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Maintaining end-expiratory transpulmonary pressure prevents worsening of ventilator-induced lung injury caused by chest wall constriction in surfactant-depleted rats

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Abstract

Objective—To see whether in acute lung injury (ALI) 1) compression of the lungs caused by thoracoabdominal constriction degrades lung function and worsens ventilator-induced lung injury (VILI), and 2) maintaining end-expiratory transpulmonary pressure (P_L) by increasing positive end-expiratory pressure (PEEP) reduces the deleterious effects of chest wall constriction.

Design—Experimental study in rats.

Setting—Physiology laboratory.

Interventions—ALI was induced in 3 groups of 9 rats by saline lavage. Nine animals immediately sacrificed served as control group. Group L had lavage only, group LC had the chest wall constricted with an elastic binder, and group LCP had the same chest constriction but with PEEP raised to maintain end-expiratory P_L . After lavage, all groups were ventilated with the same pattern for 1½ hr.

Measurements and Main Results— P_L , measured with an esophageal balloon-catheter, lung volume changes, arterial blood gasses and pH were assessed during mechanical ventilation (MV). Lung wet-to-dry ratio (W/D), albumin, TNF- α , IL-1 β , IL-6, IL-10, and MIP-2 in serum and bronchoalveolar lavage fluid (BALF), and serum E-selectin and von Willebrand Factor (vWF) were measured at the end of MV. Lavage caused hypoxemia and acidemia, increased lung resistance and elastance, and decreased end-expiratory lung volume. With prolonged MV, lung mechanics, hypoxemia, and W/D were significantly worse in group LC. Pro-inflammatory cytokines except E-selectin were elevated in serum and BALF in all groups, with significantly greater levels of TNF- α , IL-1 β , and IL-6 in group LC, which also exhibited significantly worse bronchiolar injury and greater heterogeneity of airspace expansion at a fixed P_L than other groups.

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Conclusions—Chest wall constriction in ALI reduces lung volume, worsens hypoxemia, and increases pulmonary edema, mechanical abnormalities, pro-inflammatory mediator release, and histological signs of VILI. Maintaining end-expiratory P_L at prestriction levels by adding PEEP prevents these deleterious effects.

Keywords

esophageal pressure; respiratory mechanics; rat; acute lung injury; chest wall

INTRODUCTION

Acute respiratory distress syndrome and acute lung injury (ALI/ARDS) are devastating conditions that place heavy burdens on public health resources (1). Mechanical ventilation (MV) is often lifesaving, but it can also cause further lung injury. Indeed, ventilator-induced lung injury (VILI) is widely recognized as an important contributor to morbidity and mortality in ALI/ARDS.

Proposed mechanisms of VILI in ARDS include ‘volutrauma’, the excessive stretch of lung tissue, reduced by avoiding high tidal volumes and high airway pressures, and ‘atelectrauma’, mechanical shear stress caused by repetitive collapse and recruitment of air spaces (2), prevented by sufficient levels of positive end-expiratory pressure (PEEP). Whereas the protective effect of low tidal volume ventilation was established in a multi-center clinical trial (3), the optimal level of PEEP has been more difficult to determine. Numerous animal studies of experimental lung injury have shown that higher levels of PEEP can reduce the airway and parenchymal injury caused by repeated airspace collapse (4-16), but the simple expedient of increasing PEEP has sometimes not proven protective in controlled clinical trials (17-19). Why are animals clearly protected by higher PEEP whereas humans are not?

A likely explanation is that humans, unlike small animals, have a relatively stiff chest wall (rib cage and abdomen) that can apply a significant compressive force to the lungs' surface, changing the relationship between PEEP and the end-expiratory transpulmonary pressure (P_L) expanding the lungs. Many critically ill patients exhibit high intra-abdominal pressures (20) and high esophageal pressures (21) suggesting that differences in pleural pressure could cause a given level of PEEP to be excessive in some patients and insufficient in others. Following this rationale, Talmor et al. (22) measured esophageal pressure and compared two methods of setting PEEP; in the intervention group, PEEP was set high enough to maintain a positive P_L , and in the control group PEEP was set according to a sliding scale based on blood oxygenation (3). The intervention group showed improved respiratory compliance and oxygenation, and a trend toward improved survival, suggesting that P_L , estimated using an esophageal balloon, can be used to determine an appropriate level of applied PEEP.

To explore mechanisms that might explain the results of this clinical trial, we developed a rat model of ALI in which chest wall pressure-volume characteristics could be varied in a controlled manner and measured P_L using an esophageal balloon-catheter. Our hypothesis was that chest wall constriction at fixed PEEP would lower P_L , reduce lung volume, impair

lung function, and exacerbate VILI, whereas compensatory increases in PEEP that maintain precontraction levels of P_L would prevent the deleterious effects of chest wall constriction.

METHODS

Thirty-six male Sprague-Dawley rats (380–460 g) were premedicated with diazepam (10 mg·kg⁻¹), anesthetized with pentobarbital (40 mg·kg⁻¹) and chloral hydrate (170 mg·kg⁻¹), paralyzed with pancuronium (2 mg·kg⁻¹), intubated and ventilated. Ringer bicarbonate solution was infused at 4 ml·kg⁻¹·h⁻¹, and epinephrine was occasionally administered to maintain normal blood pressure.

Airflow, measured with a heated Fleisch pneumotachograph (no.0000, HS Electronics, March-Hugstetten, Germany), was numerically integrated to give volume change ($\dot{V}$). Pressures were measured at a side tap of the tracheal cannula (P_{tr}), in an esophageal balloon (P_{es}), and in the carotid artery (P_a). P_L was obtained as $P_{tr}-P_{es}$. The adequacy of P_{es} as a measure of pleural pressure was tested by measuring the ratio P_{tr}/P_{es} during rapid, manual rib cage compressions with closed airways, similar to the occlusion test (23). The esophageal pressure offset, determined after removal of lungs and heart (range: ± 1.2 cmH₂O [0.12 kPa]; average difference 0.3 ± 0.1 cmH₂O [0.03 kPa]) was subtracted from all P_{es} values. Arterial blood gasses (P_{aO_2} , P_{aCO_2}) and pH were measured with a blood gas analyzer (IL 1620, Instrumentation Laboratory, Milan, Italy).

Procedure and data analysis

Nine animals, instrumented as above, were immediately killed with an overdose of anesthetic to assess normal lung histology, lung wet-to-dry weight (W/D), and levels of albumin and inflammatory markers in serum and broncho-alveolar lavage fluid (BALF).

Using a computer-controlled ventilator (24), the remaining 27 rats were ventilated with fixed tidal volume (V_T ; 8 ml·kg⁻¹), inspiratory and expiratory times (0.25, 0.5 s), and an end-inspiratory pause (0.2 s).

After an initial 10-minute control period on MV with 21% oxygen and zero PEEP, the animals were ventilated with 90% oxygen and 6 cmH₂O (0.6 kPa) PEEP. ALI was induced by repeated intratracheal instillation and withdrawal of warm (38 °C) physiological saline in aliquots of 30 ml·kg⁻¹ until P_{aO_2} fell below 80 mmHg (10.7 kPa), and MV was continued for 1½ hours. Rats with ALI were randomly assigned to three groups of nine animals each: group L had no further intervention; group LC had elastic compression of the chest wall to cause a decrease in end-expiratory P_L of about 6 cmH₂O (0.6 kPa) at fixed PEEP; and group LCP had compression of the chest wall as above with restoration of end-expiratory P_L to pre-compression level by increased PEEP. Compression of the chest wall was accomplished by tightening a thin rubber sheet around the body from shoulders to pelvis. Measurements of respiratory mechanics, P_a , P_{aO_2} , P_{aCO_2} , and pH_a were performed at control, immediately after lavage, after chest wall compression, and at the end of MV.

After administration of a lethal dose of anesthetic, ~2 ml of blood were withdrawn from the heart for the assessment of cytokines and albumin. The isolated right lung, fixed at a P_L of

20 cmH₂O (2.0 kPa), was processed for histology by standard methods (6, 25). The main left bronchus was cannulated, the left lung removed, weighed immediately, lavaged with 4.3 ml·kg⁻¹ of normal saline in two aliquots of which ~60% was recovered, left overnight in an oven at 120 °C, and weighed again to compute W/D. The effluents were pooled, centrifuged for 10 min, and the supernatant frozen and stored at -20° C for subsequent assessment of cytokines and albumin concentration in BALF.

The study conformed to the American Physiological Society's guidelines for animal care and was approved by Ministero della Salute, Rome, Italy.

Respiratory system mechanics

Lung (L) and chest wall (W) interrupter resistance ($R_{int} = [\text{peak inflation pressure} - \text{end-inspiratory occlusion pressure}] / \text{inspiratory flow rate}$) and dynamic elastance during tidal ventilation ($E_{dyn} = [\text{end-inspiratory occlusion pressure} - \text{end-expiratory pressure}] / \text{tidal volume}$) were determined with the rapid end-inspiratory occlusion method (24). Pressure-volume (P-V) curves were obtained at control, immediately after lavage, after chest compression, and at the end of MV by slowly inflating the animal at 1 ml·s⁻¹ from end-expiratory lung volume (EELV) to a P_{tr} of 35 cmH₂O (3.5 kPa). Before all measurements, the lungs were inflated 3-4 times to P_{tr} of ~30 cmH₂O (3.0 kPa) to standardize volume history. After each P-V curve, the lungs were deflated to -20 cmH₂O (-2.0 kPa), and the volume expired between EELV and residual volume (EELV-RV) was used to assess changes in EELV.

Markers

Markers of inflammation known to be increased in animal models of ALI and human ARDS were used as indicators of lung injury. Analyses for TNF- α (26-28), IL-1 β (26), IL-6 (26, 27, 29), IL-10 (30), and MIP-2 (28) were carried out in duplicate in blinded fashion on BALF and serum using specific ELISA kits (Quantikine, R&D Systems, Inc., Minneapolis, MN and IBL, Japan). Sandwich enzyme immunoassays of E-selectin (31) and vWF (32) were performed on serum using goat (R&D System Inc, MN, USA) and sheep anti-rat antibodies (Affinity Biologicals Inc, Ancaster, Ontario, Canada). Albumin concentrations in the BALF supernatant and serum were assessed with the BCG method using a clinical chemistry analyzer (ADVIA 2004, Bayer Diagnostics Europe, Dublin, Ireland).

Histological analysis

Histological evaluation, performed as previously described (6, 25, 33) included: 1) the mean linear intercept (Lm) and its coefficient of variation, a measure of heterogeneity of airspace dimensions; 2) the bronchiolar injury score (IS), the percentage of membranous bronchioles exhibiting epithelial necrosis and sloughing (12, 33); and 3) the percentage of abnormal bronchiolar-alveolar attachments, an index of parenchymal damage.

In addition, parenchymal and vascular injury was assessed semi-quantitatively by four parameters (34): focal alveolar collapse in specimens fixed at a constant pressure, perivascular and peribronchial edema, recruitment of granulocytes to the air spaces, and hemorrhage.

Statistics

Analyses were performed using SPSS 11.5 (SPSS Inc., Chicago, IL). Results, except those below, are presented as mean $\pm$ SE. Comparisons among group mean values obtained under a given condition were performed by one-way ANOVA and Bonferroni post-hoc test. Comparisons between data obtained in the same group under subsequent conditions were performed by paired *t*-test. Results from marker assessments and histological studies are expressed as median and range. Comparisons among groups were performed by Kruskal-Wallis test, those between groups by Mann-Whitney test. The level for statistical significance was taken at *P* 0.05.

RESULTS

Under control conditions, arterial blood gasses, pH_a, systemic blood pressure (Figure 1), respiratory mechanical variables (Figure 2), and inflation P-V curves (Figure 3) were similar in all groups. All animals survived lung lavage and the subsequent period of MV. The groups did not differ in the fraction of lavage fluid retained by the lung (9 $\pm$ 1%) or in the total time of the experiment (225 $\pm$ 6 min).

Immediate effects of lung lavage and PEEP

After lung lavage, application of a PEEP of 6 $\pm$ 0.1 cmH₂O (0.6 kPa) maintained EELV-RV at pre-lavage levels in all groups (Figure 2). PaO₂ and pH_a decreased significantly, while PaCO₂ and Pa were unchanged (Figure 1).

Tidal (Ptr,_T) and peak tracheal pressure (Ptr,pk), and end-expiratory (P_L,e-exp) and end-inspiratory transpulmonary pressure (P_L,e-insp) increased in all groups (Table 1). The increases of Rint,_L and Edyn,_L were similar in all groups, while Rint,_w and Edyn,_w were unchanged.

While the chest wall P-V curve during inflation from EELV was unaffected, both lung and respiratory system P-V curves were shifted rightwards and downwards, indicating increased elastic recoil at any lung volume and reduced quasi-static compliance; these changes were similar in all groups (Figure 3).

Immediate effects of chest wall compression and increased PEEP

Chest compression increased both Ptr,_T and Ptr,pk (Table 1). PaO₂, PaCO₂, pH_a, and Pa were unaffected (Figure 1). In group LC, in which PEEP was kept at 6 cmH₂O (0.6 kPa), P_L,e-exp and EELV-RV decreased significantly, whereas they were unchanged in group LCP (Table 1, Figure 2), in which PEEP was increased to 11.0 $\pm$ 0.4 cmH₂O (1.1 kPa) to maintain end-expiratory P_L at pre-compression levels. While Rint,_w was unaffected, Rint,_L, Edyn,_L, and Edyn,_w increased in both groups, the last becoming slightly but significantly higher in group LCP (Figure 2).

The chest wall inflation P-V curve shifted rightwards, with an increase in elastic recoil pressure of ~5 cmH₂O (0.5 kPa) at EELV (Figure 3). In group LC, P_L at EELV decreased substantially, and the lung inflation P-V curve shifted downwards and rightwards, while in group LCP, it was unchanged (Figure 3).

Comparisons between groups LCP and LC reveal the effects of increased PEEP after chest wall constriction. Higher PEEP decreased $P_{tr,T}$ and increased $P_{L,e-exp}$ without increasing $P_{L,e-insp}$ (Table 1). Indeed, after lung lavage the pulmonary P-V curves became markedly concave upward at low lung volumes (Figure 3), so that increasing PEEP increased lung compliance.

Effects of prolonged mechanical ventilation

Prolonged mechanical ventilation increased $P_{tr,T}$ and $P_{tr,pk}$ in group LC only, PEEP being kept constant in all groups (Table 1). While P_{aCO_2} , pH_a , and P_a did not change significantly, P_{aO_2} increased markedly in group LCP, becoming significantly higher than that in group LC and similar to that in group L (Figure 1).

EELV-RV remained essentially unchanged throughout the ventilation period in all groups (Figure 2); hence, EELV-RV and the corresponding P_L were lower in group LC than in groups L and LCP, which were similar (Table 1 and Figure 3). While $R_{int,w}$ remained at control values, $Edyn,w$ increased in groups LC and LCP; it was similar in these groups and significantly greater than in group L (Figure 2). $R_{int,L}$ and $Edyn,L$ increased significantly in group LC only; they were similar in groups L and LCP, and significantly lower than in group LC (Figure 2).

Markers

Serum levels of TNF- α , IL-6, MIP-2, IL-10, and vWF were increased relative to normal values in all groups, whereas E-selectin (late endothelial factor) and IL-1 β were not. There was no difference among groups in serum levels of biomarkers (Figure 4).

In BALF, TNF- α , IL-1, IL-6, MIP2, and IL-10 were all increased relative to normal values in all groups. None of these markers differed significantly between groups L and LCP. In contrast, TNF- α , IL-1, and IL-6 levels were significantly higher in group LC than group LCP (Figure 4).

Histology

Small airway injury (bronchiolar injury score) and parenchymal damage (disruption of bronchiolar-alveolar attachments) were significantly greater than normal in all groups, bronchiolar injury score being significantly higher in group LC than in other groups. At an inflation pressure of 20 cmH₂O (2.0 kPa), the mean value of L_m was not significantly different from normal in any group (Table 2), but the coefficient of variation of L_m was substantially greater than normal in group LC, indicating greater heterogeneity of airspace expansion.

Parenchymal and vascular injury scores were significantly higher than normal in all groups, and although more pronounced in group LC, they were not significantly different among groups (Table 3). W/D and A_{BALF}/A_{SER} ratios were significantly greater than normal in all groups (Table 3). W/D was significantly higher in group LC than in groups L and LCP. A_{BALF}/A_{SER} , though somewhat greater in group LC, did not differ among groups.

DISCUSSION

In this animal model, saline lavage followed by mechanical ventilation increased pulmonary elastance and resistance, lowered arterial P_{O_2} , caused release of markers of inflammation into blood and BALF, and produced physical and histological evidence of airway and parenchymal injury. The imposition of chest constriction caused further deterioration of pulmonary mechanics, worsened hypoxemia, increased release of markers of inflammation, and increased VILI as evidenced by pulmonary edema, heterogeneity of postmortem alveolar expansion at a given transpulmonary pressure, and bronchiolar injury score. However, when animals with similar chest constriction had their transpulmonary pressure maintained by additional PEEP, the deleterious effects of chest constriction, including hypoxemia, lung resistance and elastance, mediator release, edema formation, heterogeneity of postmortem lung expansion and bronchiolar damage, were reduced or prevented.

Why did chest constriction make gas exchange, lung mechanics, and VILI worse? Thoracoabdominal binding shifted the P-V characteristic of the chest wall (Figure 3) to higher pleural pressure, lowering transpulmonary pressure and EELV at a constant PEEP (Figures 2 and 3). In numerous animal models, such reduction in end-expiratory pressure or volume in ALI has been shown to worsen VILI and increase surfactant dysfunction and inflammatory cytokine release (4-16). In those models, a relatively compliant chest wall and/or widely opened chest (6, 24, 25, 33) assured that varying levels of PEEP produced corresponding levels of end-expiratory transpulmonary pressure. However, this is not the case in human disease or our animal model, where altered chest wall characteristics increased end-expiratory pleural pressure, decreased transpulmonary pressure and EELV at a given level of PEEP, and facilitated the development of VILI, thus providing the first demonstration that thoracoabdominal constriction can worsen lung injury in ALI, and that the deleterious effects of chest constriction can be prevented by maintaining end-expiratory transpulmonary pressure estimated with an esophageal balloon.

Both PEEP and chest wall constriction can be protective or harmful depending on transpulmonary pressure. For example, chest wall constriction, harmful in our study, can protect the lungs from overdistension by reducing transpulmonary pressure (35, 36), and adding PEEP, beneficial in our study, can exacerbate lung damage by increasing transpulmonary pressure (27). The unmeasured effects of chest constriction and PEEP may explain why clinical trials in ARDS that applied higher PEEP without estimating transpulmonary pressure (or reducing tidal volume) have not shown a survival benefit (17-19), calling into question the protective role of PEEP (37). Although pleural pressure is usually unmeasured in critical illness, esophageal and intra-abdominal pressures are known to vary widely and are often markedly elevated (20, 21, 38). If pleural pressures are similarly variable, a given level of PEEP could be inadequately low in patients with high pleural pressure or dangerously high in patients with a low pleural pressure. Failure to take into account differing levels of pleural pressure could confound the attempts to determine optimum PEEP in patients with ALI. Gattinoni and others have emphasized the importance of chest wall elastance in determining peak and tidal excursions of transpulmonary pressure (4, 37), but they have not evaluated the end-expiratory esophageal pressure, which is the relevant variable in setting PEEP. Since end-expiratory transpulmonary pressure is not

correlated with chest wall elastance (38), it can be predicted only by measuring end-expiratory esophageal pressure.

Esophageal balloon-catheters in rats provided estimates of pleural pressure consistent with principles of respiratory physiology (39). The lung inflationary P-V curves showed the characteristic changes associated with ALI, including a decrease in compliance and an increase in recoil pressure at a given lung volume. Importantly, the P-V curves of the chest wall were unaffected by lavage, as has been found in a dog model of ARDS (40). Similarly, chest wall compression caused predictable changes in the chest wall P-V curve without substantially affecting the pulmonary P-V curves, which were nearly superimposed over the same volume range in groups LC and LCP. These results suggest, moreover, that even with injured lungs the absolute value of P_{es} can be a useful reflection of the overall pleural pressure. Indeed, in a given animal, the P_L computed from P_{es} at end-expiration just before opening the chest and P_L computed from P_{tr} immediately after clamping the trachea and widely opening the chest agreed within ± 1.2 cmH₂O (0.1 kPa).

Talmor et al. (22) showed that patients with ALI/ARDS whose PEEP was set to maintain transpulmonary pressure in a prescribed range had better blood oxygenation and dynamic compliance than those whose PEEP was set based on oxygenation. Those physicians adopted this strategy because, in contrast with the present experimental model, they could not know how the pressures they measured were related to chest wall compression of the lungs. Our experimental results, showing for the first time that maintaining $P_{L,e-exp}$ in the face of chest wall constriction can be protective in ALI, support the clinical use of the strategy adopted by Talmor et al.

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REFERENCES

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005; 353:1685–1693. [PubMed: 16236739]
2. Slutsky AS. Lung injury caused by mechanical ventilation. *Chest*. 1999; 116:9S–15S. [PubMed: 10424561]
3. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. *N Engl J Med*. 2000; 342:1301–1308. [PubMed: 10793162]
4. Chiumello D, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999; 160:109–116. [PubMed: 10390387]
5. Chu EK, Whitehead T, Slutsky AS. Effects of cyclic opening and closing at low- and high-volume ventilation on bronchoalveolar lavage cytokines. *Crit Care Med*. 2004; 32:168–174. [PubMed: 14707576]
6. D'Angelo E, Pecchiari M, Baraggia P, et al. Low-volume ventilation causes peripheral airway injury and increased airway resistance in normal rabbits. *J Appl Physiol*. 2002; 92:949–956. [PubMed: 11842025]
7. Duggan M, McCaul CL, McNamara PJ, et al. Atelectasis causes vascular leak and lethal right ventricular failure in uninjured rat lungs. *Am J Respir Crit Care Med*. 2003; 167:1633–1640. [PubMed: 12663325]

8. Halter JM, Steinberg JM, Schiller HJ, et al. Positive end-expiratory pressure after a recruitment maneuver prevents both alveolar collapse and recruitment/derecruitment. *Am J Respir Crit Care Med.* 2003; 167:1620–1626. [PubMed: 12615628]
9. Herrera MT, Toledo C, Valladares F, et al. Positive end-expiratory pressure modulates local and systemic inflammatory responses in a sepsis-induced lung injury model. *Intensive Care Med.* 2003; 29:1345–1353. [PubMed: 12698249]
10. Ko SC, Zhang H, Haitisma JJ, et al. Effects of peep levels following repeated recruitment maneuvers on ventilator-induced lung injury. *Acta anaesthesiologica Scandinavica.* 2008; 52:514–521. [PubMed: 18261196]
11. Monkman SL, Andersen CC, Nahmias C, et al. Positive end-expiratory pressure above lower inflection point minimizes influx of activated neutrophils into lung. *Crit Care Med.* 2004; 32:2471–2475. [PubMed: 15599153]
12. Muscedere JG, Mullen JB, Gan K, et al. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med.* 1994; 149:1327–1334. [PubMed: 8173774]
13. Nakazawa K, Yokoyama K, Yamakawa N, et al. Effect of positive end-expiratory pressure on inflammatory response in oleic acid-induced lung injury and whole-lung lavage-induced lung injury. *Journal of anesthesia.* 2007; 21:47–54. [PubMed: 17285413]
14. Tremblay L, Valenza F, Ribeiro SP, et al. Injurious ventilatory strategies increase cytokines and c-fos m-rna expression in an isolated rat lung model. *The Journal of clinical investigation.* 1997; 99:944–952. [PubMed: 9062352]
15. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis.* 1974; 110:556–565. [PubMed: 4611290]
16. Wyszogrodski I, Kyei-Aboagye K, Taeusch HW Jr. et al. Surfactant inactivation by hyperventilation: Conservation by end-expiratory pressure. *J Appl Physiol.* 1975; 38:461–466. [PubMed: 1097385]
17. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The multicenter trial group on tidal volume reduction in ards. *Am J Respir Crit Care Med.* 1998; 158:1831–1838. [PubMed: 9847275]
18. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004; 351:327–336. [PubMed: 15269312]
19. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and volume-limited ventilation strategy group. *N Engl J Med.* 1998; 338:355–361. [PubMed: 9449728]
20. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: A multicentre epidemiological study. *Intensive Care Med.* 2004; 30:822–829. [PubMed: 14758472]
21. Talmor D, Sarge T, O'Donnell CR, et al. Esophageal and transpulmonary pressures in acute respiratory failure. *Crit Care Med.* 2006; 34:1389–1394. [PubMed: 16540960]
22. Talmor D, Sarge T, Malhotra A, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med.* 2008; 359:2095–2104. [PubMed: 19001507]
23. Baydur A, Behrakis PK, Zin WA, et al. A simple method for assessing the validity of the esophageal balloon technique. *Am Rev Respir Dis.* 1982; 126:788–791. [PubMed: 7149443]
24. D'Angelo E, Pecchiari M, Saetta M, et al. Dependence of lung injury on inflation rate during low-volume ventilation in normal open-chest rabbits. *J Appl Physiol.* 2004; 97:260–268. [PubMed: 15020576]
25. D'Angelo E, Pecchiari M, Della Valle P, et al. Effects of mechanical ventilation at low lung volume on respiratory mechanics and nitric oxide exhalation in normal rabbits. *J Appl Physiol.* 2005; 99:433–444. [PubMed: 15761084]
26. Oeckler RA, Hubmayr RD. Ventilator-associated lung injury: A search for better therapeutic targets. *Eur Respir J.* 2007; 30:1216–1226. [PubMed: 18055706]

27. Villar J, Herrera-Abreu MT, Valladares F, et al. Experimental ventilator-induced lung injury: Exacerbation by positive end-expiratory pressure. *Anesthesiology*. 2009; 110:1341–1347. [PubMed: 19417614]
28. Wolthuis EK, Vlaar AP, Choi G, et al. Mechanical ventilation using non-injurious ventilation settings causes lung injury in the absence of pre-existing lung injury in healthy mice. *Critical care* (London, England). 2009; 13:R1.
29. Vaneker M, Joosten LA, Heunks LM, et al. Low-tidal-volume mechanical ventilation induces a toll-like receptor 4-dependent inflammatory response in healthy mice. *Anesthesiology*. 2008; 109:465–472. [PubMed: 18719444]
30. Belperio JA, Keane MP, Lynch JP 3rd, et al. The role of cytokines during the pathogenesis of ventilator-associated and ventilator-induced lung injury. *Seminars in respiratory and critical care medicine*. 2006; 27:350–364. [PubMed: 16909369]
31. Okajima K, Harada N, Sakurai G, et al. Rapid assay for plasma soluble e-selectin predicts the development of acute respiratory distress syndrome in patients with systemic inflammatory response syndrome. *Transl Res*. 2006; 148:295–300. [PubMed: 17162250]
32. Ware LB, Eisner MD, Thompson BT, et al. Significance of von willebrand factor in septic and nonseptic patients with acute lung injury. *Am J Respir Crit Care Med*. 2004; 170:766–772. [PubMed: 15201135]
33. D'Angelo E, Pecchiari M, Gentile G. Dependence of lung injury on surface tension during low-volume ventilation in normal open-chest rabbits. *J Appl Physiol*. 2007; 102:174–182. [PubMed: 16959911]
34. Taskar V, John J, Evander E, et al. Surfactant dysfunction makes lungs vulnerable to repetitive collapse and reexpansion. *Am J Respir Crit Care Med*. 1997; 155:313–320. [PubMed: 9001330]
35. Dreyfuss D, Soler P, Basset G, et al. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis*. 1988; 137:1159–1164. [PubMed: 3057957]
36. Hernandez LA, Peevy KJ, Moise AA, et al. Chest wall restriction limits high airway pressure-induced lung injury in young rabbits. *J Appl Physiol*. 1989; 66:2364–2368. [PubMed: 2745302]
37. Gattinoni L, Caironi P, Carlesso E. How to ventilate patients with acute lung injury and acute respiratory distress syndrome. *Curr Opin Crit Care*. 2005; 11:69–76. [PubMed: 15659948]
38. Loring SH, O'Donnell CR, Behazin N, et al. Esophageal pressures in acute lung injury: Do they represent artifact or useful information about transpulmonary pressure, chest wall mechanics, and lung stress? *J Appl Physiol*. 108:515–522. [PubMed: 20019160]
39. Agostoni, E.; Hyatt, RE. Static behavior of the respiratory system.. In: Macklem, PT.; Mead, J., editors. *Handbook of physiology*. Vol. III. American Physiological Society; Bethesda, MD: 1986. p. 113-130.
40. Pelosi P, Goldner M, McKibben A, et al. Recruitment and derecruitment during acute respiratory failure: An experimental study. *Am J Respir Crit Care Med*. 2001; 164:122–130. [PubMed: 11435250]

1.

Arterial blood pressure (Pa), pH, P_{CO_2} , and P_{O_2} , under various conditions in groups L, LC, and LCP. * Significant difference from preceding condition. + Significant difference from other groups under the same condition.

2.

Interrupter resistance (Rint), dynamic elastance (Edyn) of the chest wall (W) and lung (L), and difference between end-expiratory lung volume and residual volume (EELV-RV), under various conditions in groups L, LC, and LCP. * Significant difference from preceding condition. + Significant difference from other groups under the same condition.

3.

Quasi-static inflation P-V curves of the respiratory system (P_{RS}), chest wall (P_w) and lung (P_L) before lavage (control), immediately after lavage (and before chest constriction in groups LC and LCP), and at the end of the experiment. Volumes are ml above RV. Bars are SE.

4.

Box plots of cytokine concentrations (whiskers indicate 90th and 10th percentiles) in serum and broncho-alveolar lavage fluid (BALF) at the end of the experiment in all groups. Cytokine levels in both serum and BALF were greater than normal values, except IL-1 β in serum. + Significantly greater in group LC than in group LCP.

Table 1

Body weight and ventilation parameters in rats with lavage only (Group L), with lavage and chest compression (Group LC), and with lavage, chest compression, and increased PEEP (Group LCP).

			Group L	Group LC	Group LCP
Body wt.	kg		0.40±0.01	0.40±0.01	0.40±0.01
V _T	ml		3.22±0.08	3.22±0.07	3.18±0.09
Ṡ	ml/min		203.7±5.2	203.2±4.2	200.9±5.8
PEEP	control	cmH ₂ O	0	0	0
	lavage	cmH ₂ O	6.0±0.1	6.0±0.1	6.0±0.1
	binding	cmH ₂ O		6.0±0.1	11.0±0.4
	final	cmH ₂ O	6.1±0.1	6.1±0.1	11.1±0.4
Ptr, _T	control	cmH ₂ O	8.1±0.3	8.4±0.2	8.2±0.4
	lavage	cmH ₂ O	18.4±1.1 [†]	19.6±0.7 [†]	19.2±0.8 [†]
	binding	cmH ₂ O		26.3±0.8 [†]	23.2±1.2 [†]
	final	cmH ₂ O	20.3±1.2	29.2±0.7 ^{†§}	24.5±1.2
Ptr, _{pk}	control	cmH ₂ O	8.2±0.3	8.4±0.2	8.2±0.4
	lavage	cmH ₂ O	24.4±1.1 [†]	25.6±0.8 [†]	25.2±0.8 [†]
	binding	cmH ₂ O		32.3±0.9 [†]	34.2±1.1 [†]
	final	cmH ₂ O	26.4±1.1	35.3±0.7 [†]	35.6±1.2
Pl, _{e-exp}	control	cmH ₂ O	1.2±0.1	1.1±0.1	1.1±0.1
	lavage	cmH ₂ O	7.3±0.1 [†]	7.0±0.1 [†]	7.0±0.1 [†]
	binding	cmH ₂ O		1.3±0.1 [†]	7.0±0.2
	final	cmH ₂ O	7.3±0.2	1.4±0.1 ^{†§}	6.9±0.2
Pl, _{e-insp}	control	cmH ₂ O	6.1±0.3	5.8±0.2	5.6±0.4
	lavage	cmH ₂ O	21.2±0.9 [†]	22.1±0.7 [†]	21.4±0.8 [†]
	binding	cmH ₂ O		21.5±0.8	23.7±0.9
	final	cmH ₂ O	23.1±1.1	24.3±0.7 [†]	24.0±0.9

Measurements were made under control conditions and immediately after lavage, chest compression (binding), and prolonged ventilation (final).

V_T, tidal volume; Ṡ, pulmonary ventilation; PEEP, positive end-expiratory airway pressure; Ptr,_T, tidal excursion in tracheal pressure; Ptr,_{pk}, peak tracheal pressure during tidal ventilation; Pl,_{e-exp} and Pl,_{e-insp}, end-expiratory and end-inspiratory transpulmonary pressure. Values are mean ±SE. Significantly different from preceding condition

[†]P 0.05; significantly different from Groups L and LCP

[§]P 0.05.

Table 2

Indices of airspace expansion and bronchiolar injury in normal and lavaged rats after 1½ hours of mechanical ventilation without (Group L) and with chest compression at lowered (Group LC) or preserved end-expiratory transpulmonary pressure (Group LCP).

	N	Lm (μ)	CV of Lm (%)	IS (%)	A-A (%)
Normal	9	74±3	20±1	8.9 (7-14)	11.8 (10-17)
Group L	9	69±3	29±2	13.5 (8-31) [†]	17.4 (12-20) [†]
Group LC	9	67±3	41±5 [†]	21.3 (11-31) ^{†§}	20.9 (12-29) [†]
Group LCP	9	67±3	30±5	16.2 (10-25) [†]	13.3 (9-19) [†]

N, number of animals; Lm, mean linear intercept; CV, coefficient of variation; IS, bronchiolar injury score; A-A, percentage of ruptured bronchiolar-alveolar attachments. Values are median with range in parentheses, except for Lm and CV which are mean±SE.

[†] Significantly different from normal: P 0.05

[§] significantly different from Groups L and LCP: P 0.040.

Table 3

Indices of parenchymal and vascular injury in normal and lavaged rats after 1½ hours of mechanical ventilation without (Group L) and with chest compression at lowered (Group LC) or preserved end-expiratory transpulmonary pressure (Group LCP)

Parameters		Injury score/ Number of rats			
		-	+	++	+++
Normal	focal alveolar collapse	9			
	perivascular edema	9			
	peribronchial edema	9			
	hemorrhage	9			
	alveolar granulocytes	9			
	W/D				4.2±0.1
	ABALF/ASER, %				1.5±0.1
Group L	focal alveolar collapse [†]	1	7	1	
	perivascular edema [†]	3	3	3	
	peribronchial edema	9			
	hemorrhage [†]	4	3	2	
	alveolar granulocytes [†]	1	4	4	
	W/D [†]				8.1±0.1
	ABALF/ASER, % [†]				11.3±1.5
Group LC	focal alveolar collapse [†]		4	4	1
	perivascular edema [†]	1	4	3	1
	peribronchial edema	8	1		
	hemorrhage [†]	7	2		
	alveolar granulocytes [†]	1	4	2	2
	W/D [†]				8.6±0.1 [§]
	ABALF/ASER, % [†]				15.3±1.3
Group LCP	focal alveolar collapse [†]	3	4	2	
	perivascular edema [†]	3	4	2	
	peribronchial edema	9			
	hemorrhage [†]	7	2		
	alveolar granulocytes [†]	2	4	3	
	W/D [†]				8.1±0.2
	ABALF/ASER, % [†]				12.5±2.0

Injury score: - absent, + mild, ++ moderate, +++ marked. Values of W/D and ABALF/ASER are mean±SE. W/D, lung wet-to-dry ratio; ABALF/ASER, ratio of broncho-alveolar lavage fluid to serum albumin concentration.

[†]Significantly different from normal: P 0.05

[§]significantly different from Groups L and LCP: P 0.042.