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EXPERIMENTAL

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# Alveolar edema dispersion and alveolar protein permeability during high volume ventilation: effect of positive end-expiratory pressure

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**Abstract** *Objectives:* To evaluate whether PEEP affects intrapulmonary alveolar edema liquid movement and alveolar permeability to proteins during high volume ventilation. *Design and setting:* Experimental study in an animal research laboratory. *Subjects:* 46 male Wistar rats. *Interventions:* A $^{99m}$Tc-labeled albumin solution was instilled in a distal airway to produce a zone of alveolar flooding. Conventional ventilation (CV) was applied for 30 min followed by various ventilation strategies for 3 h: CV, spontaneous breathing, and high volume ventilation with different PEEP levels (0, 6, and 8 cm$H_2O$) and different tidal volumes. Dispersion of the instilled liquid and systemic leakage of $^{99m}$Tc-albumin from the lungs were studied by scintigraphy. *Measurements and results:* The instillation protocol produced a zone of alveolar flooding that stayed localized during CV or spontaneous breathing. High volume ventilation dispersed alveolar liquid in the lungs. This dispersion was prevented by PEEP even when tidal volume was the same and thus end-inspiratory pressure higher. High volume ventilation resulted in the leakage of instilled $^{99m}$Tc-albumin from the lungs. This increase in alveolar albumin permeability was reduced by PEEP. Albumin permeability was more affected by the amplitude of tidal excursions than by overall lung distension. *Conclusions:* PEEP prevents the dispersion of alveolar edema liquid in the lungs and lessens the increase in alveolar albumin permeability due to high volume ventilation.

**Keywords** Pulmonary edema · Pneumonia · Intermittent positive pressure ventilation · Radionuclide Imaging

## Introduction

Ventilator-induced lung injury (VILI) is an experimental concept that was first described as a consequence of lung overdistension but may also result from ventilation at low lung volume in surfactant depleted/injured lungs [1]. The clinical relevance of this concept was highlighted by the Acute Respiratory Distress Syndrome (ARDS) Network trial [2] that showed 22% reduction of mortality in patients with ARDS when the mechanical stress applied to the lungs was lessened by a reduction in tidal volume ($V_T$). Application of positive end expiratory pressure (PEEP) may also lessen lung injury during ventilation at low lung volume [3] by avoidance of lung collapse or airway closure. Mechanical ventilation may favor intrapulmonary and systemic dissemination of sepsis and inflammation during bacterial pneumonia. It has been speculated that dissemination risk and severity depend on the occurrence of concomitant VILI [4, 5, 6]. Nahum et al. [5] found more positive blood cultures when dogs intratracheally instilled with *Escherichia coli* were ventilated with high $V_T$ and low PEEP rather than with low $V_T$ and high PEEP. We extended these findings to a model of unilateral *Pseudomonas aeruginosa* pneumonia in rats [4]. We found

that ventilation with high PEEP reduced dissemination of bacteria to the contralateral lung and prevented systemic sepsis.

Understanding these observations require better knowledge of how ventilation interacts with the liquid present in airspaces. We have previously shown that ventilation above 20–25 $cmH_2O$ end-inspiratory pressure (Pei) and no PEEP dispersed alveolar edema liquid in the lungs and increased protein leakage from airspaces in rats [7]. We hypothesized that PEEP would prevent alveolar edema liquid dispersion and reduce the increase in alveolar permeability due to higher Pei ventilation modalities. Partial results of this study were presented in abstract form at the 2006 meeting of the ATS.

## Methods

### Animals

All experiments were conducted on male Wistar rats (weighting 281 ± 22 g; Harlan, Gannat, France) in compliance with the recommendations for laboratory animal research of the European Union and the French Ministry of Agriculture. Rats were anesthetized by intraperitoneal injection of pentobarbital (75 and 40 mg/kg 2 h later; Sigma, Saint-Quentin Fallavier, France) and remained deeply anesthetized for 4 h. They were tracheostomized and ventilated with a rodent Harvard volume ventilator (Ealing, Courtaboeuf, France).

### Localized alveolar edema

$^{99m}$Tc-labeled albumin was prepared using a commercial kit (Vasculocis; Cis Bio International, Gif sur Yvette, France). Paper chromatography using methanol as a solvent [8] was performed to verify the amount of free $^{99m}$Tc (0.03 ± 0.08%) and the stability of $^{99m}$Tc binding to albumin in the final solution. Osmolarity of the $^{99m}$Tc solution was made twice that of plasma adding mannitol (120 mg/ml). This solution was supplemented with bovine serum albumin (80 mg/ml), and $Na^+$ transport inhibitors (1 mM amiloride and 1 mM phloridzin) to reduce its absorption by alveolar/airway epithelium. The $^{99m}$Tc-labeled albumin solution (500 μCi in 250 μl) was slowly instilled in a distal airway after a short period of ventilation with $FIO_2$ of 1. The instilled volume was much less than functional residual capacity, that is, about 3 ml in 300 g Wistar rats [9]. This protocol produced a localized zone of alveolar flooding [7].

### Scintigraphic imaging

Acquisition was performed in the planar mode with a small γ-camera (γ Imager, Biospace, Paris, France). Acquisition window was 114–157 KeV. Each experiment lasted 210 min without interruption. A dedicated collimator was used. The decay of $^{99m}$Tc activity was corrected.

### Ventilation strategies

Pei was measured with a piezoelectric transducer (AST, Vanves, France) connected to the tracheal cannula. Conventional ventilation (CV) was applied for 30 min, followed by various ventilation strategies for 3 h. Control groups consisted of spontaneous breathing (SB, $n = 8$) and CV in ventilation with 8 ml/kg $V_T$, 2 $cmH_2O$ PEEP, respiration rate (RR) 70/min and $FIO_2$ 1 ($n = 10$). Three other groups were ventilated such that (plateau) Pei was approx. 30 $cmH_2O$, with three different levels of PEEP: 0, 6, and 8 $cmH_2O$. Therefore these ventilation modalities were: zero PEEP (ZEEP) and high $V_T$ ($HV_1$ZEEP; $V_T = 29$ ml/kg, RR = 18/min, $n = 8$), 6 $cmH_2O$ PEEP and a lower $V_T$ ($HV_2$PEEP6; $V_T$ 24 ml/kg, RR 24/min, $n = 6$), 8 $cmH_2O$ PEEP and low $V_T$ (LVPEEP 8, $V_T = 8$ ml/kg; RR = 70/min, $n = 8$). Another group was ventilated with the same $V_T$ as $HV_2$PEEP 6 but without PEEP ($HV_2$ZEEP; $V_T$ 24 ml/kg, RR 24/min, $n = 8$) to better determine the effect of varying $V_T$ and/or PEEP. The latter ventilation modality resulted in Pei of 23.5 $cmH_2O$. Respiratory rate was adjusted so that ventilation/min was the same in all groups. Ventilation strategies are summarized in Table 1.

**Table 1** Ventilation modalities applied between $t_{30}$ and $t_{180}$ (*SB* spontaneous breathing, *CV* conventional ventilation, $HV_1$ high volume, $HV_2$ less high volume, *LV* low volume, *PEEP* positive end-inspiratory pressure, *ZEEP* zero end-inspiratory pressure)

| Ventilation modalities at $t_{30}$ | $V_T$ (ml/kg) | RR (/min) | PEEP ($cmH_2O$) | Pei ($cmH_2O$) | Fluid ventilated |
|---|---|---|---|---|---|
| SB ($n = 8$) | – | – | – | – | Ambient air |
| CV ($n = 10$) | 8 | 70 | 2 | 15.1 ± 0.55 | $O_2$ |
| $HV_1$ZEEP ($n = 8$) | 29.1 ± 0.46 | 18.1 ± 0.35 | 0 | 30 | $O_2$ |
| $HV_2$PEEP 6 ($n = 6$) | 24.0 ± 0.89 | 23.5 ± 0.43 | 6 | 30 | $O_2$ |
| $HV_2$ZEEP ($n = 5$) | 24.0 | 24 | 0 | 23.5 ± 0.65 | $O_2$ |
| LVPEEP 8 ($n = 8$) | 8 | 70 | 8 | 31.7 ± 3.91 | $O_2$ |

### Data analysis

Pulmonary and systemic dispersions of the tracer were studied. Regions of interest (Gamma-vision+, Biospace, Paris, France) were drawn around initial focus ("edema", $ROI_E$), the apex of the same lung ("apex", $ROI_A$), the opposite lung ("contralateral", $ROI_{CL}$), and a ROI including the whole cardiopulmonary region ("total", $ROI_T$). Activity was integrated in each ROI over 150-s steps, expressed as percentage being divided by concurrent total, i.e., $ROI_T$, activity. We have previously shown [7] that the clearance of $^{99m}$Tc-labeled albumin instilled in rat airspaces follows a two-phase exponential decay. The initial decay slope, which is proportional to alveolar permeability-surface area product to albumin ($PS_A$), was evaluated by linear regression [7]. $PS_A$ is the product of this initial slope and of alveolar liquid volume, about 0.5 ml, because we instilled 250 µl of a ×2 hypertonic solution.

### Statistical analysis

Results are expressed as mean ± SEM. Comparisons between groups were made by anova and Bonferroni's post-hoc test or the Kruskal–Wallis test and the Dunn post-hoc test. Differences at the level of $p < 0.05$ were considered statistically significant (Prism, GraphPad, San Diego, Calif., USA).

## Results

### End-inspiratory pressure during ventilation

Figure 1 shows Pei values at $t_{30}$ and $t_{210}$. Pei was steady (mean $15.1 \pm 0.55\,cmH_2O$) in CV controls. Pei at $t_{30}$ was by design significantly higher in LVPEEP8, $HV_1$ZEEP, $HV_2$PEEP6, and $HV_2$ZEEP groups ($p < 0.001$) than in controls. Pei increased significantly during ventilation in the $HV_1$ZEEP group ($30.1 \pm 0.91$ at $t_{30}$ and $42.5 \pm 2.89\,cmH_2O$ at $t_{210}$, $p < 0.001$) and in the $HV_2$ZEEP group ($23.5 \pm 0.65$ at $t_{30}$ and $29.2 \pm 1.03\,cmH_2O$ at $t_{210}$, $p < 0.001$).

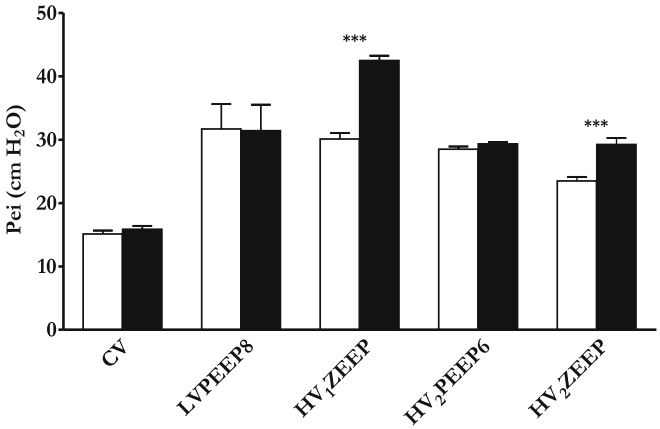


**Fig. 1** Pei at the beginning ($t_{30}$, *open bars*) and the end of the tested ventilation period ($t_{210}$, *filled bars*). Pei increased during ventilation in $HV_1$ZEEP (29 ml/kg $V_T$), and $HV_2$ZEEP (24 ml/kg $V_T$) groups; ***$p < 0.001$

### Intrapulmonary dispersion

Figure 2a shows representative images obtained in a rat of the group CV. The alveolar edema remained localized and stable during 210 min. By contrast, after $HV_1$ZEEP (applied at $t_{30}$; Fig. 2b) there was an almost immediate homo- and contralateral dispersion of the tracer. Applica-

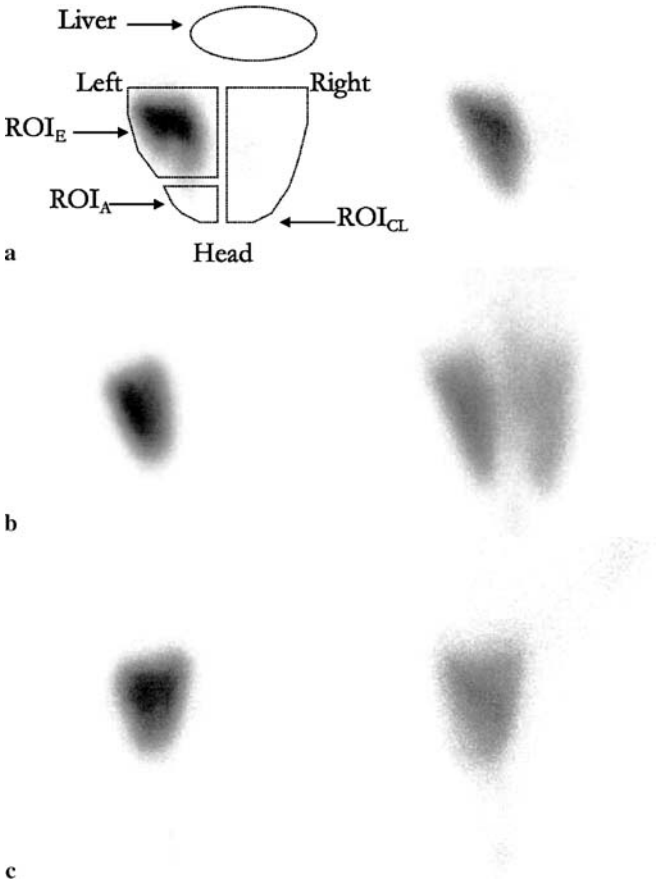


**Fig. 2** Examples of scintigraphy images integrating the 15 min following instillation ($t_0$–$t_{15}$, *left panels*) and in the last 15 min of the experiment ($t_{195}$–$t_{200}$, *right panels*). *Left panels* Focalized localization of the tracer in the left lung. In CV group (**a**) the tracer remained remarkably confined in the initial zone; there was no contralateral and slight homolateral dissemination. $HV_1$ZEEP ventilation (**b**) induced strong homo- and contralateral dispersion of the tracer and systemic leakage, as attested by the evident decrease in overall activity. $HV_2$PEEP 6 ventilation (**c**) induced systemic, but not contralateral, dissemination of the tracer

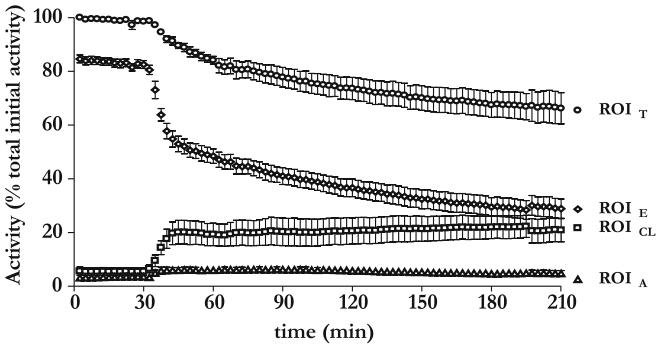


**Fig. 3** Activity changes in the four ROIs expressed as proportion of initial total activity. $HV_1$ZEEP induced an almost immediate decrease in activity in $ROI_E$ and $ROI_T$ and a dramatic increase in $ROI_{CL}$. Changes in $ROI_T$ activity displayed a two phase's exponential decay; activity decreased fastly between $t_{30}$ and $t_{60}$ and more slowly between $t_{60}$ and $t_{210}$

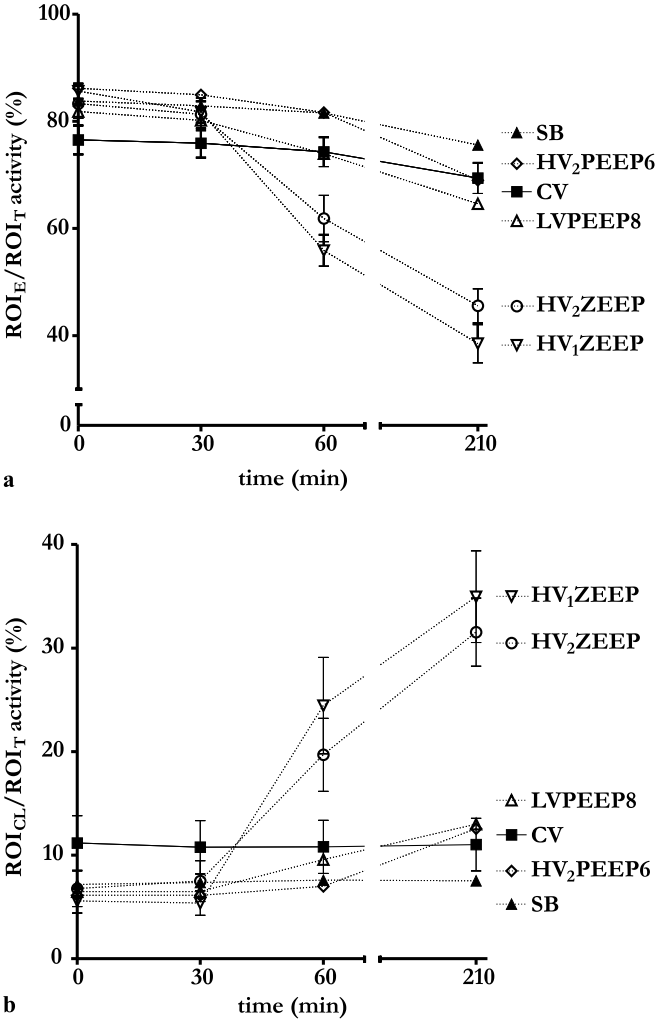


**Fig. 4** **a** Activity in $ROI_E$ relative to that in $ROI_T$ did not vary significantly between $t_{30}$ and $t_{210}$ in CV and $HV_2$PEEP 6 groups. Activity significantly decreased in $HV_1$ZEEP and $HV_2$ZEEP groups between $t_{30}$ and $t_{60}$ ($p < 0.001$ and $p < 0.01$, respectively) and in $HV_1$ZEEP group between $t_{60}$ and $t_{210}$ ($p < 0.05$). **b** Activity in $ROI_{CL}$ relative to that in $ROI_T$ increased significantly between $t_{30}$ and $t_{60}$ in $HV_1$ZEEP, $HV_2$ZEEP ($p < 0.001$), and LVPEEP 8 groups ($p < 0.05$). This increase in activity remained significant between $t_{60}$ and $t_{210}$ in $HV_1$ZEEP and $HV_2$ZEEP groups ($p < 0.001$ and $p < 0.01$, respectively)

tion of PEEP abrogated this contralateral dispersion (see $HV_2$PEEP 6 group, Fig. 2c).

As changes in the different ROIs activities relative to that of $ROI_T$ were almost linear between the time of instillation ($t_0$) and $t_{30}$, $t_{30}$ and $t_{60}$, $t_{60}$ and $t_{210}$ (see example in Fig. 3), data are shown at these times only, for the sake of simplicity. Activity in $ROI_E$ did not vary appreciably between $t_{30}$ and $t_{210}$ in CV or SB groups (Fig. 4a). An almost immediate decrease in $ROI_E$ activity was observed between $t_{30}$ and $t_{60}$ in $HV_1$ZEEP and $HV_2$ZEEP groups ($p < 0.001$ and $p < 0.01$, respectively) that was almost completely abolished by PEEP application (changes did not reach significance). The tracer did not disperse to the apex, as no significant change in $ROI_A/ROI_T$ activity was observed.

The increase in contralateral lung $^{99m}$Tc-labeled albumin activity mirrored that in the instilled lung (Fig. 4b). Activity in $ROI_{CL}$ increased significantly between $t_{30}$ and $t_{60}$ ($p < 0.001$) and between $t_{60}$ and $t_{210}$ in $HV_1$ZEEP and $HV_2$ZEEP groups ($p < 0.001$ and $p < 0.01$, respectively). A slight increase in activity was observed in the LVPEEP 8 group between $t_{30}$ and $t_{60}$ ($p < 0.05$), reflecting a very limited tracer movement.

## Systemic albumin leakage

Figure 5 shows $PS_A$ for all ventilation strategies. In the CV group $PS_A$ was $6.2\times10^{-3} \pm 6.63\times10^{-3}$ ml/h (the initial slope was $2.0\times10^{-2}$/min which corresponded to a clearance rate of $^{99m}$Tc-labeled albumin of 1.2%/h). $PS_A$ was similar during SB but was significantly higher during $HV_1$ZEEP, $HV_2$PEEP 6, and $HV_2$ZEEP ($p < 0.001$) and in $HV_1$ZEEP than during $HV_2$PEEP 6 and $HV_2$ZEEP ($p < 0.001$). This albumin leakage did not increase noticeably blood $^{99m}$Tc activity, as no signal (data not shown but this is seen in from Fig. 2b and 2c) was measured in a ROI drawn over the liver, as previously observed [7]. It is thus unlikely that the $^{99m}$Tc-labeled albumin present in the systemic circulation participated in the increase in contralateral lung activity. There was a trend toward an increase in $PS_A$ in the LVPEEP 8 group, but this did not reach statistical significance ($0.1 > p > 0.05$). There was no significant correlation between intrapulmonary $^{99m}$Tc-labeled albumin redistribution ($\Delta ROI_{CL}$/h) and $^{99m}$Tc-labeled albumin leakage from airspaces ($\Delta ROI_T$/h) in $HV_1$ZEEP and $HV_2$ZEEP groups ($R^2 = 0.05$, NS).

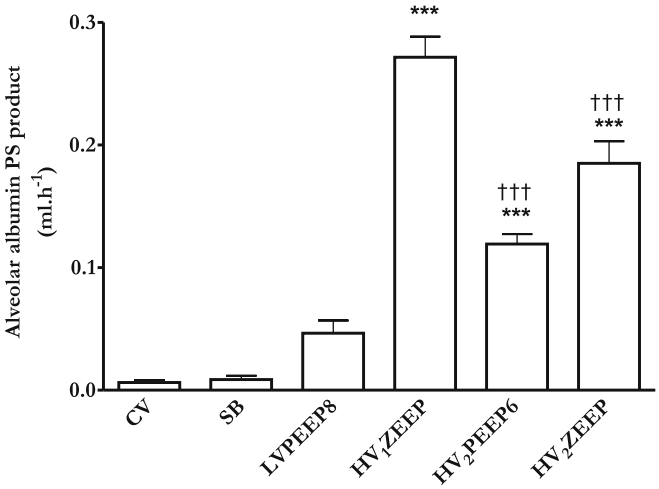


**Fig. 5** Alveolar albumin permeability–surface (*PS*) product; *** $p < 0.001$ vs. control groups (spontaneous breathing, *SB*; conventional ventilation, *CV*); ††† $p < 0.001$ vs. $HV_1ZEEP$

## Discussion

This study shows that PEEP may affect the dispersion of a zone of alveolar flooding and affect alveolar permeability to albumin: (a) High volume ventilation with no PEEP promoted contralateral dispersion of the liquid contained in a zone of alveolar flooding. (b) This dispersion was prevented by PEEP. (c) The increase in alveolar permeability to albumin due to high volume ventilation was lessened by PEEP.

### Pulmonary dispersion of the tracer

We have previously shown [7] that our protocol produces a stable zone of alveolar flooding, much of the alveolar flooding coming from the circulation as during actual pulmonary edema. Hypertonic solutions in this range are not injurious [10]. This was further attested by the low systemic leakage of $^{99m}$Tc-labeled albumin observed during SB or CV. Recruitment of this flooded zone by ventilation was demonstrated by computed tomography imaging [7].

Ventilation with a high $V_T$ and no PEEP ($HV_1ZEEP$, $HV_2ZEEP$) dispersed the labeled alveolar liquid by contrast to CV, SB or $V_T$ resulting in a Pei less or equal to 20 $cmH_2O$ [7]. Ventilation at 20 $cmH_2O$ Pei and no PEEP resulted in a $V_T$ of 14 ml/kg, a modality intermediary between CV and $HV_2$. HV is of course never used in the clinical situation, but the inhomogeneity of ventilation distribution in patients with acute lung injury together with the "baby lung" effect [11] may lead to localized overventilation and overinflation. Ventilation with a similarly high $V_T$ is usual to mimic this situation [12, 13, 14].

Contralateral liquid dispersion began almost immediately after high $V_T$ ventilation was started (Fig. 3). Thus it can be speculated that this dispersion may be the consequence of a convective movement induced by ventilation [15], but it may also be the consequence of the compression of liquid filled zones by contiguous recruited units. Aerated lung zones may not have emptied as if there were no liquid in adjacent zones, because their conducting airways may have been obstructed earlier during expiration by liquid menisci (gas trapping) due to the back and forth movement of this liquid in airways. High flow rate is unlikely to be the only determinant of this dispersion. Peak flow rate (that is roughly proportional to Pei assuming respiratory system mechanical properties were similar in all rats) was about the same in $HV_1ZEEP$ and $HV_2PEEP$ 6 group; however, liquid dispersion was observed in the former but not in the latter. PEEP may have prevented dispersion by avoiding lung collapse and stabilizing edema fluid in the distal airways. This displacement of alveolar liquid by high $V_T$ ventilation in the absence of PEEP helps explain the intrapulmonary dissemination of bacteria that we observed in a model of unilateral *P. aeruginosa* pneumonia [4] during a similar ventilation modality. In the present study contralateral dispersion was abolished by PEEP application, regardless of whether $V_T$ ($HV_2PEEP$ 6 vs. $HV_2ZEEP$) or Pei (LVPEEP vs. $HV_1ZEEP$, $HV_1ZEEP$ vs. $HV_2PEEP$ 6) was the same. It is worth noting that PEEP had the same effect during a real, organized, pneumonia, as it prevented contralateral seeding in our model of unilateral *P. aeruginosa* pneumonia in rats [4].

### Airspace albumin leakage

Albumin is passively absorbed from airspaces through the paracellular pathway according to its concentration gradient [16]. Leakage of $^{99m}$Tc-labeled albumin from airspaces was low during CV (as well as during SB); albumin clearance being about 1.2%/h was in keeping with previous data [7, 17]. Static inflation at 40 $cmH_2O$ airway pressure did not significantly increase alveolar albumin permeability [18]. Stretching a cultured alveolar epithelium to a magnitude corresponding approx. to strains experienced in vivo at 100% total lung capacity (36% increase in surface area) produced a significant increase in permeability, whereas no alteration was observed for 12% and 25% changes in surface area [19]. Furthermore, cyclic changes between 0% to 50% produced more cell death than changes between 25% and 50% surface area [20]. The absence of a significant systemic leakage of alveolar albumin in the LVPEEP 8 group is in keeping with these observations. However, systemic leakage was significant in $HV_1ZEEP$, $HV_2PEEP$ 6 and $HV_2ZEEP$ despite equivalent ($HV_1ZEEP$, $HV_2PEEP$ 6) or even lower ($HV_2ZEEP$) Pei. We have previously reported that ventilation with high $V_T$ induced a pressure-dependent increase in alveolar protein permeability when Pei was higher

than 20 $cmH_2O$ in rats [7]. The present study confirms this observation. The two-exponential shape of albumin disappearance from the lungs may be due to the presence of an intermediate, interstitial compartment [7]. The later development of pulmonary edema during high-volume ventilation may have increased the back-flux of labeled albumin from this interstitial compartment to airspaces, making it impossible to calculate an unbiased permeability value. Alveolar albumin permeability was thus calculated from the first data obtained after increasing $V_T$, before any back-flux was significant. $PS_A$ was higher during $HV_1$ZEEP than during $HV_2$ZEEP ventilation ($p < 0.001$). Interestingly, $PS_A$ was also significantly higher during $HV_1$ZEEP than during $HV_2$PEEP 6 ventilation despite equivalent Pei (approx. 30 $cmH_2O$), suggesting that other mechanisms than overall lung inflation were involved. Intrapulmonary dispersion might have contributed to this systemic leakage by increasing exchange surface area. However, some albumin leakage was also observed in the $HV_2$PEEP 6 group despite the absence of significant intrapulmonary redistribution, and no correlation was found between albumin leakage and the importance of intrapulmonary redistribution in the $HV_1$ZEEP and $HV_2$ZEEP groups. These observations suggest that higher than usual tidal changes in surface area in the flooded zone contributed to this increase in permeability, with, but more likely without, (considering that this increase was almost immediate) production of cell lesions. PEEP prevented the development of epithelial lesions during high $V_T$ ventilation [21], and keeping the lung open may reduce the shear stress associated with the repeated opening of collapsed peripheral units or the movement of fluid in small airways, thus possibly reducing VILI [22, 23, 24]. This is the first time, to our knowledge, that an effect of the amplitude of tidal excursions on alveolar permeability is described. High flow rates, however, are known to affect microvascular permeability in isolated lungs [25]. Uneven ventilation distribution during acute lung injury [11] may produce by places higher than expected flow rates and ventilation that increases alveolar permeability to proteins. It has been shown that patients with acute lung injury unable to increase protein concentration in pulmonary edema fluid had poorer outcome [26]. An increase in alveolar epithelial permeability to proteins may contribute to decrease liquid clearance and limit the increase in alveolar protein concentration, although alveolar edema liquid is cleared by places. Ventilation inhomogeneity may have been an unnoticed negative prognostic factor in these patients. This could have been facilitated by a rather high $V_T$, as 46% of the patients with submaximal or impaired clearance were ventilated with more than 12 ml/kg $V_T$.

In conclusion, this study shows that tidal volume changes may affect intrapulmonary alveolar edema liquid movement and increase alveolar permeability to albumin. PEEP prevents the intrapulmonary redistribution of edema liquid and reduces alveolar permeability to albumin. This effect of PEEP may account for the lessening of sepsis and inflammation dissemination observed during ventilation of rats with bacterial pneumonia.

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