this pressure is greater than the superimposed pressure and at least part of the lung parenchyma will be kept open through the respiratory cycle [21]. If we apply a PEEP to the model lung described above, part of the lung will be kept open and the fraction of the lung undergoing intratidal collapse and decollapse will be reduced (**Fig. 2a**). If the applied PEEP is increased in a model of “higher PEEP”, a further reduction in intratidal collapse and decollapse is expected (**Fig. 2b**). To summarize, higher PEEP keeps the lung open through the whole respiratory cycle, reducing opening and closing; in turn, the reduction in opening and closing would reduce VILI and improve patient survival.

The open lung theory and the lung protective strategy

The possible clinical translation of the experimental results, considering both the effects of high pressures/tidal volumes and intratidal collapse and decollapse can be summarized in the “lung protective strategy.” The lung protective strategy prescribes low tidal volumes to reduce lung stress and strain and high PEEP to make the lung homogeneous and abolish intratidal opening and closing. This strategy, as a whole, was tested in two randomized clinical trials, a small one by Amato [1] and a larger one by Villar et al. [40], both showing improved survival in the treatment arm. When the effects of tidal volume and PEEP were separated, tidal volume reduction was associated with improved survival [36], while higher PEEP was not [6, 28, 30, 41]. The ARDS network trial showed that 6 ml/Kg ideal body weight compared with 12 ml/Kg ideal body weight led a 10% reduction of mortality [36] and 6 ml/Kg is now recommended for the mechanical ventilation setting. Higher PEEP (approximately 15 cmH₂O) was compared with lower PEEP (approximately 8 cmH₂O or 13 cmH₂O in the ART trial) in four ran-

domized clinical trials enrolling 3264 patients (1010 in the ART trial [27] and 2264 in the ALVEOLI [6], ExPress [30], and LOV [28] trials). Average PEEP levels applied in randomized clinical trials are summarized in ■ Table 1. None of the trials showed improved survival in the higher PEEP group even if meta-analyses of the first three trials (ALVEOLI, LOV, ExPress) suggested a survival benefit in the more sick patients [5]. The ART trial [41], surprisingly, gave the paradoxical result of increased mortality in the higher PEEP group.

Bedside implementation of PEEP setting strategy

Several possible explanations for the failure of higher PEEP to provide increased survival have been proposed. A first possibility is that the random application of higher PEEP levels in an unslected patient population led to a reduction in intra-tidal collapse and decollapse in patients with higher recruitability and overdistension and damage in lower recruiters [22]. This hypothesis is supported by the results of meta-analyses that showed a possible benefit for higher PEEP in more severe and hypoxemic patients, who, putatively, have the greatest recruitability [5, 24]. The PEEP mechanism in protecting patients from VILI consists in abolishing lung inhomogeneity [15, 27] and opening and closing [32], which both target the anatomical lung status. These phenomena are not visible at the bedside and the better ventilatory treatment to heal the lung is not necessarily mirrored by an improvement in the parameters directly observable by the physician. Patients in the treatment group of the ARDS Network [36] that had lower mortality presented with worse oxygenation, higher carbon dioxide tension, and lower compliance (see ■ Table 2). An extreme example of what could have happened in the control group of the ARDS network is shown in ■ Fig. 3, where end-expiratory and end-inspiratory CT scans of an experimental ARDS model are shown [15]. The lung is completely collapsed at end-expiration, but re-inflates completely at end-inspiration. $\text{PaO}_2/\text{FiO}_2$ was 365 ± 160 , PaCO_2

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Does high PEEP prevent alveolar cycling?

Abstract

Acute respiratory distress syndrome (ARDS) patients need mechanical ventilation to sustain gas exchange. Animal experiments showed that mechanical ventilation with high volume/plateau pressure and no positive end-expiratory pressure (PEEP) damages healthy lungs, while low tidal volumes and the application of higher PEEP levels are protective. PEEP makes the lung homogeneous, reducing the pressure multiplication at the interface between lung units with different inflation statuses and keeps the lung open through the whole respiratory cycle, avoiding intratidal opening and closing. Four randomized clinical trials tested a higher PEEP strategy compared to a lower PEEP strategy but failed to show any survival benefit. These results, which apparently contradict preclinical data, may be explained by CT scanning, which investigates the behaviour of ARDS lung upon inflation and deflation demonstrating that:

(1) 15 cmH₂O PEEP is insufficient to overcome the closing pressures of the lung and keep it open through the whole respiratory cycle; (2) lung recruitment is continuous along the volume-pressure curve. The application of a PEEP level around 15 cmH₂O does not abolish opening and closing, but the lung region undergoing opening and closing is simply shifted downward, i. e. becomes more vertebral in the supine patient. (3) Recruited lung tissue becomes poorly inflated and not well inflated; poorly inflated tissue is inhomogeneous: while increasing PEEP the reduction in lung inhomogeneity is small or non-existent.

Keywords

Acute respiratory distress syndrome · Respiration, artificial · Ventilator-induced lung injury · Collapse and decollapse · Opening and closing

Verhindert ein hoher PEEP den zyklischen Kollaps der Alveolen?

Zusammenfassung

Patienten mit akutem Lungenversagen („acute respiratory distress syndrome“ [ARDS]) müssen beatmet werden, um den Gasaustausch aufrechtzuerhalten. Tierversuche belegen, dass eine Beatmung mit hohen Atemzugvolumina bzw. hohem Plateaudruck und ohne positiven endexpiratorischen Druck (PEEP) die gesunde Lunge schädigt, während niedrige Atemzugvolumina und die Anwendung eines hohen PEEP protektiv wirken. Der PEEP sorgt für einen homogenen Zustand der Lunge, indem er die starke Druckerhöhung an Grenzflächen zwischen Lungenabschnitten mit unterschiedlich starker Belüftung verringert. Zudem hält er die Lunge über den gesamten Atemzyklus hinweg offen und vermeidet ein intratidales Öffnen und Schließen. In vier randomisierten klinischen Studien wurden Beatmungsstrategien mit hohem und niedrigem PEEP verglichen. Ein Überlebensvorteil konnte aber nicht belegt werden. Diese Ergebnisse widersprechen offensichtlich präklinischen Daten und könnten mithilfe computertomographischer Untersuchungen zum Verhalten der ARDS-

Lunge bei Be- und Entlüftung erklärt werden. Hier zeigt sich: 1. Ein PEEP von 15 cmH₂O reicht nicht aus, um die Verschlussdrücke der Lunge zu überwinden und die Lunge über den gesamten Atemzyklus offen zu halten; 2. Die Lungenrekretierung nimmt entlang der Volumen-Druck-Kurve einen kontinuierlichen Verlauf. Mit einem PEEP von etwa 15 cmH₂O lässt sich das Öffnen und Schließen nicht unterbinden. Der sich öffnende und schließende Lungenabschnitt wird schlicht nach unten verschoben, das heißt, er wird bei einem Patienten in Rückenlage vertebraler. 3. Rekrutiertes Lungengewebe wird nicht etwa gut, sondern schlecht belüftet. Schlecht belüftetes Gewebe ist inhomogen; bei Erhöhung des PEEP nimmt die Lungeninhomogenität nur geringfügig oder gar nicht ab.

Schlüsselwörter

Akutes Lungenversagen · Beatmung · Beatmungsinduzierter Lungenschaden · Kollaps und Wiedereröffnung · Öffnen und Schließen

Fig. 3 ▲ Dissociation between bedside data and ventilator-induced lung injury. ■ Fig. 3 presents the end-expiratory and end-inspiratory CT scans of an experimental model of ARDS ventilated with a tidal volume close to the total lung capacity, which is always lethal within 54 h (Cressoni, Anesthesiology, [15]). $\text{PaO}_2/\text{FiO}_2$ was 365 ± 160 , PaCO_2 17 ± 7 (cmH₂O), and pH 7.53 ± 0.17

Table 1 PEEP levels used in randomized clinical trials at day 1. Table 1 summarizes the PEEP levels (cmH₂O) applied in randomized clinical trials at day 1. Data represent mean and standard deviation except for the ART trial, where they are reported as mean and 95% confidence interval

	Lower PEEP group	Higher PEEP group
ALVEOLI N Engl J Med 2004;351:327–36 [6]	8.9 ± 3.5	14.7 ± 3.5
LOV JAMA.2008;299(6):637–645 [28]	10.1 ± 3	15.6 ± 3.9
ExPress JAMA.2008;299(6):646–655 [30]	7.1 ± 1.8	14.6 ± 3.2
ART trial JAMA.2017, Sept 27 [41]	13 (12.7–13.3)	16.4 (16–16.7)

Table 2 Bedside variables in lower and higher tidal volume groups of the ARDS Network study. Table 2 summarizes data of $\text{PaO}_2/\text{FiO}_2$, PaCO_2 , and compliance of the respiratory system in the ARDS network trial (New England Journal of Medicine, 2000 [36]). Compliance of the respiratory system is computed from the averages presented in Table 3 of the original manuscript as: (minute ventilation/respiratory rate)/(plateau pressure—PEEP)

	Low tidal volume group	High tidal volume group
$\text{PaO}_2/\text{FiO}_2$	158 ± 73	176 ± 76
PaCO_2 (mm Hg)	40 ± 10	35 ± 8
Respiratory system compliance (ml/cmH ₂ O)	28	32

17 ± 7 mm Hg, and pH 7.53 ± 0.17 as gas exchange occurred during tidal ventilation but the ventilatory setting was lethal and the lung became unventilable within a few hours [15]. All these data taken together suggest that inflation-based methods like lung mechanics (applied in the Express trial, [30], stress-index [25], lung ultrasound [4], electrical impedance tomography [EIT], [12], or the absolute esophageal pressure values [9, 35]) do

not target the underlying pathophysiology and, in randomized clinical trials, did not select the patients who needed higher PEEP. The lung mechanics-based methods tend to select higher PEEP in less severe patients [9]. This may be relevant in explaining the results of the ART trial where PEEP was selected according to lung compliance, even if the PEEP difference in the two groups was limited to few cmH₂O. Oxygenation-based

methods (applied in the LOV [28] and ALVEOLI [6] trials) are roughly related to recruitability [9], but the sensibility and specificity in predicting recruitability is poor [22]. A second possible explanation for the failure of higher PEEP in improving survival is the possible detrimental effects of high PEEP on the right heart. High pressure levels during ventilation lead to the development of West zone 2 with increased shunt, dead space, and right ventricle afterload [39], leading to both the need to increase mechanical ventilation/power on the lung to maintain gas exchange and hemodynamic failure.

Is opening and closing real and what is the “real” effect of PEEP?

As clinical trials failed to show any clear survival benefit, one may wonder whether the “opening and closing” theory is real or if it is a mechanism occurring only in some experimental models, mainly rats [32]. Direct proof of VILI is nearly impossible to obtain in “real” ARDS patients, but a recent PET study [16] showed that the non-homogeneous lung regions at the interface between collapsed and inflated lung tissue, where putatively intra-tidal collapse and decollapse occur, are always inflamed.

Despite the relevance of the issue of opening and closing, just two studies measured intra-tidal collapse and decollapse at two different PEEP levels keeping the tidal volume constant and both were unable to demonstrate a significant intra-tidal collapse and decollapse reduction [11, 18]. We measured intra-tidal collapse and decollapse in 34 ARDS patients (18 severe ARDS) keeping the tidal volume constant at two PEEP levels, 5 and 15, which are close to the PEEP levels applied in all clinical trials. Intra-tidal collapse and decollapse was similar at the two PEEP levels (see ■ Fig. 4) and this pattern was similar independently of ARDS severity [18]. The absolute and percentage amount of collapse and decollapse increased with ARDS severity, but the effect of PEEP was similar in the three groups [18].

In fact, when a high PEEP is applied keeping the tidal volume unchanged, two

Fig. 4 ▲ Effect of higher and lower PEEP on intra-tidal collapse and decollapse at constant tidal volume in 34 ARDS patients. The amount of intra-tidal collapse and decollapse (gram of lung tissue) at PEEP 5 and 15 cmH₂O as mean and standard deviation, keeping the tidal volume constant. Data are taken from 34 ARDS patients published in Cressoni, Intensive Care Medicine [18]

Fig. 5 ▲ The “real” effect of higher PEEP. A lung model of lower and higher PEEP: as shown with higher PEEP, the region of intra-tidal collapse and decollapse is shifted downwards in the more dependent lung region

different phenomena occur simultaneously: first, the increased PEEP level keeps open a greater fraction of lung parenchyma located in the more dependent lung regions; second, at the same time, the tidal volume opens up some lung regions in the more dependent lung, shifting downwards the area of intra-tidal collapse and decollapse (■ Fig. 5). This explains why higher PEEP do not abolish intra-tidal collapse and decollapse.

The second assumption beyond the use of higher PEEP is that the lung would become more homogeneous upon recruitment. This would happen in a pure atelectasis model where all recruited lung units would re-gain normal gas/tissue status and normal mechanical properties; in ARDS, this does not happen, as the recruited lung units mainly become poorly inflated [10]. Upon recruitment, especially in the more severe patients,

one may see an increase in poorly inflated tissue, [10], which is strongly related to the lung inhomogeneity [15]. The lung inhomogeneity itself is not completely abolished, but is slightly reduced or may paradoxically increase [18].

Conclusions

In conclusion, the application of 15 cmH₂O PEEP does not reduce intra-tidal collapse and decollapse and lung inhomogeneity [18]. In consequence, the “open lung strategy” has never been tested as a whole in the published randomized clinical trials. One may wonder how a mechanical ventilation protocol aimed at the “open lung strategy” should be designed and if it would reduce mortality, as the effect on lung inhomogeneity is limited/non-existent [10, 13, 18]. To really apply the “open lung” strategy, a PEEP level sufficient to overcome the lung superimposed pressure [14, 21, 33], to keep the lung parenchyma open thorough the whole respiratory cycle, and to lift the chest wall is needed [9, 14]. This PEEP level would be around 20 cmH₂O, [14] greater than the one applied in clinical trials and higher than the one selected by the absolute esophageal pressure [9]. A recruitment maneuver performed at 45 cmH₂O should completely open up the lung and a PEEP around 20 cmH₂O should keep it open. Afterwards, one should set a tidal volume, perhaps keeping a plateau pressure limit of 30 cmH₂O (i. e., allowing for a driving pressure up to 10 cmH₂O). Two questions remain unsolved: first, what would happen to the lung units with opening pressure between 30 and 45 cmH₂O: would they stay open as PEEP overcomes their closing pressure or collapse again in the next few breaths? Second, would the tidal volume be sufficient to allow carbon dioxide removal?

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Compliance with Ethical Guidelines

Conflict of interest. M. Cressoni and L. Gattinoni hold an Italian patent (0001409041) and US patent (14/364,551) for the determination of lung inhomogeneities. C. Chiurazzi and D. Chiumello declare that they have no competing interests.

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