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EXPERIMENTAL

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Infectious and inflammatory dissemination are affected by ventilation strategy in rats with unilateral pneumonia

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Abstract *Objective:* To evaluate the effect of V_T reduction and alveolar recruitment on systemic and contralateral dissemination of bacteria and inflammation during right-side pneumonia. *Design:* Interventional animal study. *Setting:* University hospital research laboratory. *Subjects:* A total of 54 male Wistar rats. *Interventions:* One day after right lung instillation of 1.4×10^7 *Pseudomonas aeruginosa*, rats were left unventilated or ventilated for 2 h at low V_T (6 ml/kg) with different strategies of alveolar recruitment: no PEEP, 8 cm H_2O PEEP, 8 cm H_2O PEEP in a left lateral position, 3 cm H_2O PEEP with partial liquid ventilation, or high V_T (set such as end-inspiratory pressure was 30 cm H_2O) without PEEP (ZEEP). After ventilation the lungs, spleen and liver were cultivated for bacterial counts. Global bacterial dissemination was scored considering the percentage of positive spleen, liver and left lung cultures. TNF-α was assayed in plasma before and after mechanical ventilation. *Measurements and results:* All rats had right-side pneumonia with similar bacterial counts. All mechanical ventilation strategies, with the exception of low V_T-PEEP 8, promoted contralateral lung dissemination. Overall bacterial dissemination was less in non-ventilated controls (22%) and low V_T-PEEP 8 (22%) than in high V_T-ZEEP (67%), low V_T-PEEP 8 in left lateral position (59%) and low V_T-ZEEP (56%) ($p<0.05$). Partial liquid ventilation prevented systemic bacterial translocation, but at the expense of contralateral bacterial seeding. Plasma TNF-α concentration increased significantly after mechanical ventilation with no PEEP at both high and low V_T. *Conclusions:* Our results suggest that PEEP might reduce the risk of ventilation-induced bacterial and inflammatory mediator dissemination during pneumonia.

Keywords Mechanical ventilation · Pneumonia · *Pseudomonas* · End-expiratory pressure · Cytokine

Introduction

Aggressive ventilation strategies (e.g. high volume, no positive end-expiratory pressure) worsen lesions of previously injured lungs and exacerbate local and systemic inflammation [1, 2, 3]. Understanding the mechanism by which ventilation damages lungs comes from experimental studies that have shown the role of overdistension [4] or of shear forces resulting from the repeated opening and closing of terminal units [5, 6]. Ventilation-induced lung injury (VILI) is no longer an experimental concept. The ARDS network has shown that reducing V_T improves patient's outcome with a significant reduction in multiple organ system failure [7]. A strong consensus exists to limit end-inspiratory volume and pressure, by keeping the plateau pressure below 30–35 cm H_2O [8, 9]. Avoidance of lung collapse and/or airway closure by positive end-expiratory pressure (PEEP) is also generally accepted,

even though the optimal pressure level to use is not well defined [8, 10].

Adverse ventilation strategies can worsen lung injury during bacterial pneumonia [11]. Bacterial, endotoxin and inflammatory mediator translocation is a possible mechanism by which mechanical ventilation may contribute to systemic dissemination of sepsis and inflammation [12],although there is some debate on the sequence of events [13]. This translocation may be abrogated by the use of PEEP [14, 15, 16, 17]. Because spleen and liver cultures have been shown to be more consistent for estimating systemic bacterial translocation during experimental pneumonia [18, 19], firm conclusions could not be drawn from previous studies which focused on blood cultures only [14, 15, 17, 20]. Moreover, pneumonia was either missing because bacterial instillation was immediately followed by mechanical ventilation (in other words pneumonia had not time to develop) [15, 20], or was not documented by histological examination [14]. Further, because PEEP was associated with V_T reduction, it is difficult to ascertain whether a benefit came from alveolar recruitment or V_T limitation. The objective of our study was to evaluate the precise contribution of V_T amplitude together with application of a PEEP on systemic bacterial and inflammatory dissemination during pneumonia. Different strategies of alveolar recruitment that have been used to improve oxygenation in patients were considered: PEEP, partial liquid ventilation (PLV) and lateral positioning, in a model of unilateral *Pseudomonas aeruginosa* pneumonia in rats.

Methods

The experiments conformed to the recommendations for laboratory animal research of the French Ministry of Agriculture.

Male Wistar rats weighing 275–300 g were used for this study. Pneumonia was produced by the selective instillation under light anesthesia of 1.4×10^7 (7.15 log) colony forming units (cfu) of non-mucoid *Pseudomonas aeruginosa* (PAO1 strain) in the right main bronchus. This resulted in a macroscopically well developed regional pneumonia of the right lung 24 h after instillation. Pneumonia was further authenticated by microscopy examination and *Pseudomonas aeruginosa* counts between 3 log and 6 log cfu were retrieved from the right lung (see on-line supplementary material).

During preliminary studies, we found a clear threshold at 6 log cfu/right lung for spontaneous bacterial dissemination. When animals had a diffuse right pneumonia with easily recognizable abscesses 24 h after bacteria instillation, the *Pseudomonas* count was always $\geq$6 log cfu/right lung and the positive organ ratio was high (86%) (see online supplementary material for details). We decided prospectively not to include in the analysis rats with abscessed pneumonia at autopsy because systemic dissemination was constant and independent of the mechanical ventilation strategy in these animals. Similarly, but for the opposite reason, rats without macroscopic right lung lesions and *Pseudomonas aeruginosa* below the detection level (10^2 cfu) in the right lung were also not included in the analysis. It is unlikely that abscesses form in 2 h only or that bacterial clearance was effective enough to clear pneumonia macroscopic lesions in 2 h only. The study was completed when 9 rats in each group were available for analysis.

One day after *P. aeruginosa* instillation, the rats were anesthetized, paralyzed and ventilated during 2 h with 100% FiO_2 with one of the following five settings. In the HV/0 group, PEEP was zero and V_T set such as to result in 30 cm H_2O end-inspiratory (plateau) pressure (27±2.0 ml/kg), breath rate was 25/min. Other gas ventilation strategies were LV/0: low V_T-ZEEP (6 ml/kg V_T, zero end-expiratory pressure), LV/8: low V_T-PEEP (6 ml/kg V_T, 8 cm H_2O PEEP) and LLP/8: low V_T-PEEP in a left lateral position. The breath rate was 70/min in these groups. A level of 8 cm H_2O was selected for PEEP because it was the highest that did not appreciably affect hemodynamics. Partial liquid ventilation (PLV) was done with perflubron (Liquivent, Alliance Pharmaceutical, San Diego, CA). Rats were oxygenated (100% FiO_2) during 5 min with 6 ml/kg V_T.Pre-oxygenated perflubron was slowly instilled in the tracheal cannula until a meniscus of fluid became apparent during expiration. This required in average 10±2 ml/kg perflubron. Ventilatory settings were 6 ml/kg V_T, 3 cm H_2O PEEP, 70/min breath rate. Controls (NV) were left to breathe spontaneously after anesthesia. No experiment could be performed with a high tidal volume and 8 cm H_2O of PEEP because hemodynamic tolerance was poor.

Quantitative cultures of the right and left lung, liver, and spleen were carried out according to routine procedures. Overall bacterial dissemination was defined as the percentage of organs (spleen, liver and left lung) with positive *P. aeruginosa* cultures in each group. Bacterial counts are expressed per gram for the spleen and liver and per organ for the lungs because accurate wet lung weighing was not possible after PLV. Quantitative blood culture was done before and at 1 and 2 h after the start of mechanical ventilation.

TNF-alpha was assayed by an enzyme-linked immunosorbent assay with a rat specific kit (Genzyme SA, Cergy-Pontoise, France) in plasma samples obtained before and after mechanical ventilation.

All details on the methods are given in the online electronic supplementary material.

Statistical analysis

Results are presented as mean±SD. Analysis was performed with GraphPad Prism 3 (GraphPad Software, San Diego, CA), proportions were compared by the Fischer's exact test and bacteria counts were analyzed by non-parametric ANOVA. When the analysis was statistically significant, each group was compared with the other groups using the Mann-Whitney *U*-test. Airway pressures were compared by ANOVA for repeated measurements. A p-value of <0.05 was considered as significant.

Results

All rats were alive 24 h after inoculation. The number of rats that did not fulfill inclusion criteria because of having abscessed pneumonia at autopsy was 16 (NV=2, LV/0=2, LV/8=3, HV/0=2, LLP/8=1 and PLV=6) or less than 100 cfu *P. aeruginosa* in the right lung was 5 (NV=1, LV/0=1 LV/8=1, HV/0=1, LLP/8=1 and PLV=0). Right lung cultures in rats included in the analysis are shown in Fig. 1 and none had a macroscopically visible left pneumonia at autopsy. Baseline mean end-inspiratory pressure was 15.2±1.86 cm H_2O for LV/8, 9.2±1.48 cm H_2O for LV/0, 30 cm H_2O for HV/0, 14.8±0.83 cm H_2O for LLP/8 and 13.8±0.97 cm H_2O for PLV. Pressures increased significantly during the 2 h of mechanical

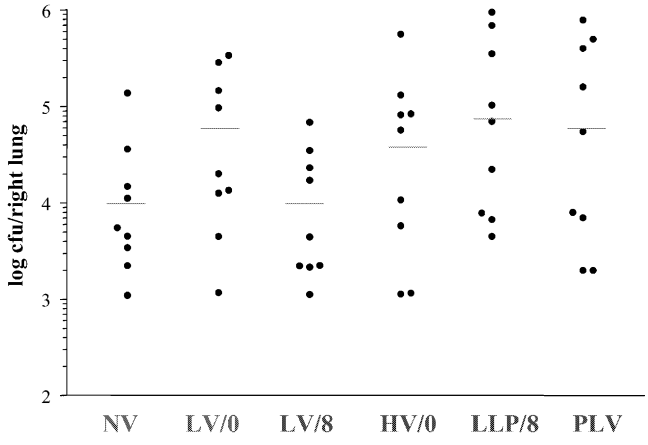

Fig. 1 Right lung quantitative cultures in the different groups (*NV* non ventilated controls, LV/0=6 ml/kg V_T no PEEP, LV/8=6 ml/kg V_T 8 cm H_2O PEEP, HV/0=V_T set such as end-inspiratory pressure was 30 cm H_2O no PEEP, LLP/8=6 ml/kg V_T, 8 cm H_2O PEEP, rat in the left lateral position; *PLV* partial liquid ventilation. Horizontal bars indicate mean values

ventilation in the high tidal volume ZEEP group only (from 30 to 36.4±5.70 cm H_2O, $p<0.05$).

Effects of mechanical ventilation strategy on bacterial dissemination

No rat had pleural effusion at autopsy and left lung cultures were sterile in all non-ventilated controls (Fig. 2). Left lung cultures were positive in variable proportions in all ventilated groups and significantly differed from the controls, except for the LV/8 group. Before mechanical ventilation 18 rats had a positive blood culture (NV=3, LV/0=5, LV/8=3, HV=4, LLP/8=3 and PLV=0) with an average colony count of 2.4±0.74 log cfu/ml. Blood cultures became positive during mechanical ventilation in only five animals in which bacteremia was not initially detected (2 in LV/0, 2 in LV/8 and 1 in HV/0, NS) and one rat in the LV/8 group had a positive blood culture before but not after mechanical ventilation.

The spleen was more frequently positive for *P. aeruginosa* after mechanical ventilation in the HV/0, LV/0 and LLP/8 groups than in the control group ($p<0.05$, Fig. 3). The number of animals with positive liver cultures was similar in the six groups (Fig. 3). However, the number of rats with systemic bacterial dissemination (i.e. positive spleen and/or liver) was significantly higher in the LV/0 (n=8), HV/0 (n=8) and LLP/8 (n=8) groups than in the LV/8 group (n=3), $p<0.05$. No significant difference was found with the PLV (n=4) and NV (n=6) groups.

The results are similar when comparing bacterial counts in each organ instead of the number of animals with positive organ cultures (see online supplementary material).

Overall bacterial dissemination (the percentage of positive organs in each group excluding the right lung) was significantly higher in the HV/0, LV/0 and LLP/8 groups than in NV controls and in the LV/8 group (Fig. 4). The higher (however not significantly) global dissemination in the PLV group was due to a more frequent positive cultures of the left lung.

The number of rats with no detectable *P. aeruginosa* in the left lung, spleen and liver was significantly higher in the LV/8 (n=5) than in LV/0 (n=0), LLP/8 (n=0) and HV/0 (n=0) groups, $p<0.05$.

The very high overall bacterial dissemination in the 16 rats with abscessed pneumonia regardless of ventilation strategy was confirmed (NV=100%, LV/0=83%, LV/8=100%, HV/0=100%, LLP/8= 66%, PLV=61%).

No relationship was found between the *P. aeruginosa* load in the right lung and bacterial dissemination (Fig. 5).

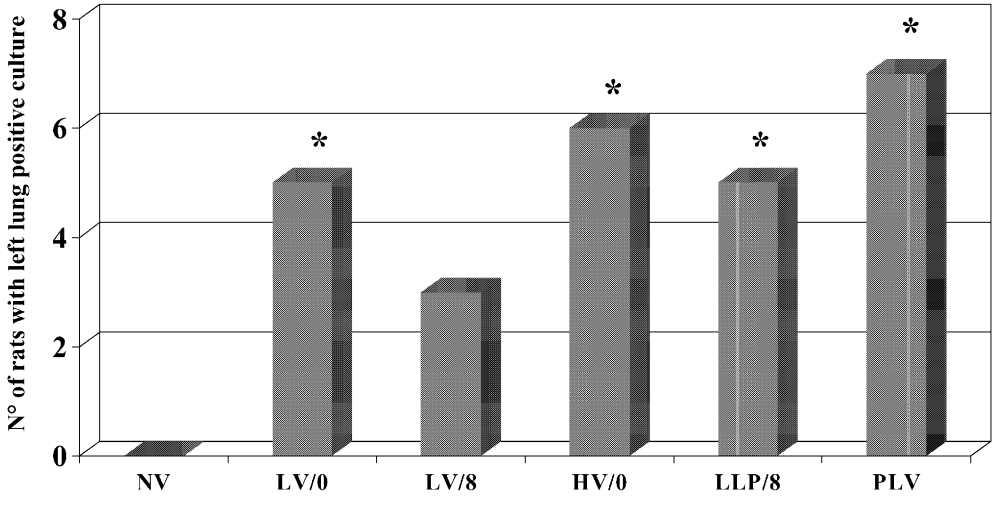

Fig. 2 Effect of the ventilation strategy on left lung bacterial contamination. Same abbreviations as for Fig. 1,* $p<0.05$ versus NV

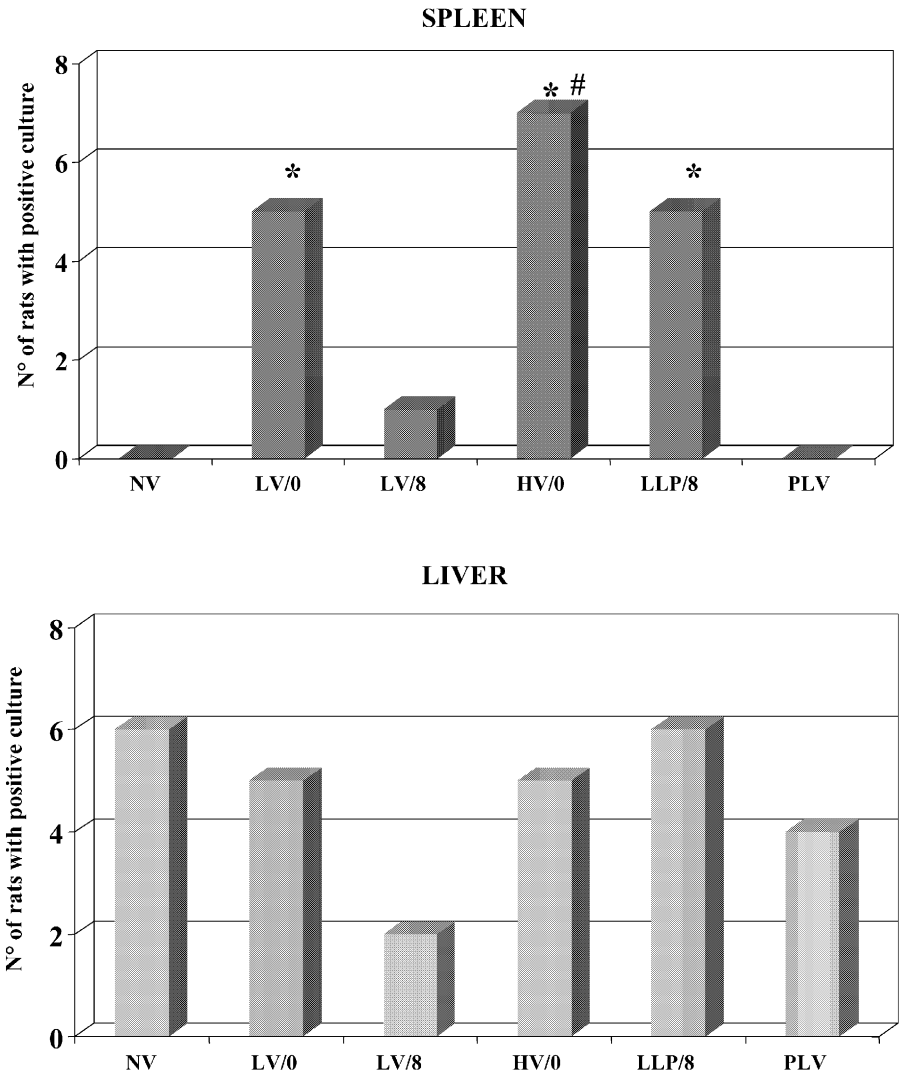

Fig. 3 Effect of the ventilation strategy on spleen (*upper panel*) and liver (*lower panel*) bacterial uptake. Same abbreviations as for Fig. 1. *p<0.05 versus NV, #p<0.05 versus LV/8 and PLV

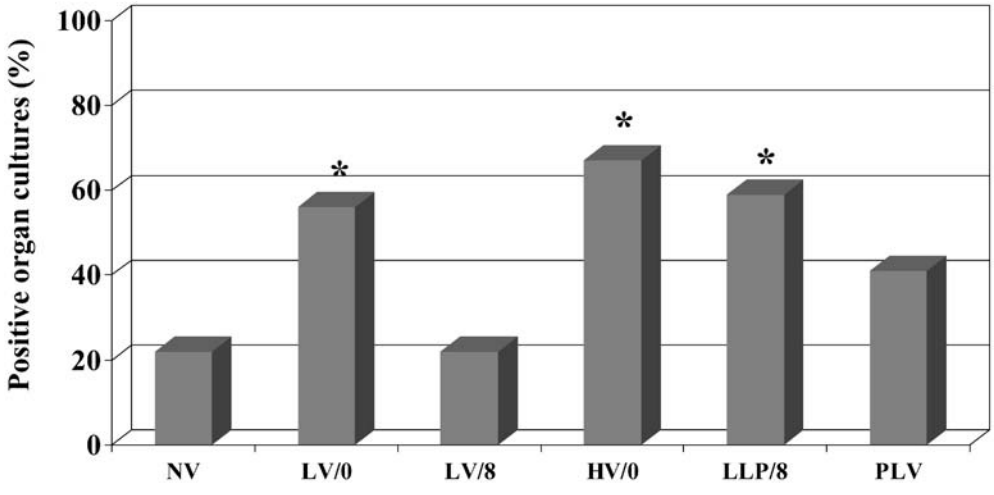

Fig. 4 Effect of ventilation strategy on the overall bacterial dissemination. Overall dissemination was defined as the percentage of positive left lung, spleen or liver cultures. Same abbreviations as for Fig. 1, *p<0.05 versus NV and LV/8

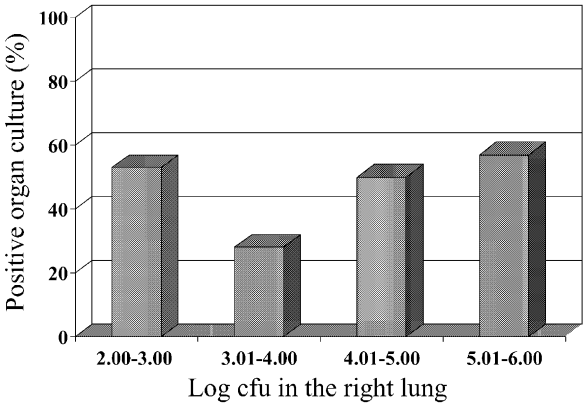

Fig. 5 Effect of the right lung bacterial count on overall bacterial dissemination. Overall dissemination was defined as the percentage of positive left lung, spleen or liver cultures. No significant difference was found between groups

Effects of mechanical ventilation strategy on plasma TNF-alpha

Plasma TNF-alpha before mechanical ventilation was below the detection threshold in most animals. TNF-alpha after mechanical ventilation significantly increased only in the two groups ventilated without PEEP (HV/0 and LV/0, Fig. 6) and there was a trend toward TNF-alpha increase in the LLP/8 group. The *P. aeruginosa* count in the right lung was similar in rats with and without a serum TNF-alpha increase after ventilation (4.38 log cfu vs. 4.19 log cfu/right lung, NS).

Discussion

Patients with ARDS seldom die from hypoxemia but rather from MOSF [21]. It was initially postulated that MOSF results from uncontrolled infection but recently, the ventilation strategy was also suspected as a potential culprit. This study provides some unifying evidence in favor of both theories. To the best of our knowledge, this is the first report that shows that the ventilation strategy influences distant organ seeding during a documented pneumonia. The main finding was that mechanical ventilation at low end-expiratory lung volume (no PEEP) exacerbates systemic bacterial dissemination, whether the tidal volume was high or low. This dissemination was associated with a significant increase in plasma TNF-alpha. By contrast, less dissemination and no increase in systemic TNF-alpha was observed when lung volume was increased by PEEP or lungs were recruited by partial liquid ventilation. Ventilation in the left lateral position and PLV were associated with contralateral seeding.

Assessment of bacterial translocation

We did not observe that the mechanical ventilation strategy affected bacteremia, in contrast to three recent studies [14, 15, 17]. Assessment of the effect of ventilatory strategies on bacterial dissemination during animal pneumonia experiments is complex because bacteremia is common after bacteria instillation. Indeed, several rats in our study were bacteremic before the onset of ventilation, in keeping with previous works [18, 22] which found that most animals with fully developed pneumonia are bacteremic. Thus, we studied the effect of the mechanical ventilation strategy on dissemination exacerbation assess-

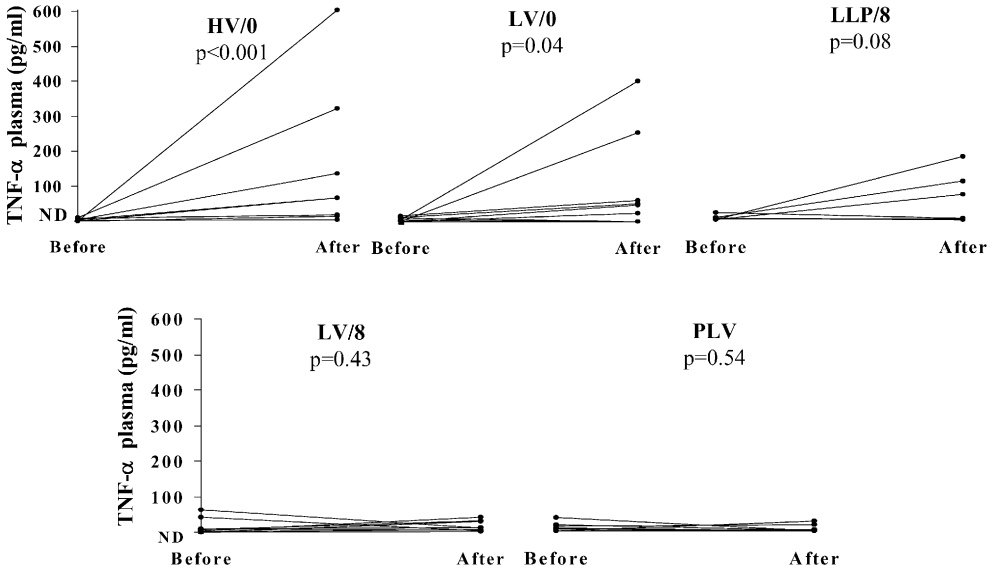

Fig. 6 Changes in plasma tumor necrosis factor-alpha (TNF-α) concentration after 2 h of mechanical ventilation in rats ventilated with the different strategies. Same abbreviations as for Fig. 1, *ND* not detectable

ing distant organ seeding and scoring global bacterial dissemination (spleen, liver and left lung positive cultures).

In the Nahum and colleagues study [15], dogs were ventilated immediately after tracheal instillation of *E. coli*. This model ensured the absence of bacteremia before rats were designated for a specific mechanical ventilation strategy. However, this situation is different from a fully developed pneumonia. They observed that bacteremia was significantly more frequent in animals ventilated without PEEP than in those ventilated with PEEP 30 min after the beginning of mechanical ventilation and using a one-tailed statistical test only. The blood culture result was thereafter variable and no longer differed between groups. It has indeed been well demonstrated that bacteremia is a transient and intermittent phenomenon [18, 22]. Verbrugge and colleagues [14] studied the effect of PEEP 22 h after *Klebsiella pneumoniae* instillation in rats and found that the number of positive blood cultures was significantly lower in rats ventilated with PEEP. However, few rats were bacteremic and the number of bacteria in blood was extremely low, between 0.5 and 2.5 cfu/ml, which is surprising for a pneumonia state. It may be that *K. Pneumoniae* is hardly freed by ventilation or that there was no well developed pneumonia (no tissue lesions). More recently Lin and colleagues observed a trend (2/18 vs. 5/15 rats) suggesting that injurious ventilatory strategy preceding bacterial instillation might predispose animals to bacteremia [17].

To assess the mechanical ventilation effect on bacteremia, Verbrugge and colleagues excluded animals having a baseline positive blood culture from their analysis [14]. However baseline negative blood culture does not rule out intermittent bacteremia because is an extremely transient phenomenon. Because hematopoietic organs quickly achieve blood bacterial clearance [23], spleen, liver and pleural fluid cultures are more sensitive and specific for sustained bacterial dissemination than blood cultures in experimental models of pneumonia [19, 24]. We found significant differences in the number of positive spleen cultures according to the ventilation strategy, suggesting that the strategy influences the intensity of systemic diffusion, which may be relevant with respect to the possible exacerbation of a systemic inflammatory state [25]. However, we found no difference between liver cultures which were on the whole more often positive than spleen cultures. It may be that liver bacterial uptake was more efficient because of the larger organ size and blood flow, and that the uptake before mechanical ventilation precluded recognition of the impact of ventilation. Although liver seeding was similar between groups, systemic bacterial dissemination (i.e. positive rate and/or liver) significantly differed according to the ventilation modality. The lowest systemic dissemination was found in low V_T-PEEP group.

Since spleen, liver, and left lung are normally sterile, we found it more appropriate to compare the rate of bacterial contamination rather than the number of bacteria detected in each organ. In addition, there are no data indicating that the bacterial burden might differently alter the inflammatory reaction, outcome or anything else in these organs. Moreover, only one rat from the low V_T-PEEP group had a positive spleen culture making mean bacterial counts not suitable for result presentation. Result significance was not affected comparing the mean bacterial count in each organ instead of the number of animals with positive organ culture.

As explained, we found that rats with abscessed pneumonia had *P. aeruginosa* counts higher than 6 log cfu and constant spontaneous bacterial dissemination during preliminary experiments. We considered that keeping abscessed pneumonia for analysis could confound the effects of the mechanical ventilation strategy and thus prospectively excluded these animals. Similarly, but for the opposite reason, rats without macroscopic right lung lesions were also not included in the analysis. This exclusion also resulted in similar bacterial counts in right lungs in all groups and allowed a meaningful analysis of the effect of the ventilation strategy.

It seems unlikely that mechanical ventilation for 2 h will affect lung infection to such an extent that it resulted in abscess formation or, on the contrary, complete recovery. The trend for a lower right lung bacterial count in the non-ventilated and low V_T-PEEP group could have explained a lesser bacterial dissemination. However, it is worth noting that no rat of the PLV group had a positive spleen culture whereas the right lung *Pseudomonas* counts were similar to rats of groups with intense spleen seeding.

Lung bacterial cross contamination

The effect of mechanical ventilation on bacterial dissemination to the contralateral lung has never been evaluated. The convective movement of alveolar exsudate and bronchial secretions during mechanical ventilation may explain contralateral seeding. The risk of contralateral dissemination is likely to be higher when excess fluid is present in airways, such as edema fluid resulting from high V_T ventilation [26], or during partial liquid ventilation. PLV facilitates airway reopening by displacing secretions from small to large bronchi and may thus transfer contaminated mucus to the other lung [27]. The effect of gravity probably explains contralateral lung seeding during lateral positioning. The only modality that was not responsible for significant contralateral dissemination was ventilation in the supine position with a low tidal volume and PEEP. PEEP application may have prevented lung collapse and maintained infected fluid in distal air spaces, thus avoiding cross contamination. This

protective effect of PEEP was probably not sufficient when the less contaminated lung was in a lower position because lateral positioning favors downhill liquid movement. Contamination of the left lung from the systemic circulation seems unlikely as the PLV group had low systemic dissemination but exhibited frequent left lung contamination.

Effect of mechanical ventilation strategy on systemic bacterial dissemination

PEEP application significantly reduces bacterial [14, 15, 17] and endotoxin [16] translocation from infected lungs. We show that spleen contamination was significantly less in rats ventilated with a low 6 ml/kg V_T in the presence of PEEP, despite higher lung distension. It may be speculated that the risk and the severity of bacterial and inflammatory dissemination depends on the severity of VILI during acute lung infection. Savel and co-workers [11] found that reducing V_T from 15 ml/kg to 6 ml/kg lessened lung injury during *P. aeruginosa* pneumonia in rabbits ventilated with 3–5 cm H_2O PEEP. High V_T favors dissemination (Fig. 4), but, besides the V_T level, PEEP is clearly an important factor. In the saline lavage-lung model, Argiras and colleagues [5] have shown that mechanical ventilation exacerbates preexisting lung injury when PEEP is set below the lower inflexion point on the pressure volume curve. Using an appropriate level of PEEP could, therefore, limit alveolo-capillary barrier lesions and reduce the risk of bacterial translocation from the septic lung. Further, mechanical ventilation at low end-expiratory volume results in surfactant inactivation by compression and rupture during reexpansion, a phenomenon that could be avoided by PEEP application [5, 6]. After rupture, surfactant may be driven out from distal airways. Because of its antibacterial property, inactivation of surfactant might also play an important role in the occurrence of bacterial translocation [28].

The effect of PLV on bacterial dissemination during pneumonia has never been evaluated. We found that PLV significantly decreased bacterial translocation. PLV might have reduced local overinflation [29] and, thus, the stress applied to the lungs during ventilation. It might also operate by its "liquid PEEP" effect, stabilizing distal air spaces in a way similar to PEEP. Anti-inflammatory effects of PFCs have also been reported [30] but take longer times to develop. Attenuated inflammatory response during pneumonia could influence the host defense processes and facilitate the broad spreading of infection [31]. Our results suggest, however, that PLV could lessen bacterial translocation, but at the expense of contralateral bacterial seeding. Surprisingly, systemic bacterial dissemination in the low V_T PEEP group was more frequent when rats were placed in the left lateral than in the supine position. PEEP application in a lateral position may ease overdistension of the infected right lung placed in the upper position and facilitate bacterial translocation.

Other mechanisms than bacterial translocation from the lung to distant organs might explain differences in spleen cultures. The course of bacterial mobilization might be altered by hemodynamics. The low bacterial dissemination in the low V_T PEEP group could be due to an alteration in hemodynamics and a decrease in liver and spleen perfusion, but we have previously shown that hemodynamics are not affected by ventilation with a similar low tidal volume and 10 cm H_2O PEEP in rats with previous lung injury [32]. The probability of hemodynamic changes was higher with the high tidal volume ventilation modality than with the low V_T-PEEP one because intrathoracic pressures were higher with the former (mean pressure 30 vs. 15 cmH_2O). To the best of our knowledge, there are no data suggesting that PEEP or high V_T ventilation differently affect splanchnic blood flow. In addition, should the low spleen seeding in the supine low V_T PEEP group be related to a decrease in splanchnic blood flow, a similar result should have been found in the left lateral position group because it was ventilated with the same V_T-PEEP level. The blood TNF-alpha increase related to the ventilation modality might have influenced *Pseudomonas* counts in spleen. However, in vivo studies on *Pseudomonas* pneumonia did not confirm a higher bacterial count in lungs and spleen in animals with high serum TNF-alpha concentration [33]. In addition, it has been shown that TNF had no influence on the bacterial clearance process [34].

Role of mechanical ventilation strategy on serum TNF-alpha concentration

Ventilator-associated pneumonia is often associated with a systemic inflammatory response [35] despite occasional finding of pathogens in the bloodstream [36]. This suggests a role for the release of inflammatory mediators from the lungs. Serum TNF-alpha levels less than 100 pg/ml 24 h after bacterial instillation are usual in similar models of pneumonia [37] because cytokines remain compartmentalized in the lungs [38]. TNF-alpha leaks more easily from injured lungs [25, 39].

We found that systemic TNF-alpha concentration increased more frequently in rats ventilated with a high V_T or in the absence of PEEP. These results agree with the finding that plasma TNF-alpha was 7-fold higher after tracheal endotoxin instillation in animals ventilated with 12 ml/kg V_T without PEEP than in those ventilated with a low V_T and PEEP [16]. The beneficial role of PLV in reducing systemic inflammation has also been observed after hydrochloric acid instillation in rats. TNF-alpha levels are high in lungs with pneumonia [38], thus, TNF-alpha dosage in lung homogenates would have provided

little information on the origin of the systemic increase. Because TNF-alpha increased in the same groups as those that exhibited systemic bacterial dissemination, the origin of the circulating cytokine may have been extrapulmonary as well.

Conclusion

This study shows a strong interaction between the mechanical ventilation strategy and the risk of contralateral lung contamination and the severity of systemic dissemination during *P. aeruginosa* pneumonia. Our results suggest that a protective ventilation strategy associating reduced V_T and PEEP reduces exacerbation of bacterial and inflammatory dissemination during unilateral lung infection. V_T reduction alone seems not sufficient to reduce bacterial and inflammatory dissemination and adjunction of PEEP is likely to be necessary. The best level of PEEP to use remains to be determined, but this complex issue is not particular to this specific diseased state. Partial liquid ventilation seems to be as beneficial as PEEP but might be associated with a higher risk of contralateral lung bacterial dissemination.

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