



Recruitment Maneuver Does not Increase the Risk of Ventilator Induced Lung Injury

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ABSTRACT

Background: Mechanical ventilation (MV) may induce lung injury.

Aims: To assess and evaluate the role of different mechanical ventilation strategies on ventilator-induced lung injury (VILI) in comparison to a strategy which includes recruitment manoeuvre (RM).

Study design: Randomized animal experiment.

Methods: Thirty male Sprague-Dawley rats were anaesthetised, tracheostomised and divided into 5 groups randomly according to driving pressures; these were mechanically ventilated with following peak alveolar opening (Pao) and positive end-expiratory pressures (PEEP) for 1 hour:

Group 15-0: 15 cmH₂O Pao and 0 cmH₂O PEEP; Group 30-10: 30 cmH₂O Pao and 10 cmH₂O PEEP; Group 30-5: 30 cmH₂O Pao and 5 cmH₂O PEEP; Group 30-5&RM: 30 cmH₂O Pao and 5 cmH₂O PEEP with additional 45 cmH₂O CPAP for 30 seconds in every 15 minutes; Group 45-0: 45 cmH₂O Pao and 0 cmH₂O PEEP

Before rats were sacrificed, blood samples were obtained for the evaluation of cytokine and chemokine levels; then, the lungs were subsequently processed for morphologic evaluation.

Results: Oxygenation results were similar in all groups; however, the groups were lined as follows according to the increasing severity of morphometric evaluation parameters: Group 15-0: (0±0.009) < Group 30-10: (0±0.14) < Group 30-5&RM: (1±0.12) < Group 30-5: (1±0.16) < Group 45-0: (2±0.16). Besides, inflammatory responses were the lowest in 30-5&RM group compared to all other groups. TNF-α, IL-1β, IL-6, MCP-1 levels were significantly different between group 30-5&RM and group 15-0 vs. group 45-0 in each group.

Conclusion: RM with low PEEP reduces the risk of ventilator-induced lung injury with a lower release of systemic inflammatory mediators in response to mechanical ventilation.

Key Words: Recruitment manoeuvre, ventilator-induced lung injury, TNF-α, IL-1β, IL-6, MCP-1

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Introduction

Mechanical ventilation is the most frequently used supportive treatment in intensive care units. However, there are increasing evidences that mechanical ventilation may induce lung injury (1); therefore, pressure limited ventilation strategies like lower tidal volumes with increasing positive end-expiratory pressure (PEEP) levels, and prone positioning have been developed to reduce ventilator-induced lung injury (VILI). Animal experiments have repeatedly demonstrated that mechanical ventilatory settings are important determinants of VILI (1). Recently, a large clinical trial that consisted of 861 Acute lung injury/Acute respiratory distress syndrome (ALI/ARDS) patients showed that a low tidal volume (VT, 6mL/kg) as compared to a high tidal volume (12 mL/kg) setting during mechanical ventilation significantly decreased mortality (2). Amato et al. (3) were the first group to demonstrate that the mechanical ventilation strategy is an important de-

terminant of mortality in ARDS patients. They proposed to set PEEP based on the inflation pressure volume (PV) curve's lower inflection point, and limit VT to maintain end-inflation plateau pressures under the upper inflection point of the P-V curve. In this study, sustained inflation manoeuvres were used to recruit collapsed lung units after suctioning or loss of PEEP (3). In accordance with this study, the routine limitation of inspiratory pressure does not necessarily improve outcome (4, 5). It is also recommended to use intermittent recruitment manoeuvres like sustained inflation or sigh for improving oxygenation and protecting the lungs from injury due to shear stresses of repetitive opening and closing (6-9).

Rimensberger et al. (10) have previously shown that low PEEP levels (lower than inflection point) with sustained inflation are protective against the augmentation of injury in surfactant-depleted rabbit lung. However, lung diseases that necessitate mechanical ventilation, like ALI and ARDS, are not diffuse and consist of healthy and damaged lung regions (11).



Recently it has been shown that recruitment manoeuvre (RM) in a healthy rat model RM does not cause bacterial translocation (12). However, the role of RM in inducing VILI is not clear.

We hypothesised that RM does not induce VILI. To test this hypothesis we compared different mechanical ventilation strategies with different PEEP and peak airway pressures against a strategy which includes RM.

Materials and Methods

Animal Preparation

The study protocol was approved by the Istanbul University, Experimental Medicine and Research Institute, Animal Investigation Committee. Thirty male 250-300 g Sprague-Dawley rats were used. After the induction of anaesthesia (1-2% enflurane (Ethrane, Abbott Labs., North Chicago, USA), 35% nitrous oxide, 65% oxygen) the rats were tracheostomised and ventilated using pressure controlled ventilation (Siemens Servo 900C, Siemens-Solna, Sweden) with 15 cmH₂O peak airway opening pressure (Pao), 0 cmH₂O PEEP, 30 breaths per minute, inspiratory/expiratory (I/E)=1/2, and fraction of inspired oxygen (FiO₂) =1.0. Intraperitoneal ketamine (70-80 mg/kg) was used for maintenance of anaesthesia and vecuronium bromide (0.5 mg/kg Norcuron, Organon Teknika B.V., Boxtel, The Netherlands) for muscle relaxation, respectively. A 24 G catheter (Insite-W, Becton Dickinson Infusion Therapy systems Inc., Utah, USA) was introduced into the left or right carotid artery after surgical exploration for drawing blood samples and arterial blood pressure monitoring (Mercury, Mennen Medical Inc., New York, USA) and disposable transducers (Deltran ABL system, Medical product Inc, Utah, USA) were used. Rectal temperature was monitored on the same monitor and kept constant at 37±1°C by using a heating pad. Blood gas analysis was performed (ABL 700, Radiometer, Copenhagen, Denmark) under anaerobic conditions immediately after sampling.

Experimental Protocol

The rats were subsequently separated into one of five groups according to ventilatory driving pressures, and, after drawing 0.5 mL blood for a baseline blood gas analysis, ventilation was set as follows in each group:

1. Group 15-0: 15 cmH₂O Pao and 0 cmH₂O PEEP
2. Group 30-10: 30 cmH₂O Pao and 10 cmH₂O PEEP
3. Group 30-5: 30 cmH₂O Pao and 5 cmH₂O PEEP
4. Group 30-5&RM: 30 cmH₂O Pao and 5 cmH₂O PEEP with additional 45 cmH₂O CPAP for 30 seconds in every 15 minutes

5. Group 45-0: 45 cmH₂O Pao and 0 cmH₂O PEEP.

The remaining ventilator parameters were kept as at baseline. Mean arterial pressure and ventilator parameters were measured continuously and recorded during the experiment every 5 minutes. We infused fluids when mean arterial blood pressure decreased by more than 20% of the baseline value. At the end of the experiment, 5.5 mL blood was drawn for blood gas analysis (0.5 mL) and cytokine level measurement (5mL). Then, the animals were sacrificed using 120 mg/kg of sodium thiopental.

Cytokine and Chemokine Levels

Five millilitres of anti-coagulated blood that was drawn at the end of the experiment was centrifuged. The plasma was stored at -80°C until cytokine and chemokine levels were measured. Tumour necrosis factor-a (TNF-a, Bender Medsystem, Diagnostic GmbH, A-1030-Rennweg, Vienna, Austria; assay range: 39-2500 pg/mL), interleukin-1b (IL-1b, Bender Medsystem, Diagnostic GmbH, A-1030-Rennweg, Vienna, Austria; assay range: 25.6-2500 pg/mL), interleukin-6 (IL-6, Bender Medsystem, Diagnostic GmbH, A-1030-Rennweg, Vienna, Austria; assay range: 31.25-2000 pg/mL), monocyte chemoattractant protein-1 (MCP-1, Biosource Cyto Screen Int., Camarillo, CA, USA; assay range: 11.7-750 pg/mL) levels were measured by enzyme-linked immunosorbent assay (ELISA) on the same day. These analyses were performed in a blinded fashion. There was no cross-reactivity between the measured variables.

Morphologic evaluation

The histopathological analysis was performed by a pathologist who was also blinded to the study groups. At the end of the study, lungs were removed and fixed with intratracheal instillation of 10% formalin, and also floated in formalin for at least 24 hours. The lungs were then serially sectioned in a caudal to coronal fashion into 2-3 parts from apex to base and embedded in paraffin; 2-3.5 µm sections from each paraffin block were taken at random and stained with haematoxylin and eosin. Ten random fields were read for each animal. The sections were evaluated according to a grading scale (0-4) for twelve different lesions (Table 1).

Statistical analysis

Data for morphologic evaluation scores, cytokine and chemokine levels, pH, PaO₂, PaCO₂ and MAP values are reported as mean and standard deviation (SD). Intergroup comparisons were analysed by Kruskal Wallis ANOVA and Dunn's test was used for post-hoc analysis if p<0.05. Wilcoxon test was used for intragroup analysis.

Results

Thirty rats were used, with six in each of five groups. Mean arterial pressure (MAP) and fluid replacement during the study protocol are shown in Table 2. MAP and total fluid replacements were quite similar in each group through the study. Excluding group 45-0, pH, PaO₂, and PaCO₂ values were similar during baseline and end-experiment conditions for the four remaining groups (Table 3).

As compared to baseline, PaCO₂ values were significantly different at the end of the experiment only in group 45-0 (p=0.03). Other intragroup changes in blood gases were not statistically significant.

After morphological evaluation of twelve lesions, statistical differences were observed in microscopic emphysema (p=0.0058), congestion (p=0.0091), alveolar haemorrhage (p=0.016), interstitial polymorphonuclear leukocyte (PMN) infiltration (p=0.0061), and hyaline membrane formation (p=0.0001) parameters. While interstitial PMN infiltration and hyaline membrane formation differences were higher in group

Table 1. Grading scale for morphologic evaluation.

	0	1	2	3	4
Microscopic Amphysema & Atelectasia	None	Focal in 1 or 2 fields	Focal, in 3 or 4 fields	Conspicuous in 3 or 4 fields	Diffuse
Perivascular & Perbronchial Oedema	None	Focal in a few fields	Disseminated but in a few fields	Disseminated in many fields	Disseminated in too many fields
Alveolar& Perivascular Haemorrhage	None	Focal, rare	Disseminated, septal	filling the alveoli focally	filling the alveoli diffusely
Congestion	None	Focal, rare	Focal but significant	Disseminated and significant	Disseminated and enlarged
Alveolar Oedema	None	Focal in 1 or 2 fields	Focal, in 3 or 4 fields	Disseminated	The whole lung
Alveolar Mononuclear Cell Infiltration	None	Focal, a few	Disseminated, a few	A few but in all alveoli	Brisk in all alveoli
Interstitial PMNs Infiltration	None	Focal, rare	Disseminated rare	In all fields but a few cells	In all fields, many cells
Hyaline Membrane & Type II Cells	None	Focal in 1 or 2 fields	Focal in 3 or 4 fields	Disseminated	The whole lung
PMNs: Polymorphonuclear leukocytes					

Table 2. Mean arterial pressure (MAP), amount of fluid replacement during the study (mean±SD).

	Group 15-0	Group 30-10	Group 30-5	Group 30-5&RM	Group 45-0	p
MAP (mmHg)	69.3±27	67.1±21.35	73.3±19.5	71.5±18.1	65.5±20.7	0.96
Fluid replacement (mL)	4.5±1.2	4.9±1.4	4.8±1.4	4.2±1.6	5.1±2	0.81

p: Non parametric Kruskal-Wallis ANOVA (Intergroup statistics); MAP: mean arterial pressure, RM: Recruitment Manoeuvre

Table 3. Intergroup analysis of blood gas parameters (mean±SD).

	Group 15-0	Group 30-10	Group 30-5	Group 30-5&RM	Group 45-0	p
pH-b	7.24± 0.05	7.17±0.06	7.27±0.02	7.20±0.05	7.17±0.07#	0.48
pH-e	7.23±0.05	7.25±0.06	7.26±0.02	7.17±0.02	7.25±0.04	0.30
PaO ₂ -b (mmHg)	394±45	492±56	423±169	473±28	530±31	0.22
PaO ₂ -e (mmHg)	551±41	473±69	404±14	475±32	554±74	0.22
PaCO ₂ -b (mmHg)	51±5	69±3	60±1.2	61±7	78±6	0.07
PaCO ₂ -e (mmHg)	46±13	58±15	56.9±4	64±5	32±9	0.15

p: Non parametric Kruskal-Wallis ANOVA (Intergroup statistics); b: baseline, e: end experimental, RM: Recruitment Manoeuvre; #: Statistical difference of PaCO₂ between baseline and end experiment in Group 45-0 is (p=0.03)

45-0 compared to all other groups, microscopic emphysema was lower only in group 15-0 compared to other groups. However, congestion was lower in both group 15-0 and group 30-5&RM, but alveolar haemorrhage was higher in group 30-5&RM and group 45-0. Figure 1 shows some morphologic changes of each group. When the cumulative mean values of the morphologic evaluation scores were analysed, a statistical difference was observed between group 45-0 vs. group 15-0 ($p<0.001$) and group 45-0 vs. group 30-10 ($p<0.01$). There was no difference between the other groups (Table 4). According to the arithmetic mean values' of morphologic evaluation scores, the groups were categorised from mild to severe injury as follows: Group 15-0 < Group 30-10 < Group 30-5&RM < Group 30-5 < Group 45-0.

TNF- α , MCP-1, IL-1 β , and IL-6 levels were higher in Group 45-0 and lower in group 30-5&RM compared to all other groups. Intergroup statistical evaluation of each group for che-

mokine and cytokines were significant ($p<0.0001$). The differences for each chemokine and cytokine can be seen in Table 5. All measured cytokine and chemokine levels were lower in the recruitment manoeuvre group compared to the other groups.

Discussion

The main findings of our study were as follows: 1) Ventilation with low PEEP and intermittent RM (Group 30-5&RM) caused the least systemic inflammatory response; 2) High PEEP with moderate Pao (Group 30-10) and low pressure ventilation groups (Group 15-0) caused significantly less morphologic injury in lungs than the high Pao group (Group 45-0).

Mechanical ventilation with high airway pressures can cause lung injury (13-15), which is appreciated as atelectasis, severe congestion, interstitial oedema, and alveolar oedema upon microscopic examination. The magnitude of peak airway

Table 4. Morphologic evaluations (mean ± SD).

	Group 15-0	Group 30-10	Group 30-5	Group 30-5&RM	Group 45-0	P
Microscopic amphysema	0.5±0.4	4±0.34	3.5±0.61	3±0	3±0	0.0058
Microscopic atelectasia	0±0.16	0±0	1±0.4	0±0.21	0±0.16	0.12
Perivascular Oedema	1±0.42	1±0.47	3±0.16	2±0.16	3±0.21	0.053
Perivascular haemorrhage	0±0	0±0.16	0±0	0±0	0.5±0.22	0.51
Congestion	1±0.34	2±0.5	3±0.4	1±0	3±0.44	0.0091
Alveolar Haemorrhage	0±0	0±0.16	1±0.55	2±0.11	3±0.71	0.016
Alveolar oedema	0±0.16	0±0.66	0±0.33	1.5±0.22	2±0.55	0.064
Alveolar mononuclear cell infiltration	0.5±0.33	0±0.21	0.5±0.47	2.0±0.34	0.5±0.22	0.32
Peribronchial oedema		1.0±0	1.0±0	0±0.66	1.0±0.16	1.0±0
Interstitial PMNs infiltration	1.0±0.3	1.0±0.25	1.5±0.42	1.0±0.2	3.0± 0	0.0061
Hyaline membrane	0±0	0±0	0±0	0±0	2.5±0.47	0.0001
Type II cells	0±0	0±0	0±0	0±0	0±0.16	0.4
Total	0±0.009*	0±0.14 #	1±0.16	1±0.12	2±0.16*#	0.0001

p: Kruskal-Wallis ANOVA; *: Group 45-0 – Group 15-0: p<0.001; #: Group 45-0 – Group 30-10: p<0.01; PMNs: Polymorphonuclear leukocytes; RM: Recruitment Manoeuvre

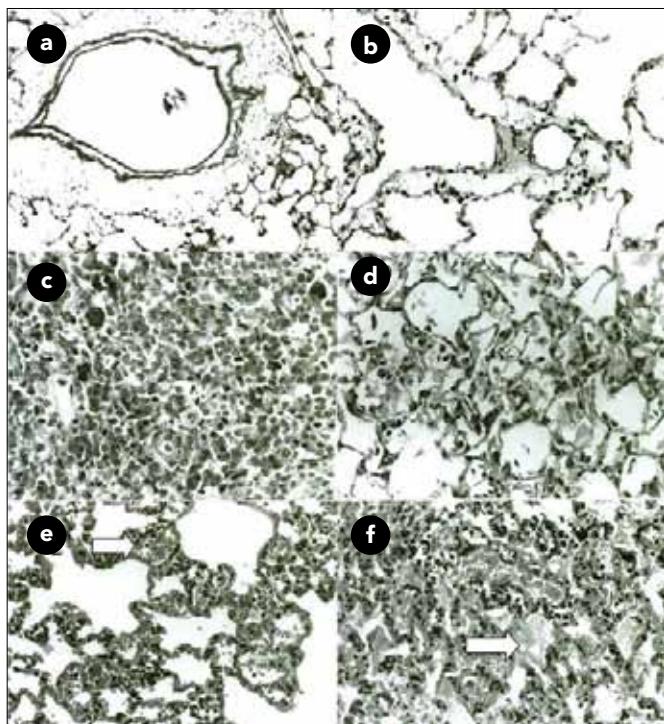


Figure 1. a-f. Fields from: (a) Group 15-0: Slight oedema in perivascular areas (Scored as Grade 1) (b) Group 30-10: Conspicuous oedema in perivascular areas (Scored as Grade 3) (c) Group 30-5: Severe alveolar mononuclear cell infiltration (Grade 4) (d) Group 30-5&RM: Mild alveolar mononuclear cell infiltration (Grade 2) (e) Group 45-0: Alveolar haemorrhage (Blank arrow) (Grade 4) (f) Group 45-0: Hyaline membrane formation (Blank arrow)

pressure and duration of mechanical ventilation are important parameters determining the degree of lung injury (13, 14). We decided to use 15 cmH₂O peak Pao as control, 30 cmH₂O peak Pao with 10 cmH₂O PEEP as a protective, and 45 cmH₂O peak

Pao as an injurious ventilation pressure in the study groups according to the study by Webb and Tierney (14). We used high levels of pressures (45 cmH₂O) that were capable of inducing lung injury and low safe levels of pressures (15 cmH₂O) as the control group for our protocol. This difference would allow us to differentiate the role of other mechanical ventilation strategies on lung injury.

The beneficial effect of R in ARDS and ALI has been reported in animals by Cakar et al. and Van Der Kloot et al. (7, 16), and in humans by Lapinsky et al. (9) and Grasso et al. (17). The latter two studies demonstrated an improvement in oxygenation; however, Grasso et al. (17) found an increase in oxygenation only in early ARDS patients.

In our study, cytokine and chemokine levels were significantly different between groups. Group 30-5&RM had the lowest levels of systemic inflammatory mediators, which were even lower than those in Group 15-0. However, Group 30-5, which has same level of ventilation pressures as Group 30-5&RM (except 45 cmH₂O sustained inflation in every 15 minutes), produced a higher inflammatory response than Group 30-5&RM and Group 15-0, but it was lower than Group 30-10. In a recent study, this finding was also observed, which shows that repeated RM at an inadequate/low PEEP of 2 cmH₂O aggravated VILI compared with RM at a high PEEP of 6 cmH₂O (18).

Naik et al. (19) evaluated different PEEP levels on preterm lambs and found that 4 cmH₂O PEEP caused less of an inflammatory response than 0 and 7 cmH₂O PEEP after 2 hours of ventilation. They also concluded that physiological amounts of PEEP, like 3-4 cmH₂O, are more protective against ventilator-induced injury. Our results were similar to this study. We observed less of an inflammatory response with low PEEP but additive RM decreased the cytokine levels compared to the control group's (Group 15-0) cytokine levels.

Proinflammatory cytokines play a significant role in the pathogenesis of ventilator-induced lung injury by inducing

Table 5. Cytokine and chemokine levels (mean ± SD).

	Group 15-0	Group 30-10	Group 30-5	Group 30-5&RM	Group 45-0	p
TNF- α (pg/mL)	700.0±529.6*	1169.1±282.1***	958±325.7**	619.6±224.2*	1757.9±162.81	<0.0001
MCP-1 (pg/mL)	338.6±95.8*	653.6±95.9 ^{R,C}	522.2±182.7 ^{RR, CC}	335.4±120.0*	782.1±513.0	<0.0001
IL-1 β (pg/mL)	356.1±218.8*	630.2±85.1*, R, C	672±78.1*, R, C	284.4±102.5*	1115.4±464.4	<0.0001
IL-6 (pg/mL)	500.4±67.2*	680.4±136.8 ^{R, CC}	561.3±47.1***, R	258±78.3*	841.2±554.7	<0.0001

p: Kruskal-Wallis ANOVA, RM: Recruitment Manoeuvre; * vs. Group45-0 is p<0.001; ** vs. Group45-0 is p<0.01; *** vs. Group45-0 is p<0.05; R vs. Group30-5&RM is p<0.001; RR vs. Group30-5&RM is p<0.05; C vs. Group15-0 is p<0.001; CC vs. Group15-0 is p<0.01

other proinflammatory mediators, sequestration and accumulation of neutrophils and increasing vascular permeability (20). We have not performed lung lavage to evaluate the vascular permeability with protein amount and the inflammatory cell recruitment but morphometry showed us that congestion and interstitial PMN infiltration was significantly lower in Group 15-0 and Group 30-5&RM. In our study, we evaluated the role of different ventilatory strategies on systemic inflammatory response by using the proinflammatory cytokines, especially IL-1 β , IL-6, and TNF- α , as they have been reported to also be increased in adult lung injury models (21), and they are the early markers of injury.

To determine whether different ventilation strategies change the expression of these biological markers of lung injury, we used two different levels of PEEP and RM including ventilation strategies. Our data indicates that 5 cmH₂O PEEP&RM is more protective against inflammatory response compared to other groups, but, according to morphometry, Group 30-5&RM came after Group 15-0 and Group 30-10. However, 0 and 10 cmH₂O PEEP may cause lung injury by different mechanisms. The morphology is consistent with observations in animal models that with 0 cmH₂O of PEEP the lung was being repetitiously opened and closed, leading to increased surfactant inactivation, neutrophil infiltration, and progressive lung injury (22). Ventilation with 10 cmH₂O PEEP causes over distension with stress failure of pulmonary capillaries causing injury (23). The use of PEEP in low levels (5 cmH₂O) with intermittent sustained inflation may protect the lung from injury because it minimises the inflammatory response which is caused by ventilation. Expression of MCP-1 was the lowest in the Group 30-5&RM, as were TNF- α , IL-1 β and IL-6 levels. MCP-1 levels have been shown to be correlated with 7 to 21 days injury levels in lungs (24). These high levels of chemokines and pro-inflammatory cytokines may also increase lung damage incidence in long-term ventilation because of biotrauma as a component of VILI.

Large volumetric fluctuations delivered as a sigh were shown to improve surfactant function (25). A sustained inflation delivered as an RM may lead to the same improvement in surfactant activity, which may have a protective role against shear stress and inflammatory response. These results also pointed out that RM could be a protective manoeuvre on healthy regions of the lung during mechanical ventilation, since ALI and ARDS are heterogeneous lung diseases and consist of both healthy and injured lung regions. The protective ventilation strategies for intact lung regions are just as important as for the injured areas.

In our study, lung injury was demonstrated by morphologic evaluation, blood gas changes and inflammatory response. However, the wet weight/dry weight ratio of lungs and protein concentration changes in alveolar fluid, which are among the evaluation criteria of VILI (26), were not evaluated; this could have strengthened our findings if had been done. Although this study has major limitations (which are not concerning the findings) the findings from this study about potentiation of VILI during different ventilatory strategies will provide rationale for further studies.

In conclusion, our study demonstrates that mechanical ventilation with high pressures in an intact lung is injurious and different ventilatory strategies influence this injury. We tried to minimise the lung injury by using low PEEP and RM. However, indicators of lung injury still increased with mechanical ventilation. Our results are compatible with previous data. In a recent study it was demonstrated that VILI production was obvious when high tidal volumes with low levels of PEEP are applied as a ventilation strategy (27). Our observation that mechanical ventilation induces pro-inflammatory cytokines could be provocative for clinical perspectives. This suggests that these cytokines may play a significant role in the pathogenesis of chronic lung injury in long-term ventilation on intact lungs. Van Marter et al. (28) identified enrolment to the ventilation as a major risk factor for chronic lung disease development. The use of low levels of PEEP with intermittent sustained inflation may reduce the lung injury not only with a reduced risk of atelectrauma but also with biotrauma in healthy lung regions.

Ethics Committee Approval: Ethics committee approval was received for this study from İstanbul University Experimental Medicine and Research Institute Animal Investigation Committee: 1561/16012001

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