Intensive Care Med (2007) 33:1800–1804
DOI 10.1007/s00134-007-0749-1

BRIEF REPORT

Robert A. Lachmann
Anton H. van Kaam
Jack J. Haitsma
Burkhard Lachmann

High positive end-expiratory pressure levels promote bacterial translocation in experimental pneumonia

Received: 26 October 2006
Accepted: 23 May 2007
Published online: 19 June 2007

This article is discussed in the editorial available at: http://dx.doi.org/10.1007/s00134-007-0750-8

This work was performed at the Department of Anesthesiology, Erasmus Medical Center, Rotterdam, and was financially supported by the International Foundation for Clinically Oriented Research (IFCOR).

R. A. Lachmann (✉) · J. J. Haitsma · B. Lachmann
Erasmus Medical Center, Department of Anesthesiology,
P.O. Box 2040, 3000 CA Rotterdam,
The Netherlands
e-mail: mbwana@gmail.com
Tel.: +31-10-4087314
Fax: +31-10-4089450

A. H. van Kaam
Emma Children's Hospital, Academic Medical Center, Department of Neonatology,
Amsterdam, The Netherlands

J. J. Haitsma
University of Toronto, St. Michael's Hospital, Interdepartmental Division of Critical Care Medicine,
Toronto, Canada

Abstract *Objective:* A previous study in piglets with experimental pneumonia showed that reducing atelectasis by means of open lung ventilation attenuated bacterial translocation compared to conventional ventilation settings. This study examined the effect of open lung ventilation with higher than necessary positive end-expiratory pressures (PEEP) on bacterial translocation. *Design and setting:* Prospective animal study in a university-affiliated research laboratory. *Subjects:* Thirty piglets. *Interventions:* Animals were surfactant-depleted by whole-lung lavage and infected with group B streptococci. Thereafter the animals were ventilated for 5 h according to either a conventional ventilation strategy, open lung strategy, or open lung/high-PEEP strategy. Blood samples for blood gas analysis and blood bacterial counts were taken every hour. After 5 h of ventilation surviving animals were killed, and lung colony forming units and lung mechanics parameters were determined. *Results:* All animals in both open lung groups survived but only 30% of those in the conventional ventilation group. Open lung ventilation resulted in significantly less bacterial translocation than either conventional or high-PEEP ventilation. Lung function in the conventional ventilated group was significantly less than in the two open lung groups. *Conclusions:* The lowest level of bacterial translocation was observed during optimal ventilation (open lung) which was achieved by using individually tailored settings. Deviation to either side can be harmful, as shown by the increased bacterial translocation during conventional and high-PEEP ventilation.

Keywords Open-lung · Ventilation · Atelectasis · Positive end-expiratory pressure · Pneumonia · Lavage

Introduction

Patients in intensive care units who have an endotracheal tube often experience colonization with potential pathogenic micro-organisms which may eventually lead to pneumonia [1–3]. Sepsis and/or septic shock complicate the clinical picture [4–6]. It is known that injurious ventilation with high tidal volumes using little or no positive end-expiratory pressure (PEEP) facilitate bacterial translocation while the addition of higher PEEP values can attenuate it [7–9]. Using individual PEEP settings according to the open lung concept (OLC) van Kaam

and colleagues [10] observed that bacterial translocation was less in an experimental pneumonia model than with conventional ventilation using PEEP of 5 cmH_2O and tidal volume of 7 ml/kg [11]. However, the level of PEEP applied in critically ill patients with acute respiratory distress syndrome (ARDS) is often based on general protocols and not on the severity of lung disease in the individual patient [12]. This approach increases the risk that patients are ventilated with a higher than necessary end-expiratory pressure, possibly leading to alveolar overdistension. To our knowledge, data on how these higher PEEP levels affect bacterial translocation in ventilator associated pneumonia is limited. To gain more insight into this unknown territory we used the same experimental model as van Kaam and colleagues [11] but ventilated the animals with a higher PEEP than required for optimal gas exchange and compared the number of blood colony forming units (CFU) as the main outcome variable with conventional and OLC ventilation.

Material and methods

Thirty newborn piglets were anesthetized, tracheotomized, and supplied with central lines [11]. Respiratory failure was induced through repeated saline lavage (50 ml/kg; 37°C) until PaO_2 was below 80 mmHg. After lavage two aliquots of 5 ml/kg containing a concentration of approx. 10^8 encapsulated group B streptococci (GBS) CFU/ml were injected intratracheally in the right and left lateral position to ensure equal distribution [11]. All animals received positive pressure ventilation (FIO_2 of 1.0) for 5 h after GBS instillation using different ventilation strategies depending on their group:

- Conventional positive pressure ventilation (ConV group, $n = 10$): In this group peak inspiratory pressure (PIP) was set at a level that resulted in an expiratory tidal volume of approx. 7 ml/kg. The level of PEEP was set at 5 cmH_2O and ventilatory rate at 60 breaths/min (inspiratory to expiratory ratio, I/E, 1:2) [11].
- Open lung concept positive pressure ventilation (OLC group, $n = 10$): The main objective of this ventilation strategy is to recruit atelectatic lung regions and prevent repeated alveolar collapse during expiration. Changes in intrapulmonary shunt and subsequent changes in oxygenation were used to assess alveolar collapse. For this reason a sensor for continuous blood gas monitoring was inserted through a femoral artery catheter. During recruitment collapsed alveoli were opened by a stepwise increase in PIP and PEEP (2 cmH_2O every 2 min) until PaO_2 reached 450 mmHg, the PIP at this point being defined as the opening pressure. Subsequently PIP and PEEP were reduced stepwise (2 cmH_2O every 2 min) until PaO_2 dropped below 450 mmHg, the PEEP at this point being defined as the closing pressure. Knowing opening and closing pressures, the lung was rerecruited and kept open by setting the PEEP 2 cmH_2O above the closing pressure. With the lung now being ventilated on the more compliant deflation limb of the pressure volume (P/V) curve, the pressure amplitude was minimized as much as possible and hypercapnia was prevented by using supranormal ventilatory rates (I/E 1:1, 100 bpm) [11].
- High positive end-expiratory positive pressure ventilation (high-PEEP group, $n = 10$): After alveolar recruitment (see OLC), a universal PEEP of 15 cmH_2O (vs. approx. 10 cmH_2O in the OLC group) was applied in all animals. This PEEP level was chosen based on preliminary experiments that showed that PEEP levels of 15 cmH_2O did not lead to a serious compromise in hemodynamics. Peak pressures were set to yield a tidal volume of about 6 ml/kg (approx. 25 cmH_2O, I/E 1:1, 100 bpm).

There were no intergroup differences in age, weight, or number of lavages needed to induce lung injury. No air leaks were observed in the animals during the study period. In all animals expiratory flow was observed to be zero prior to each inspiration, indicating the absence of intrinsic PEEP. Samples for blood gas analysis and blood CFUs were drawn at the end of the instrumentation period, after lung lavage, and hourly after GBS instillation. Hemodynamic support (volume substitution, dopamine infusion) was given when both mean arterial blood pressure decreased (> 10%) and heart rate increased to more than 200 (or an increase of more than 10% if baseline values were already above this level) from baseline values [11]. At the end of the experiment P/V curves, protein concentration in bronchoalveolar lavage (BAL), and lung CFUs were determined [11].

All data are expressed as mean ± SD. Data on bacterial growth were subjected to logarithmic transformation ($\log_{10}$). Intergroup differences were evaluated by analysis of variance and Bonferroni's post-hoc test. Kaplan-Meier analysis followed by a log rank test was used to compare survival and bacterial translocation. Fisher's exact test was used when appropriate. Data from the ConV group at 5 h ($n = 3$) were excluded from statistical analysis. Differences at the level of $p \leq 0.05$ were considered statistically significant.

Results

Seven of the ten animals in the ConV group died during the ventilation period, with a mean survival time of 258 ± 13 min. This differed significantly from the 100% survival in the other groups. After 5 h of ventilation the number of CFU/lung increased significantly in the ConV

Table 1 Generic and ventilatory parameters over time in the three groups. Data presented are mean ± SD. *WW/BW*, wet weight lung weight to body weight ratio; *CFU*, colony forming units; C_{Lmax}, maximal lung compliance; TLC_{35}, lung volume at a transpulmonary pressure of 35 cmH_2O (total lung capacity); V_5, lung volume at a transpulmonary pressure of 5 cm H_2O; *MawP*, mean airway pressure; *PEEP*, positive end-expiratory pressure; *PA*, pressure amplitude; V_{TEX}, expiratory tidal volume; *ConV*, lavaged + GBS + conventional ventilation; *OLC*, lavaged + GBS + open lung ventilation; *high-PEEP*, lavaged + GBS + high-PEEP ventilation

	ConV	OLC	High PEEP
WW/BW (g/kg)	49 ± 8*	37 ± 3	34 ± 6
log_{10} GBS (CFU injected)	9.9 ± 0.2	9.8 ± 0.3	9.9 ± 0.1
log_{10} GBS lung (CFU) (after 5 h)	11.2 ± 0.5[a]	9.9 ± 0.3	9.7 ± 0.5
C_{Lmax} (ml/cmH_2O/kg)	1.3 ± 0.7*	5.0 ± 1.6	5.8 ± 1.6
TLC_{35} (ml/kg)	24 ± 8*	59 ± 15	69 ± 14
V_5 (ml/kg)	11 ± 6*	39 ± 11**	51 ± 14
Protein (mg/ml)	1.39 ± 0.54*	0.79 ± 0.19	0.8 ± 0.18
MawP (cmH_2O)			
1 h	11.2 ± 1.5*	14.8 ± 1.4**	20.4 ± 0.7
3 h	12.2 ± 1.9*	14.9 ± 1.2**	20 ± 0.7
5 h	10.3 ± 0.6	13.5 ± 1.7**	20.8 ± 0.7
PEEP (cmH_2O)			
1 h	4.5 ± 0.7*	10.9 ± 0.9**	15 ± 0.0
3 h	4.9 ± 1.0*	10.8 ± 0.9**	15 ± 0.0
5 h	4.0 ± 0.0	9.1 ± 1.5**	15 ± 0.0
PA (cmH_2O)			
1 h	19.5 ± 3.0*	7.2 ± 1.1**	10 ± 0.8
3 h	21.6 ± 4.25*	8.1 ± 0.7	9.4 ± 1.1
5 h	18.0 ± 1.7	8.8 ± 0.8**	11 ± 1.0
V_{TEX} (cmH_2O)			
1 h	7.3 ± 0.8*	6.0 ± 0.3	6.2 ± 0.3
3 h	6.6 ± 0.7	6.0 ± 0.4	6.1 ± 0.1
5 h	7.3 ± 1.2	6.3 ± 0.4	6.0 ± 0.3

* $p < 0.05$ vs. OLC and high PEEP, ** $p < 0.05$ vs. high PEEP
[a] $p < 0.001$ vs. GBS injected, OLC, and high-PEEP

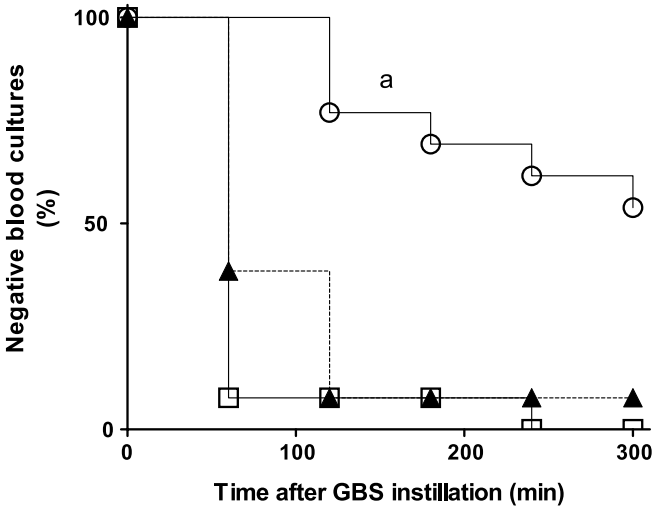

Fig. 1 Kaplan–Meier curves showing the percentage of animals in each group with negative blood cultures during the 5-h ventilation period. *ConV*, lavaged + GBS + conventional ventilation (*triangles*); *OLC*, lavaged + GBS + open lung ventilation (*circles*); *high PEEP* lavaged + GBS + high-PEEP ventilation (*squares*). [a] $p < 0.01$ OLC vs. ConV and high PEEP in time to bacteremia

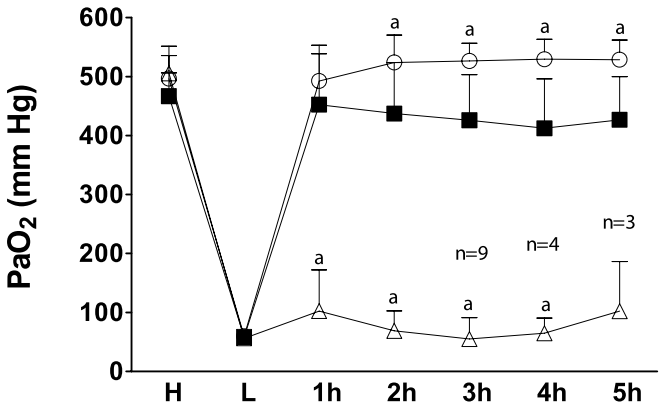

Fig. 2 Changes (mean ± SD) in PaO_2 levels in the three groups. *H*, healthy baseline value; *L*, after lavage; *ConV*, lavaged + GBS + conventional ventilation (*triangles*); *OLC*, lavaged + GBS + open lung ventilation (*circles*); *high PEEP*, lavaged + GBS + high-PEEP ventilation (*squares*). [a] $p < 0.05$ vs. the two other groups

group and was also significantly higher than in the OLC and high-PEEP groups. There was neither bacterial growth nor clearance in the latter two groups (Table 1). All but one animal in the ConV group had GBS positive blood cultures, with a mean time to bacteremia of 102 ± 23 min (Fig. 1). All animals in the high-PEEP group had positive blood cultures at the end of the ventilation period, with a mean time to bacteremia of 83 ± 16 min. The use of OLC ventilation resulted in a significant increase in time to bacteremia (210 ± 33 min), with six of the ten animals being GBS blood positive after 5 h of ventilation. In the

ConV group oxygenation was severely impaired and did not improve from postlavage values throughout the 5 h ventilation period (Fig. 2). Ventilation according to the OLC significantly improved oxygenation to healthy baseline levels for the remainder of the experiment. The animals in the high-PEEP group also showed improved oxygenation but significantly less than those in the OLC group. All ten animals in the ConV group vs. only one in the OLC group and four in the high-PEEP group required volume support ($p < 0.05$). Similarly, all but one animal in the ConV group but no animal in the other groups required dopamine infusion ($p < 0.05$). P/V curves recorded postmortem showed a severe deterioration in lung function in the ConV group but not in the OLC or the high-PEEP group (Table 1). Alveolar protein influx was most severe in the ConV group. There was no difference in BAL protein content between the high-PEEP and OLC groups (Table 1).

Discussion

The present study demonstrates that open lung ventilation with end-expiratory pressures higher than required for optimal gas exchange promotes bacterial translocation (time to bacteremia). At the same time, growth of bacteria in lungs remains similar as with open lung ventilation with optimal PEEP.

In a previous study we showed that bacterial growth and translocation can be attenuated by reducing atelectasis in an ARDS model of experimental pneumonia [11]. It was concluded that using individualized OLC resulted in less volutrauma and atelectrauma and therefore in fewer permeability disturbances with subsequently less bacterial translocation [11]. Interestingly, in the present study using a universal high PEEP (approx. 5 cmH_2O higher than required for optimal gas exchange as indicated by the OLC group) resulted in bacterial translocation rates as severe as in the ConV group. On the other hand, applying these settings prevented an influx of proteins and fluids in the alveolar space and a deterioration in lung function. However, the latter does not necessarily mean that the alveolar-capillary permeability was not increased in the high-PEEP group. Applying a small tidal volume upon a higher than necessary PEEP probably prevents atelectrauma, but it still leads to alveolar overdistension due to high end-inspiratory stretch. It is conceivable that the high PEEP levels prevented the influx of fluids and proteins into the alveolar space but not the efflux of bacteria into the blood stream.

This study has several limitations. First, we used saline lavage to create an experimental ARDS model, which may not fully reflect all aspects of this disease. Furthermore, findings as presented in this study may in part be specific to this animal model. Second, this study investigated the impact of PEEP in a model of developing pneumonia and the reported results may not be applicable to models with already established pneumonia.

Despite these limitations we think the present study is still of clinical relevance. It is known that patients with ARDS have an increased risk of pulmonary infection and often succumb to dissemination of the pulmonary infection with overwhelming sepsis and multiple organ failure [13, 14]. The present study indicates that the ventilation strategy directly affects the incidence and degree of bacterial translocation, showing that optimal ventilation according to the OLC may be beneficial in reducing the occurrence of bacteremia and sepsis in patients at risk. Deviation from these settings (to either side) can be harmful, as shown by the increased bacterial translocation in the ConV and high-PEEP groups.

Acknowledgements. We thank Stefan Krabbendam (Erasmus Medical Center) for expert technical assistance and Laraine Visser-Isles (Erasmus Medical Center) for checking the English language.

References

1. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoin MH, Wolff M, Spencer RC, Hemmer M (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 274:639–644
2. Grohskopf LA, Sinkowitz-Cochran RL, Garrett DO, Sohn AH, Levine GL, Siegel JD, Stover BH, Jarvis WR (2002) A national point-prevalence survey of pediatric intensive care unit-acquired infections in the United States. J Pediatr 140:432–438
3. Nagata E, Brito AS, Matsuo T (2002) Nosocomial infections in a neonatal intensive care unit: incidence and risk factors. Am J Infect Control 30:26–31
4. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C (1996) Nosocomial pneumonia and mortality among patients in intensive care units. JAMA 275:866–869
5. Bonten MJ, Froon AH, Gaillard CA, Greve JW, de Leeuw PW, Drent M, Stobberingh EE, Buurman WA (1997) The systemic inflammatory response in the development of ventilator-associated pneumonia. Am J Respir Crit Care Med 156:1105–1113
6. Apisarnthanarak A, Holzmann-Pazgal G, Hamvas A, Olsen MA, Fraser VJ (2003) Ventilator-associated pneumonia in extremely preterm neonates in a neonatal intensive care unit: characteristics, risk factors, and outcomes. Pediatrics 112:1283–1289
7. Verbrugge SJ, Sorm V, van't Veen A, Mouton JW, Gommers D, Lachmann B (1998) Lung overinflation without positive end-expiratory pressure promotes bacteremia after experimental Klebsiella pneumoniae inoculation. Intensive Care Med 24:172–177

8. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ (1997) Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. Crit Care Med 25:1733–1743
9. Lin CY, Zhang H, Cheng KC, Slutsky AS (2003) Mechanical ventilation may increase susceptibility to the development of bacteremia. Crit Care Med 31:1429–1434
10. Lachmann B (1992) Open up the lung and keep the lung open. Intensive Care Med 18:319–321
11. van Kaam AH, Lachmann RA, Herting E, De Jaegere A, van Iwaarden F, Noorduyn LA, Kok JH, Haitsma JJ, Lachmann B (2004) Reducing atelectasis attenuates bacterial growth and translocation in experimental pneumonia. Am J Respir Crit Care Med 169:1046–1053
12. Brower RG, Lanken PN, MacIntyre N, Matthay MA, Morris A, Ancukiewicz M, Schoenfeld D, Thompson BT (2004) Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. N Engl J Med 351:327–336
13. Estenssoro E, Dubin A, Laffaire E, Canales H, Saenz G, Moseinco M, Pozo M, Gomez A, Baredes N, Jannello G, Osatnik J (2002) Incidence, clinical course, and outcome in 217 patients with acute respiratory distress syndrome. Crit Care Med 30:2450–2456
14. Delclaux C, Roupie E, Blot F, Brochard L, Lemaire F, Brun-Buisson C (1997) Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: incidence and diagnosis. Am J Respir Crit Care Med 156:1092–1098