Effect of positive end-expiratory pressure on lung injury and haemodynamics during experimental acute respiratory distress syndrome treated with extracorporeal membrane oxygenation and near-apnoeic ventilation

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Abstract

Background: Lung rest has been recommended during extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS). Whether positive end-expiratory pressure (PEEP) confers lung protection during ECMO for severe ARDS is unclear. We compared the effects of three different PEEP levels whilst applying near-apnoeic ventilation in a model of severe ARDS treated with ECMO.

Methods: Acute respiratory distress syndrome was induced in anaesthetised adult male pigs by repeated saline lavage and injurious ventilation for 1.5 h. After ECMO was commenced, the pigs received standardised near-apnoeic ventilation for 24 h to maintain similar driving pressures and were randomly assigned to PEEP of 0, 10, or 20 cm H_2O ($n=7$ per group). Respiratory and haemodynamic data were collected throughout the study. Histological injury was assessed by a pathologist masked to PEEP allocation. Lung oedema was estimated by wet-to-dry-weight ratio.

Results: All pigs developed severe ARDS. Oxygenation on ECMO improved with PEEP of 10 or 20 cm H_2O, but did not in pigs allocated to PEEP of 0 cm H_2O. Haemodynamic collapse refractory to norepinephrine ($n=4$) and early death ($n=3$) occurred after PEEP 20 cm H_2O. The severity of lung injury was lowest after PEEP of 10 cm H_2O in both dependent and non-dependent lung regions, compared with PEEP of 0 or 20 cm H_2O. A higher wet-to-dry-weight ratio, indicating worse lung injury, was observed with PEEP of 0 cm H_2O. Histological assessment suggested that lung injury was minimised with PEEP of 10 cm H_2O.

Conclusions: During near-apnoeic ventilation and ECMO in experimental severe ARDS, 10 cm H_2O PEEP minimised lung injury and improved gas exchange without compromising haemodynamic stability.

Keywords: acute respiratory distress syndrome; extracorporeal membrane oxygenation; mechanical ventilation; positive end-expiratory pressure; ventilator-induced lung injury

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Editor's key points

- The potential benefit of lung protection strategies during extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) is unclear.
- The authors examined the effects of three different PEEP levels on lung injury whilst applying near-apnoeic ventilation in a porcine model of ARDS requiring ECMO.
- After repeated saline lavage and injurious ventilation caused severe ARDS, oxygenation on ECMO improved when PEEP 10—20 cm H_2O was applied in near-apnoeic ventilation.
- High PEEP (20 cm H_2O) caused haemodynamic collapse, but lung injury was markedly worsened if no PEEP was applied.
- This experimental model suggests that modest PEEP reduces lung injury whilst maintaining haemodynamic stability.

In patients with severe acute respiratory distress syndrome (ARDS), extracorporeal membrane oxygenation (ECMO) is increasingly being used to treat refractory hypoxaemia. One of the main advantages of ECMO is the possibility of providing lung rest, allowing for reductions in tidal volume V_T and ventilatory frequency (VF) to near-apnoeic levels. Studies have shown that further limiting V_T and driving pressures in patients with ARDS with the use of ECMO may be beneficial.[1—3]

The need to gain insight about how to optimise ultra-protective ventilation during ECMO has been recently highlighted.[4] How much PEEP should be applied during ECMO for severe ARDS remains controversial.[4] It may be argued that, as gas exchange relies fully on ECMO and as the use of very small V_T possibly minimises the risk of atelectrauma and alveolar overdistension, PEEP is no longer required.[5—7] In this scenario, however, it is unknown whether atelectasis formation may result in further lung damage.[8] Although animal and human studies have explored the use of higher levels of PEEP during ECMO in an attempt to better recruit the lungs,[9—13] excessive PEEP may lead to overdistension in poorly recruitable lungs.[14]

Using an experimental model of severe ARDS, we have shown that a protocol consisting of near-apnoeic ventilation during ECMO results in reduced histological damage and fibroproliferation, compared with conventional protective ventilation.[15] However, in that study, we applied near-apnoeic ventilation at a fixed PEEP level of 10 cm H_2O. In the present study, using the same animal model of ARDS supported with ECMO, we aimed to determine whether additional lung protection could be obtained by keeping the lungs more recruited either with higher PEEP levels or by minimising static stress and strain by avoiding the use of PEEP.

Methods

Adult male domestic pigs were included in the study. The Institutional Animal Ethics Committee approved the study (Protocol 12—029/B). We complied with all relevant aspects of the Animal Research: Reporting of In Vivo Experiments guidelines.[16] The pigs were kept in an environment with controlled temperature, with free access to water and food. At the end of the experiment, the pigs were killed by an i.v. overdose of thiopental (Biosano, Santiago, Chile) and T-61 solution (Intervet Chile, Santiago, Chile). [15]

Lung injury

The experimental set-up used in this study has been described extensively in previous publications (Fig. 1),[15,17] including the anaesthetic protocol, monitoring, and fluid therapy (Supplementary data). During preparation, adult pigs were ventilated (Dräger Evita XL®, Lübeck, Germany) with volume-controlled ventilation using tidal volume (V_T) 10 ml kg^{-1}, ventilatory frequency (VF) 16—18 bpm, inspiratory-to-expiratory (IE) ratio 1:2, and PEEP 5 cm H_2O (baseline settings). FIO_2 was maintained at 1.0 throughout the study. After baseline measurements, the animals were subjected to lung injury. Repeated lung lavages (warm saline solution 0.9% [30 ml kg^{-1}] intratracheally) were performed until P_aO_2/FIO_2 <250 mm Hg, followed by 2 h of injurious mechanical ventilation (pressure-controlled ventilation with PEEP 0 cm H_2O, inspiratory pressure 40 cm H_2O, VF 20 bpm, and IE ratio 1:1).

Extracorporeal membrane oxygenation

At the onset of ARDS, a 23F bicaval dual-lumen cannula (Avalon ELITE®, Maquet, Rochester, NY, US) was placed through the jugular vein, as described.[15,16] Baseline ventilation was then resumed for 10 min, and time 0 T_0 measurements were obtained. Thereafter, ECMO was started, targeting a blood flow greater than 60 ml kg^{-1} min^{-1}, with a sweep gas flow (FIO_2 1.0) set initially at a ratio of 1:1 to blood flow, and then titrated to keep Pa_{CO2} between 30 and 50 mm Hg. A detailed description of the ECMO equipment and set-up has been reported.[15]

Randomised intervention

The pigs were randomly allocated to one of three groups (n=7 per group) using sealed envelopes:

(i) PEEP 0: pressure-controlled ventilation, PEEP 0 cm H_2O, driving pressure 10 cm H_2O*, VF 5 bpm, IE 1:1
(ii) PEEP 10: pressure-controlled ventilation, PEEP 10 cm H_2O, driving pressure 10 cm H_2O*, VF 5 bpm, IE 1:1
(iii) PEEP 20: pressure-controlled ventilation, PEEP 20 cm H_2O, driving pressure 10 cm H_2O*, VF 5 bpm, IE 1:1

In each group, if 10 cm H_2O driving pressure resulted in V_T >3 ml kg^{-1}, driving pressure was further decreased whilst keeping the MAP constant.
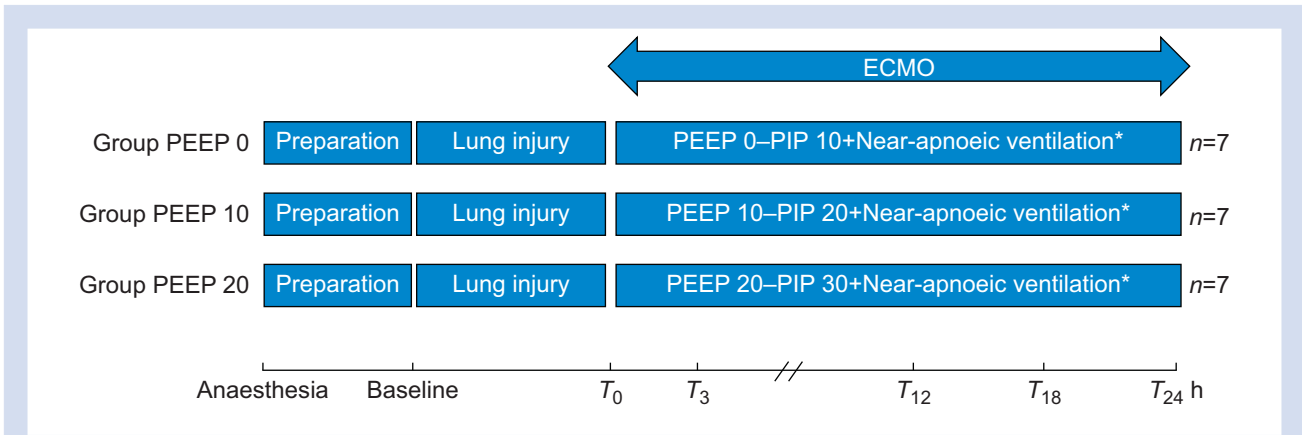
Fig 1. Study design and protocol. Preparation corresponds to anaesthesia and invasive monitoring, which took 1–1.5 h. Lung injury corresponds to the induction of lung injury by two hits: repeated saline lavages (1–1.5 h) followed by 2 h of injurious ventilation. T_0 to T_{24} correspond to the study period, during which each group received a specific ventilatory strategy. All study groups received near-apnoeic ventilation during the study period, with a ventilatory frequency 5 bpm and an IE ratio 1:1. Group PEEP 0 received PEEP 0 cm H_2O and peak inspiratory pressure (PIP) 10 cm H_2O; Group PEEP 10 received PEEP 10 cm H_2O and PIP 10 cm H_2O; Group PEEP 20 received PEEP 20 cm H_2O and PIP 30 cm H_2O. *If the resulting V_T was >3 ml kg^{-1}, the driving pressure was further decreased whilst keeping the MAP constant. ECMO, extracorporeal membrane oxygenation.

Data collection

Respiratory and haemodynamic data were obtained at baseline; T_0; and at 3, 12, and 24 h of the study period (T_3, T_{12}, and T_{24}, respectively).

Quantification of lung injury

Under deep anaesthesia, animals were euthanised at T_{24},[15] and the lungs were immediately extracted for histological analysis and wet-to-dry-weight ratio (surrogate of lung water content), as reported.[15]

Histological analysis

Briefly, a semi-quantitative histological score ranging from 0 (normal) to 3 (severe alteration) was used to evaluate three categories of acute lung injury, including alveolar disruption, neutrophil infiltration, and haemorrhage, in both dependent and non-dependent areas of the middle region of the right lung previously fixed with formaldehyde 10%. A board-certified pathologist blinded to the treatment evaluated 20 random sections (200× magnification) of the dependent and non-dependent areas, and its values were averaged. Results are reported for the dependent, non-dependent, and global (averaged dependent and non-dependent) areas.

Wet-to-dry-weight ratio

Lung sections from dependent and non-dependent areas of the middle region of the left lung were weighed before and after drying for 24 h at 120°C.

Statistical analysis

Although we did not have preliminary data to estimate the potential impact of different PEEP levels, in a previous study using the same ARDS pig model, we showed a difference of 40% between a conventional protective ventilation and a near-apnoeic ventilation during ECMO.[15] We assumed that if

PEEP had a relevant role in lung protection during ECMO, we would be able to find a similar difference in global lung injury scores studying seven animals per group, with a power of 0.9

Table 1 Haemodynamic variables. mPAP, mean pulmonary artery pressure. Because of early death of three animals, lung tissues were extracted and analysed only in four animals in Group PEEP 20. Results are mean (standard deviation). *$P<0.05$ compared with T_0. †$P<0.05$ compared with baseline. ‡$P<0.05$ compared with 0–10. ¶$P<0.05$ compared with 10–20.

| Variable Time	Group		
	PEEP 0	PEEP 10	PEEP 20
Heart rate (beats min^{-1})			
Baseline	64 (16)	86 (16)	72 (26)
T_0	78 (18)	93 (15)	74 (18)
T_3	118 (24)*	125 (28)*	131 (39)*
T_{12}	110 (21)*	118 (18)*	132 (14)*
T_{24}	102 (22)*	112 (21)*	125 (17)*
MAP (mm Hg)			
Baseline	93 (17)	94 (14)	96 (32)
T_0	87 (9)	88 (9)	85 (11)
T_3	79 (16)	72 (7)	66 (16)
T_{12}	67 (13)*	68 (4)*	64 (8)*
T_{24}	68 (13)*	67 (10)	63 (7)*
mPAP (mm Hg)			
Baseline	21 (4)	20 (5)	18 (5)
T_0	39 (10)†	41 (8)†	35 (2)†
T_3	33 (10)	37 (6)	34 (3)
T_{12}	28 (5)	25 (6)*	29 (4)
T_{24}	26 (4)	21 (5)*	26 (4)
Norepinephrine dose (µg kg^{-1} min^{-1})			
Baseline	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
T_0	0.01 (0.03)	0.05 (0.07)	0.05 (0.13)
T_3	0.08 (0.07)	0.09 (0.08)	0.39 (0.43)
T_{12}	0.09 (0.09)	0.10 (0.07)	0.10 (0.06)
T_{24}	0.22 (0.32)	0.22 (0.24)	0.65 (0.83)
Cumulative fluids (L)			
T_{24}	2.7 (0.11)	2.7 (0.4)	2.9 (0.4)
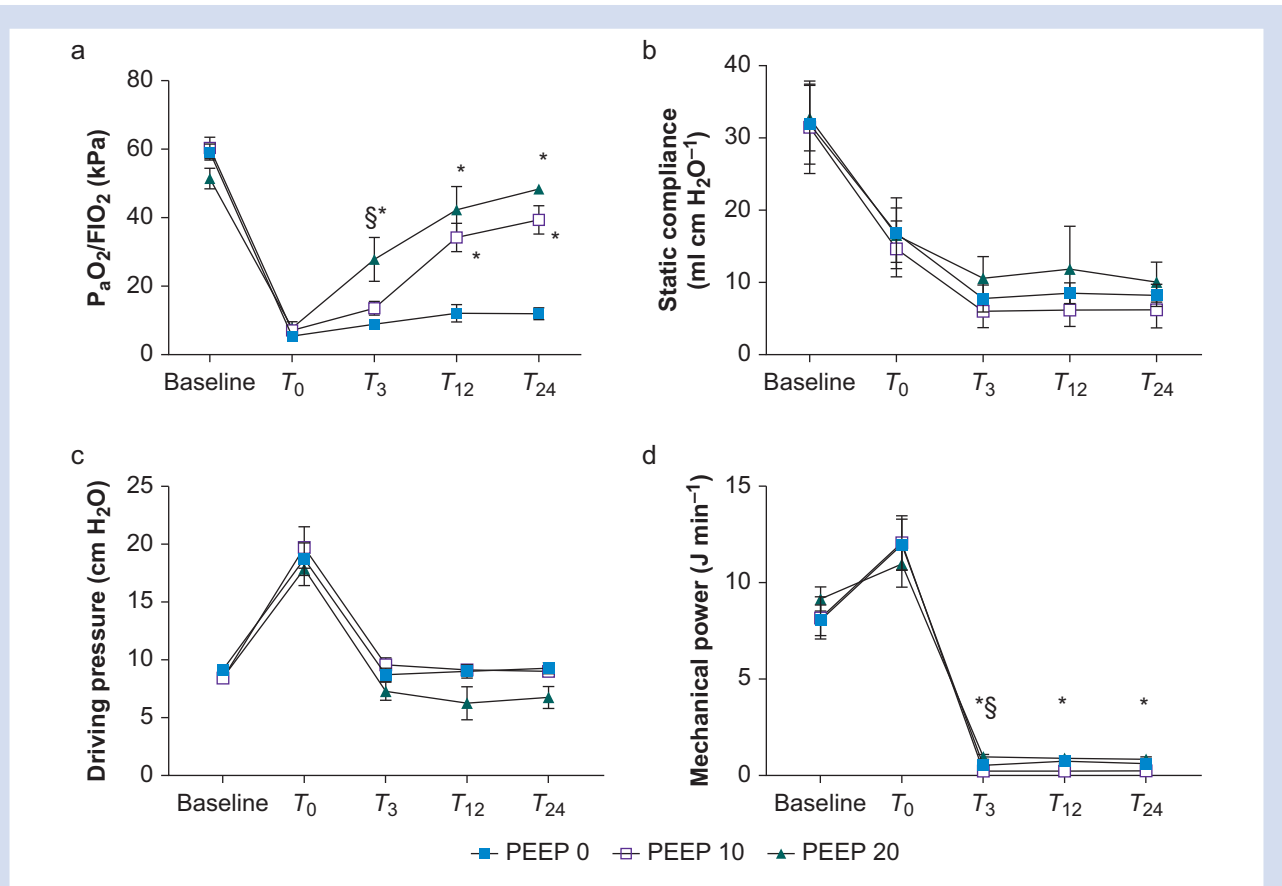
Fig 2. Respiratory variables. (a) P_aO_2/FIO_2 ratio at different time points for each study group. (b) Static compliance of the respiratory system at different time points for each study group. (c) Driving pressure of the respiratory system at different time points for each study group. (d) Mechanical power at different time points for each study group. †$P<0.05$ T_0 compared with baseline, ‡$P<0.05$ compared with T_0, §$P<0.05$ compared with PEEP 10, *$P<0.05$ compared with PEEP 0. Because of early death of three animals, data for T_{12} and T_{24} include only four animals for Group PEEP 20.

and an alpha error of 0.05 (G*Power, Heinrich Heine University Düsseldorf, Düsseldorf, Germany). Data were analysed using linear mixed effects model, with time and group as fixed effects and pig ID as random effect, followed by Tukey's multiple comparisons test, both for differences between groups (all groups compared with each other) and along time (all time points compared with T_0). Data derived from lung tissue analysis were compared with one-way analysis of variance, followed by Tukey's multiple comparisons test. Survival analysis was performed by log-rank test (Mantel−Cox). Data are expressed as mean (standard deviation). Statistical significance was set at $P<0.05$, and analyses were performed with GraphPad Prism 8 (GraphPad Software, San Diego, CA, USA) and JMP Pro Version 15 (SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of ARDS model

Similar levels of hypoxaemia and reduced compliance occurred in each group after the induction of lung injury, accompanied by pulmonary hypertension and hyperlactatemia (Table 1; Supplementary Table 1). Extracorporeal

membrane oxygenation rapidly increased P_aO_2 >8.0 kPa, although systemic hypotension and tachycardia were observed at all PEEP settings throughout the study period (Table 1).

Impact of PEEP on oxygenation

Oxygen exchange recovered progressively after PEEP 10 and 20 cm H_2O, but not with PEEP 0 cm H_2O (Fig. 2).

Impact of PEEP on respiratory variables

Compliance remained low at all PEEP levels (Fig. 2a and b). As per protocol, V_T and VF, and consequently minute ventilation, were decreased similarly for all PEEP levels (Table 2). Despite lower minute ventilation, the Pa_{CO2} levels were maintained within normal limits at each PEEP setting because of extracorporeal CO_2 removal (Supplementary Table 1). Driving pressure and mechanical power were also lower in each group after commencing ECMO (Fig. 2c and d). A larger decrease in mechanical power was observed with PEEP 0 cm H_2O, but mechanical power was <1 J min^{-1} for all three groups.

Table 2 Respiratory variables. Paw, airway pressure. Because of early death of three animals, lung tissues were extracted and analysed only in four animals in Group PEEP 20. Results are mean (standard deviation). *$P<0.05$ compared with T_0. †$P<0.05$ compared with baseline. ‡$P<0.05$ compared with PEEP 0. ¶$P<0.05$ compared with PEEP 10.

Variable Time	Group		
	PEEP 0	PEEP 10	PEEP 20
Ventilatory frequency (bpm)			
Baseline	19 (2)	16 (2)	19 (1)
T_0	20 (2)	18 (2)	19 (1)
T_3	5 (0)*	5 (0)*	6 (1)*
T_{12}	5 (0)*	5 (0)*	6 (2)*
T_{24}	5 (0)*	5 (0)*	5 (0)*
Tidal volume (ml kg^{-1})			
Baseline	9.7 (0.5)	9.8 (0.3)	9.6 (0.5)
T_0	10.2 (0.8)	10.2 (0.5)	10.0 (0.8)
T_3	2.1 (0.8)*	2.2 (0.4)*	2.5 (0.5)*
T_{12}	2.1 (0.8)*	2.6 (0.4)*	2.2 (0.6)*
T_{24}	2.1 (0.9)*	2.6 (0.3)*	2.2 (0.7)*
Minute ventilation (L min^{-1})			
Baseline	4.9 (1.2)	4.8 (0.9)	5.2 (0.8)
T_0	5.5 (1.1)	5.4 (0.8)	5.3 (0.8)
T_3	0.4 (0.3)*	0.3 (0.0)*	0.4 (0.1)*
T_{12}	0.4 (0.2)*	0.5 (0.2)*	0.4 (0.1)*
T_{24}	0.4 (0.3)*	0.4 (0.0)*	0.3 (0.1)*
Plateau pressure (cm H_2O)			
Baseline	14 (1)	14 (1)	14 (1)
T_0	25 (5)†	24 (4)†	23 (4)†
T_3	10 (1)*	20 (1)*‡	28 (1)*‡¶
T_{12}	10 (1)*	19 (1)*‡	28 (1)*‡¶
T_{24}	10 (1)*	20 (1)*‡	29 (1)*‡¶
Paw mean (cm H_2O)			
Baseline	8 (1)	9 (1)	9 (1)
T_0	12 (2)†	12 (2)†	11 (2)†
T_3	5 (1)*	15 (0)*‡	25 (1)*‡¶
T_{12}	6 (1)*	15 (1)*‡	25 (0)*‡¶
T_{24}	6 (1)*	16 (1)*‡	25 (0)*‡¶
PEEP (cm H_2O)			
Baseline	5 (0)	5 (0)	5 (0)
T_0	6 (2)	5 (0)	5 (0)
T_3	1 (1)*	11 (1)*‡	21 (1)*‡¶
T_{12}	1 (1)*	10 (1)*‡	22 (2)*‡¶
T_{24}	1 (1)*	10 (1)*‡	22 (2)*‡¶

Impact of PEEP on lung injury

Variable degrees of injury characterised by diffuse alveolar damage were observed in each group. The severity of lung injury was lowest after PEEP 10 cm H_2O in both dependent and non-dependent lung regions, compared with PEEP 0 and 20 cm H_2O (Fig. 3a). Neutrophil infiltration was higher after PEEP 0 and 20 cm H_2O, compared with Group PEEP 10 in dependent and non-dependent lung regions. Alveolar disruption was most extensive after PEEP 20 cm H_2O in dependent and non-dependent lung regions (Supplementary Table 3). Lung water content, as measured by the wet-to-dry-weight ratio, was highest after PEEP 0 cm H_2O, compared with Groups PEEP 10 and 20 in dependent and non-dependent lung regions (Fig. 3b).

Haemodynamic effects of PEEP

Haemodynamic deterioration was more severe and sustained after PEEP 20 cm H_2O, where four pigs developed shock

refractory to norepinephrine; three pigs died from shock between T_3 and T_{12} (Supplementary Figs 1 and 2).

Impact of PEEP on ECMO settings

During ECMO, sweep gas flows (L min^{-1}) and blood flows (L min^{-1}) were not different between PEEP settings (Supplementary Table 2).

Discussion

The main results of this study indicate that in a near-apnoeic ventilation strategy during ECMO, 10 cm H_2O PEEP reduced lung injury, compared with PEEP 0 or 20 cm H_2O. The absence of PEEP favoured more lung oedema and impeded recovery of gas exchange, whereas a PEEP of 20 cm H_2O was associated with a high rate of shock and associated mortality.

The role of PEEP in mechanically ventilated patients with ARDS has been a long-standing source of controversy. Despite several large clinical trials exploring different strategies to optimise PEEP, no strategy has been shown to be superior in terms of clinical outcomes. Therefore, it is not surprising that the best approach to PEEP in the specific setting of patients with ARDS on ECMO is even more uncertain. The Conventional Ventilation or ECMO for Severe Adult Respiratory Failure and Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome trials applied moderate levels of PEEP (~10—12 cm H_2O) during ECMO.[18,19] However, observational studies show that there is large variability in the levels of PEEP used by different ECMO centres and places. For instance, Schmidt and colleagues,[13] in a multicentre study of mechanical ventilation management during ECMO, reported PEEP levels of 10 (2) cm H_2O in Paris and 14 (3) cm H_2O in Melbourne. In an Italian series, Patroniti and colleagues[20] reported PEEP levels of 16 [inter-quartile range: 14—19] cm H_2O during Day 1 of ECMO. A large multicentre, prospective cohort study of patients with ARDS supported with ECMO showed that in the first 2 days of ECMO, PEEP values ranged from 0 to 25 cm H_2O.[21] In the absence of high-quality clinical trials assessing the role of PEEP during ECMO in ARDS, experimental studies may provide some insight to guide clinicians.

The rationale to apply PEEP during ECMO for ARDS is to maintain alveolar recruitment, which may reduce ventilator-induced lung injury (VILI) and promote gas exchange and oxygenation in the native lungs. Recently, two physiological studies assessed the role of different PEEP levels in patients with ARDS treated with ECMO.[1] [22] Franchineau and colleagues[22] performed a physiological study in 15 patients with ARDS treated with ECMO, in which a decremental PEEP trial was applied from 20 to 0 cm H_2O to define optimal PEEP by assessing overdistension and collapsed zones, using electric impedance tomography (EIT). Although optimal PEEP levels were variable, optimal PEEP was 10—15 cm H_2O in 13 of 15 patients, values that are consistent with the results of our study. Interestingly, in that study, PEEP levels of 20 cm H_2O induced overdistension, whilst PEEP levels of 0 and 5 cm H_2O were associated with collapse.[22] Similar to our study, oxygenation in those patients decreased at PEEP 0 cm H_2O. However, EIT-derived variables were not correlated with biomarkers of VILI, with each PEEP level assessed only for 20 min. In another study, Rozencwajg and colleagues[1] compared four randomly assigned 12 h strategies of ultra-protective ventilation in 16 patients with ARDS immediately after commencing ECMO. The four strategies involved variable levels of
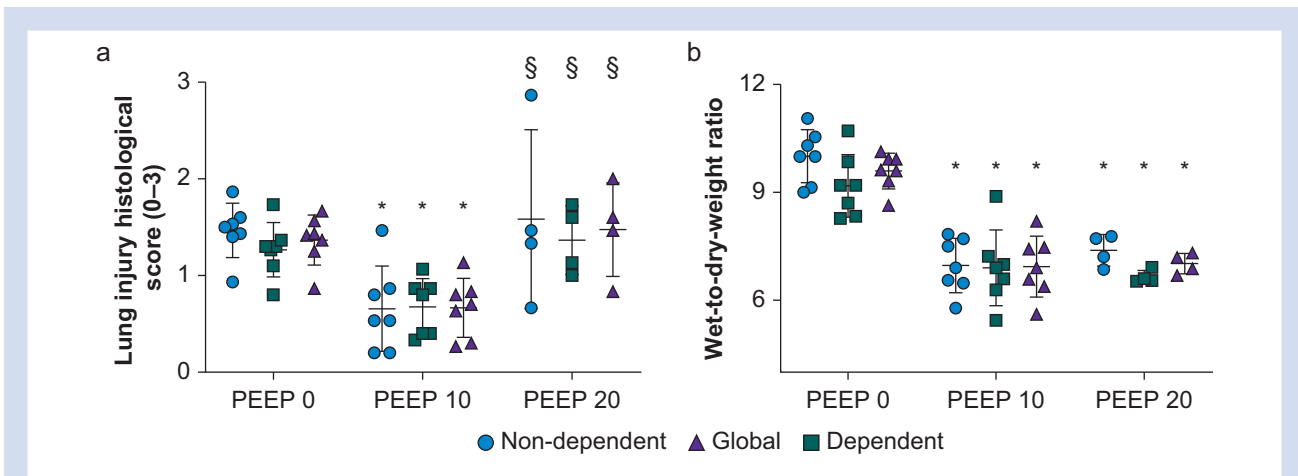
Fig 3. Assessment of lung tissue injury. (a) Histological quantitative score for lung injury (from 0=normal to 3=maximal alteration), calculated by averaging the scores for alveolar disruption, neutrophil infiltration, and haemorrhage, for dependent and non-dependent areas of the right lung, and the global score (mean of scores for dependent and non-dependent areas). *$P<0.05$ compared with PEEP 0, §$P<0.05$ compared with PEEP 10. (b) Wet-to-dry-weight ratio of dependent and non-dependent areas of the left lung. Global columns correspond to the average of the dependent and non-dependent areas. PEEP 0 showed a significantly higher ratio than PEEP 10 and PEEP 20. *$P<0.05$ compared with PEEP 0. Because of early death of three animals, lung tissues were extracted and analysed only in four animals in Group PEEP 20.

expiratory/inspiratory pressures (12/24, 20/24, 5/24, and 5/17 cm H_2O) in bi-level positive airway pressure ventilation. The authors reported several measures, including respiratory variables and biomarkers of inflammation and lung injury. As we found, oxygenation improved with higher levels of PEEP. However, no differences were detected for inflammatory markers between the four strategies. The difference between these results and ours may lie in the fact that our PEEP settings were more extreme. Moreover, their study was performed in patients with ARDS after 7 days of mechanical ventilation, whereas our experimental study was performed immediately after induction of lung injury and ECMO.

In another recent study about PEEP optimisation during ECMO, Wang and colleagues[23] randomised 102 patients with ARDS to a lung rest strategy with PEEP of 10—15 cm H_2O or to a transpulmonary pressure-guided strategy (similar to the EPVent 1 and 2 trials,[24,25] in which PEEP was titrated to achieve an end-expiratory transpulmonary pressure of 0—5 cm H_2O). They observed that the transpulmonary pressure-guided group, which received PEEP levels around 14 cm H_2O, had a higher rate of successful weaning from ECMO, compared with the lung rest group, which had PEEP levels around 12 cm H_2O. In parallel, the transpulmonary pressure-guided group had lower plasma concentrations of pro-inflammatory cytokines. Although these results are interesting, the differences in PEEP between the groups were modest, so it remains unclear which factors may explain the important differences in outcomes reported. Given the negative results of the EPVent-2 trial, the role of transpulmonary pressure-guided PEEP remains unclear, and therefore, the results of the study of Wang and colleagues[23] should be confirmed in a larger population.

As oxygenation can be provided fully by ECMO during ARDS, some authors have proposed that mechanical ventilation may not be needed.[6] However, ventilation at very low lung volumes can result in VILI by disrupting surfactant function and by generating areas of regional hypoxia, which can result in increased pulmonary vascular leak and lung inflammation.[26—29] In addition, ventilation of ARDS lungs without PEEP may favour cyclic recruitment—derecruitment,[26] although it remains unknown whether this phenomenon occurs at near-apnoeic ventilation.[27] The abrupt removal of PEEP in ventilated rats induces acute lung injury and oedema.[30] This effect appeared to be secondary to increases in left ventricular preload and afterload, resulting in elevated microvascular pulmonary pressures. These mechanisms may have played a role in the higher injury scores and lung water content observed in the lungs of pigs allocated to PEEP 0 cm H_2O, as compared with PEEP 10 cm H_2O. Conversely, application of very high PEEP levels in patients with ARDS supported by ECMO may result in alveolar overdistension.[5,27] In our study, lung injury scores were higher after PEEP 20 cm H_2O compared with Group PEEP 10 at comparable driving pressures, suggesting that high static strain may have played a role in the perpetuation or progression of lung injury.

Driving pressure and mechanical power have been proposed as relevant predictors of the risk of VILI.[31,32] As we recently showed, compared with conventional protective strategies, near-apnoeic ventilation markedly decreases both factors and results in less lung injury.[15] A recent randomised crossover physiological study in 10 patients with ARDS on ECMO confirmed those results, showing that even 10 cm H_2O of driving pressure applied during ultra-protective ventilation may increase biotrauma, compared with a strategy with zero driving pressure.[3] However, differences observed in the present study cannot be explained by differences in driving pressure or mechanical power, as these variables were comparable between the three study groups and within ranges usually considered as safe. A possible explanation is that driving pressure and mechanical power reflect the global mechanical burden of mechanical ventilation, but they may not reflect the presence of VILI at the regional level. In addition, these variables do not predict the adverse

haemodynamic consequences of mechanical ventilation, which may also indirectly promote lung injury.[33] Accordingly, these data suggest that application of ECMO with an 'ultra-protective' ventilatory strategy does not guarantee avoiding VILI and that individual parameters, such as PEEP, may influence the final impact on clinical outcomes.

Our study has important limitations. The PEEP levels were arbitrarily chosen, and groups PEEP 0 and 20 cm H_2O are somewhat extreme, although these levels are within the ranges reported in clinical practice.[34] In our study, the choice of PEEP levels was pragmatic to capture possible differences in measured outcomes and to reduce variability. Importantly, however, recent evidence suggests that PEEP levels should be titrated individually to account for differences in lung heterogeneity and in potential for successful recruitment. Therefore, the clinical message should not be to apply PEEP of 10 cm H_2O blindly, but instead to pay attention to PEEP titration and to bear in mind that insufficient or excessive PEEP levels could have deleterious effects.[22] Another limitation is that we did not evaluate regional aeration with CT scan or EIT. Use of these techniques may have been helpful to better interpret our results. Finally, the high mortality observed in Group PEEP 20 generated missing values, which may have biased the observed results. It is also possible that a different haemodynamic management, including a more comprehensive monitoring of cardiac function and fluid responsiveness, particularly after PEEP 20 cm H_2O, might have allowed the optimisation of fluid therapy to prevent haemodynamics. However, we maintained similar fluid balance between each group to facilitate intergroup comparisons and avoid excessive fluid loading, which is likely to confound the interpretation of lung histology findings.

In summary, in an established model of severe ARDS requiring ECMO, near-apnoeic ventilation without PEEP results in increased lung oedema and poor oxygenation, whereas targeting very high PEEP levels results in a high risk of haemodynamic collapse. A near-apnoeic protocol using moderate PEEP levels during ECMO for severe ARDS results in less lung injury and provides the best balance between gas exchange, lung oedema, and haemodynamic tolerance. Near-apnoeic ventilation, despite minimising tidal volume, driving pressure, and mechanical power, does not guarantee lung protection.

Authors' contributions

Study design: JA, PC, JR, GB, AB
Data acquisition and analysis: JA, LA, AG, PC, DS, BE, TS, TM, PG, SD, MCB, RB, EDV, MV, AB
Data interpretation: JA, MR, JR, RC, GB, AB
Drafting of paper: JA, MR, JR, RC, GB, AB
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Declarations of interest

All authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.07.031.

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