Mechanical Power

A Biomarker for the Lung?

Laurent Brochard, M.D., Andrew Bersten, M.D.

VENTILATOR-INDUCED lung injury is a multifaceted problem that has progressively become a preoccupation for intensivists and anesthesiologists. It has taken many years to realize that mechanical ventilation, a life-saving technique, could also induce harm. The first randomized controlled trial in critical care compared extracorporeal membrane oxygenation to mechanical ventilation in patients with severe acute respiratory distress syndrome, with the premise that this technique could improve gas exchange and save lives.[1] Because, at the end of the 1970s, the mechanical insult to the lungs caused by mechanical ventilation was not considered as a relevant or important problem (oxygen toxicity was much more of a concern), the two arms in the trials received the same "injurious" mechanical ventilation and had the same dismal outcome. Pioneer experimental work from Webb and Tierney[2] and later from Dreyfuss and Saumon[3] progressively demonstrated the potential of large volumes and pressures to cause injury either in previously healthy or already injured lungs. The concepts of atelectrauma and biotrauma were later proposed by Tremblay *et al.*[4] in Slutsky's group to explain the observed protective effects of positive end-expiratory pressure (PEEP) and to show the link between local mechanically induced inflammatory effects with both the systemic multiorgan failure observed in these patients and their high mortality. Pressure limitation in the alveoli, assessed by the plateau pressure, was introduced in clinical practice by recommendations in the early 1990s[5] and was based on the baby lung concept[6] and an early clinical report by Hickling *et al.*[7] suggesting, in 1990, a marked improvement in survival resulting from deliberately limiting pressures and volumes. The proof of concept was brought by the 12 *versus* 6 ml/kg positive pressure

"How can we determine when mechanical ventilation is harming the lung…?"

ventilation trial in 2000,[8] which showed that 25% of the actual mortality observed using 12 ml/kg of predicted body weight could be avoided by limiting tidal volume to around 6 ml/kg and plateau pressure to 30 cm H_2O. Numerous studies then discussed how far tidal volume should be reduced to remain protective in acute respiratory distress syndrome, whereas other studies have shown that lung protection needed to be extended beyond the field of acute respiratory distress syndrome, including data suggesting that this concept of lung protection could also apply to the field of intraoperative ventilation.[9]

From there, clinicians still face a number of important questions, among which two concern everyday practice: Which PEEP level is optimal for protecting the lung of mechanically ventilated patients? How can we determine when mechanical ventilation is harming the lung and/or is inducing systemic inflammation deleterious for other organs (before it is too late)? An impressive animal study by Collino *et al.*[10] from the group of Michael Quintel and Luciano Gattinoni (Department of Anesthesiology, Emergency and Intensive Care Medicine, University of Göttingen, Göttingen, Germany), published in this issue, tried to address these two questions at the same time using an animal model. They applied the concept of mechanical power as a unifying determinant of injury that describes the energy transfer to the lung to predict the potential harm generated by mechanical insufflations at increasing pressures. The mechanical power takes into account the energy delivered to the lung, popularized by the driving pressure,[11] the dynamic changes in pressure, the energy related to the increase in lung volume induced by PEEP, and the respiratory rate. They had previously shown the influence of respiratory

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rate on the generation of injury, as predicted by the change in mechanical power.[12] This has important consequences because decreasing tidal volume is often compensated by increasing respiratory rate. Knowing the respective risk (in terms of injury) of respiratory rate *versus* driving pressure will be essential for clinical practice, together with determining safe levels for Pa_{CO_2}. To increase pressures in this series of experiments, they progressively increased PEEP from 0 to 18 cm H_2O in piglets with normal lungs but under general anesthesia, a condition known to generate atelectasis. The study is impressive through the number of experiments performed and their duration but also by the number of ways in which the authors tried to capture ventilator-induced lung injury: lung weight, other organs' weights and wet to dry weights, lung histology, hemodynamics, lung volume, gas exchange including dead space and oxygenation, and multiple measures of mechanics including stress, strain, and mechanical power. The study well illustrates the complexity of the so-called ventilator-induced lung injury, including both atelectrauma (insufficient reopening of the lung at end expiration and/or repeated opening and closing of this atelectatic lung) and volutrauma inducing distension and major hemodynamic effects. As discussed by the authors, such models are complex because you cannot "isolate" the effects of PEEP from the concomitant changes in other pressures or the elastic responses induced by changes in PEEP, and one cannot imagine that a single magic marker will describe every change in every parameter at the same time. Interestingly, they found that PEEP—at "low" values—is an important component of lung protection, a key finding shown for many years, even if its mechanisms are not completely understood. This protection may also be mediated by beneficial hemodynamic effects of PEEP. PEEP can also result in volutrauma when it is too high (in part also because it results in excessively high plateau pressures). Clinical experience and clinical trials have confirmed that excessive PEEP and plateau pressures could be harmful and dangerous.

The experimental model used in the study by Collino *et al.*[10] represents the effects of potentially injurious "standard" ventilation (8 to 10 ml/kg of tidal volume) at different baseline pressures (PEEP) in the presence of general anesthesia with healthy lungs. The chosen model, piglets, makes it difficult to completely infer from these data what would be the equivalent in patients. The authors suggest that the PEEP levels of 4 to 7 cm H_2O, which seem to constitute the transition between lung protection and the start of injury, could represent 8 to 14 cm H_2O in humans, but this has to be taken with great caution. Moreover, the situation of the individual patient must be taken into account, with her/his history and current lung injury. Researchers have looked for inflammatory biomarkers of lung injury, either for prognostication of acute respiratory distress syndrome regarding mortality or for predicting the response to treatment. Because the initial injury results from a direct mechanical insult, it makes sense to propose a mechanical index as a possible biomarker of the

risk of ventilator-induced lung injury. The power of breathing is an interesting concept when directly applied to the lung, *i.e.*, using the transpulmonary pressure. Similar to the work of breathing per minute, we are reminded that Otis *et al.*[13] already described in 1950 that the breathing pattern could be optimized to minimize the power of breathing. It is remarkable that across different experiments (assessing respiratory rate or different levels of PEEP in the same animal model), the authors found a similar threshold around 12 to 13 J/min, above which mechanical ventilation may be lethal. As noticed by the authors, this does not indicate a "safe" limit, but being able to use such measurements at the bedside to define dangerous settings of ventilation seems very attractive.

The last paragraphs of the discussion list many unanswered and important questions that merit exploration. We need to see data using a relevant lung injury model where the competing issues of recruitment and overinflation may well influence the data and suggest a different safe power. We also need clinical observational data and ultimately a clinical trial before wholesale adoption of the concept and its potential use. Trying to transpose complex physiologic concepts into useful tools for clinicians at the bedside is very exciting, and the authors need to be commended for their endeavor already showing how promising the mechanical power seems to be.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Brochard: brochardl@smh.ca

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Positive End-expiratory Pressure and Mechanical Power

Francesca Collino, M.D., Francesca Rapetti, M.D., Francesco Vasques, M.D., Giorgia Maiolo, M.D.,
Tommaso Tonetti, M.D., Federica Romitti, M.D., Julia Niewenhuys, M.S., Tim Behnemann, M.S.,
Luigi Camporota, M.D., Günter Hahn, M.Sc., Verena Reupke, D.V.M., Karin Holke, M.D.,
Peter Herrmann, M.Sc., Eleonora Duscio, M.D., Francesco Cipulli, M.D., Onnen Moerer, M.D.,
John J. Marini, M.D., Michael Quintel, M.D., Luciano Gattinoni, M.D. F.R.C.P.

ABSTRACT

Background: Positive end-expiratory pressure is usually considered protective against ventilation-induced lung injury by reducing atelectrauma and improving lung homogeneity. However, positive end-expiratory pressure, together with tidal volume, gas flow, and respiratory rate, contributes to the mechanical power required to ventilate the lung. This study aimed at investigating the effects of increasing mechanical power by selectively modifying its positive end-expiratory pressure component.

Methods: Thirty-six healthy piglets (23.3 ± 2.3 kg) were ventilated prone for 50 h at 30 breaths/min and with a tidal volume equal to functional residual capacity. Positive end-expiratory pressure levels (0, 4, 7, 11, 14, and 18 cm H_2O) were applied to six groups of six animals. Respiratory, gas exchange, and hemodynamic variables were recorded every 6 h. Lung weight and wet-to-dry ratio were measured, and histologic samples were collected.

Results: Lung mechanical power was similar at 0 (8.8 ± 3.8 J/min), 4 (8.9 ± 4.4 J/min), and 7 (9.6 ± 4.3 J/min) cm H_2O positive end-expiratory pressure, and it linearly increased thereafter from 15.5 ± 3.6 J/min (positive end-expiratory pressure, 11 cm H_2O) to 18.7 ± 6 J/min (positive end-expiratory pressure, 14 cm H_2O) and 22 ± 6.1 J/min (positive end-expiratory pressure, 18 cm H_2O). Lung elastances, vascular congestion, atelectasis, inflammation, and septal rupture decreased from zero end-expiratory pressure to 4 to 7 cm H_2O ($P < 0.0001$) and increased progressively at higher positive end-expiratory pressure. At these higher positive end-expiratory pressure levels, striking hemodynamic impairment and death manifested (mortality 0% at positive end-expiratory pressure 0 to 11 cm H_2O, 33% at 14 cm H_2O, and 50% at 18 cm H_2O positive end-expiratory pressure). From zero end-expiratory pressure to 18 cm H_2O, mean pulmonary arterial pressure (from 19.7 ± 5.3 to 32.2 ± 9.2 mmHg), fluid administration (from 537 ± 403 to 2043 ± 930 ml), and noradrenaline infusion (0.04 ± 0.09 to 0.34 ± 0.31 $\mu g \cdot kg^{-1} \cdot min^{-1}$) progressively increased ($P < 0.0001$). Lung weight and lung wet-to-dry ratios were not significantly different across the groups. The lung mechanical power level that best discriminated between more *versus* less severe damage was 13 ± 1 J/min.

Conclusions: Less than 7 cm H_2O positive end-expiratory pressure reduced atelectrauma encountered at zero end-expiratory pressure. Above a defined power threshold, sustained positive end-expiratory pressure contributed to potentially lethal lung damage and hemodynamic impairment. **(ANESTHESIOLOGY XXX; XXX:00-00)**

BECAUSE expenditure of energy is required to inflict damage, we recently proposed mechanical power (the intensity of energy delivery to the respiratory system) as a unifying concept that includes all primary ventilator settings shown experimentally to influence ventilator-induced lung injury.[1] The equation for mechanical power is the product of ventilating frequency and the inflation energy of the tidal cycle. The latter consists of three components: (1) the power required to overcome tissue and airways resistance during gas movement (flow-resistive work); (2) the power required to inflate the lung and chest wall from their shared initial position (tidal volume–associated work); and (3) the

Editor's Perspective

What We Already Know about This Topic

- Positive end-expiratory pressure protects against ventilation-induced lung injury by improving homogeneity of ventilation, but positive end-expiratory pressure contributes to the mechanical power required to ventilate the lung

What This Article Tells Us That Is New

- This *in vivo* study (36 pigs mechanically ventilated in the prone position) suggests that low levels of positive end-expiratory pressure reduce injury associated with atelectasis, and above a threshold level of power, positive end-expiratory pressure causes lung injury and adverse hemodynamics

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power required to overcome positive end-expiratory pressure (PEEP)–related recoil of the lung and respiratory system. In simplified form, the airway pressure developed during inflation can be written as follows:

$$P_{total} = P_{resistive} + P_{tidal\ elastance} + PEEP$$

Multiplying each of these components by the change in volume (Vt), we obtain the mechanical energy per breath (Energy$_{tot}$).

$$Energy_{total} = Vt * (P_{resistive} + P_{tidal\ elastance} + PEEP)$$

In turn, this energy per cycle, when multiplied by the respiratory rate, yields the mechanical power applied per minute to the respiratory system.

In a previous long-term experiment on healthy piglets, we tested the following elements of the mechanical power: tidal volume (strain),[2] respiratory rate,[3] and flow.[4] We found that the tidal volume was predictably lethal when it reached the total lung capacity at 15 breaths/min,[2] whereas no major damage was observed at 6 breaths/min.[3] Furthermore, we found an association between the flow rate and the extent of ventilator-induced lung injury.[4] Therefore, in that series of experiments, all performed at zero PEEP, we confirmed the roles of the tidal volume, respiratory rate, and flow components of total power as probable contributors to ventilator-induced lung injury.[5]

Notably, at 15 breaths/min, the otherwise lethal strain did not induce any marked damage if 75% of the maximal distending volume (*i.e.*, the sum of tidal volume and PEEP volume) was due to PEEP.[6] In those experiments, therefore, PEEP appeared to be protective, as shown by Webb and Tierney in the early 1970s.[7] It remains unclear, however, whether PEEP is protective *per se* or whether its putative benefit is due to the associated reductions in tidal volume, driving pressure, and atelectrauma. Actually, because PEEP is a key element of the power equation, it theoretically has lung-damaging potential. To begin inflation, the lung requires an energy input greater than the potential energy stored in the system by PEEP at end exhalation. Recruitment diminishes and distention increases as airway pressure rises. Therefore, although its mechanical effects on atelectrauma may be, on balance, "lung-protective" over its lower range, rising PEEP is unquestionably a component of mechanical power and, as such, should favor ventilator-induced lung injury by increasing lung stress and strain.

In this study, we aimed to investigate the purely mechanical role of PEEP on healthy lungs under the unifying framework of the mechanical power hypothesis. Indeed, we wanted to test whether PEEP *per se* protects or contributes to ventilator-induced lung injury and, if so, over what range and to what extent.

St Thomas' National Health Service Foundation Trust, King's Health Partners, and Division of Asthma, Allergy and Lung Biology, King's College London, London, United Kingdom (L.C.); and Department of Pulmonary and Critical Care Medicine, Regions Hospital and University of Minnesota, Minneapolis/St. Paul, Minnesota (J.J.M.).

Materials and Methods

Thirty-six domestic piglets (~4 months of age; body weight, 23.3 ± 2.3 kg) were handled according to the European Union guidelines 2010/63 with the approval of the local authorities. The experiments were performed under general anesthesia with sufentanil (2 to 3 µg · kg^{-1} · h^{-1}), propofol (6 to 9 mg · kg^{-1} · h^{-1}), and midazolam (1.2 to 1.5 mg · kg^{-1} · h^{-1}). The animals were studied in the prone position and were instrumented with endotracheal tube, esophageal balloon, central venous, pulmonary artery, femoral artery, and urinary catheters. Infusions of Sterofundin 1/1 (B. Braun Melsungen, Germany) of 2 to 3 ml · kg^{-1} · h^{-1} were maintained during the whole experiment. When necessary, colloids (Gelafundin 4%, Braun, Germany) and norepinephrine were administered to maintain a mean arterial pressure above 60 mmHg (see Supplemental Digital Content for details, http://links.lww.com/ALN/B790).

Experimental Design

The sample size was based on our experience from previous experiments. All animals were ventilated at a constant respiratory rate of 30 breaths/min, fractional inspired oxygen tension (F$_{IO_2}$) of 0.4, and ratio between inspiratory and expiratory time of 1:2 with a tidal volume equal to the functional residual capacity (FRC) measured at baseline at zero PEEP, which corresponds to a dynamic strain of tidal volume/FRC = 1 (mean tidal volume = 14.9 ± 2.5 ml/kg). Six different levels of PEEP were applied, one PEEP level to each of six groups of randomly assigned piglets. The planned experimental duration was 50 h, during which all ventilation and PEEP settings remained constant. Respiratory rate of 30 breaths/min and tidal volume equal to FRC were chosen because in previous studies they proved sufficient to reach a sublethal mechanical power potentially associated with lung damage.[2]

Experimental Procedures

The piglets were randomly allocated to six PEEP groups (0, 4, 7, 11, 14, and 18 cm H$_2$O) of six animals each. FRC was measured with the helium-dilution technique[8] during muscle relaxation and after lung recruitment at baseline, 24 h, and 48 h.

The animals were ventilated for a targeted 50 h at the randomly assigned PEEP level. Respiratory mechanics, gas exchange, and hemodynamic variables were assessed every 6 h. The animals were euthanized at the end of the experiment and autopsied. Lung tissue samples were collected for histologic analysis and wet-to-dry ratio[6] (fig. S1, Supplemental Digital Content, http://links.lww.com/ALN/B790). We defined the wet-to-dry index as follows: $Wet-to-dry \cdot \dfrac{50}{H1}$, where H1 is the actual hours of experiment, and 50 is the hours planned for the experiment. This ratio accounts for the shorter time available for edema formation in the animals that died before intended. The $\dfrac{50}{H1}$ adjustment assumes that edema accumulates linearly with time (see Supplemental Digital Content for details, http://links.lww.com/ALN/B790).

Mechanical Power

The mechanical power was derived by multiplying each component of the motion equation by the minute ventilation.[1] Accordingly, in the respiratory system:

$$Power_{rs} = 0.098 \cdot$$

$$RR \cdot \left\{ \Delta V^2 \cdot \left[\frac{1}{2} \cdot E_{rs} + RR \cdot \frac{(1 + I:E)}{60\,s \cdot I:E} \cdot R_{RS} \right] + \Delta V \cdot PEEP \right\}$$

where 0.098 is the conversion factor from L*cm H_2O to J, RR is the respiratory rate (breaths per minute), ΔV is the tidal volume (l), E_{RS} is the elastance of the respiratory system (cm H_2O/l), I:E is the ratio between inspiratory and expiratory time, and R_{RS} is the airway and tissue resistances (cm $H_2O \cdot l^{-1} \cdot s^{-1}$). Assuming a constant rate of inflation, the term $E_{RS} \cdot \frac{1}{2} \Delta V^2$ is the energy required to inflate the respiratory system (*i.e.*, the $E_{RS} \cdot \Delta V$ product equals the driving pressure). The term $\Delta V^2 \cdot RR \cdot \frac{(1 + I:E)}{60 \cdot I:E} \cdot R_{RS}$ is the energy required to overcome the airways and tissue resistances (*i.e.*, the resistive power, when related to time). The term $\Delta V \cdot PEEP$ is the energy required to equilibrate the potential energy stored in the system at PEEP level (*i.e.*, PEEP-related mechanical power, when related to time).

The mechanical power applied to the lung was computed as follows:

$$Power_L = 0.098 \cdot RR \cdot \Delta V^2 \cdot \left(\frac{1}{2} E_L + lung\ tissue\ resistances \cdot \right.$$

$$RR \cdot \frac{(1 + I:E)}{60\,sec \cdot I:E} \right) + \Delta V \cdot \left[\left(Paw_{PEEP} - Paw_{ZEEP} \right) \right.$$

$$\left. - \left(Pes_{PEEP} - Pes_{ZEEP} \right) \right]$$

where E_L is the lung elastance and the term $RR \cdot \frac{(1 + I:E)}{60\,sec \cdot I:E}$ is 1/inspiratory time. The lung tissue resistances, which cannot be assessed during inflation, can be estimated during lung stress relaxation after end-expiratory occlusion. Thus, the tissue resistance estimate is the quotient of (PL1 – PL2)/inspiratory flow, where PL2 is the transpulmonary pressure at the end of the plateau, and PL1 is the transpulmonary pressure at the first time point of flow cessation. The product $\Delta V^2 \times$ lung tissue resistances $\times$ 1/TI has the dimensions of pressure times volume and represents the energy spent to overcome the lung tissue resistances. Paw_{PEEP} and Paw_{ZEEP} are the airway pressures measured at PEEP and zero end-expiratory pressure (ZEEP), respectively; Pes_{PEEP} and Pes_{ZEEP} are the esophageal pressures measured at PEEP and ZEEP, respectively. Driving pressure-related, resistive, and PEEP-related lung power mirror the components described above for the whole respiratory system. The power time point used relative to outcome was the one measured at baseline.

Statistical Analysis

No *a priori* statistical power calculation was conducted, and the sample size was based on our experience from previous experiments. The data are presented as means ± SD unless otherwise specified. Student's *t* test was used to compare lower *versus* higher PEEP in table 1. One-way ANOVA was used to evaluate differences among groups at baseline and at the end of the experiment and to compare different groups of PEEP. To evaluate the differences among groups over time, we used a linear mixed effects model with PEEP group, time in hours, and their interactions as fixed effects and animals as a random variable. This model ignores the missing data but generates outputs with the same numbers of observations compared with the original data set. *Post hoc* comparisons were conducted using the Tukey test. Correlation analysis was made with the Pearson method. We used Kaplan–Meier curves and log-rank tests to examine differences in morality across time. A *P* value < 0.05 was considered statistically significant (two-tailed testing). Outliers were not excluded from the analyses. To identify a possible "damaging" mechanical power threshold, we constructed receiver operating characteristic curves using the medians of the various variables as cutoffs. A logistic regression was used to identify which variables were independently associated with a lung mechanical power threshold. Analyses were performed with R software (R Project for Statistical Computing, https://www.r-project.org/).

Results

Positive End-expiratory Pressure and Mechanical Power

In figure 1, we show the mechanical power applied to the lungs and respiratory system throughout the experiment as a function of the set PEEP (fig. 1, A and B). Each stacked column shows the different components of the mechanical power. The total mechanical power applied to the lungs was similar at PEEP levels of 0, 4, and 7 cm H_2O (*P* = 0.513), because the increase caused by rising PEEP was offset by the simultaneous decreases in driving pressure and the resistive components. In contrast, at PEEP 11, 14, and 18 cm H_2O, the mechanical power increased proportionally to the applied PEEP, whereas the dynamic and resistive components of power remained unchanged. Of note, the driving pressure-related power significantly decreased from ZEEP to PEEP 4 and 7 cm H_2O (lower PEEP groups), whereas it increased to levels similar to ZEEP in the higher PEEP groups. Therefore, the driving pressure-related power was significantly lower at PEEP 4 and 7 cm H_2O and similar at ZEEP and at the higher PEEP levels of 11, 14, and 18 cm H_2O.

Mechanical power applied to the lung and to the respiratory system increased in each PEEP group over time, with a more pronounced rise after 24 to 30 h (fig. S2, A and B, Supplemental Digital Content, http://links.lww.com/ALN/B790). The different rates at which lung power increased in the higher and lower PEEP level groups are revealed by the different slopes of cumulative lung energy *versus* time (fig. S2C, Supplemental Digital Content, http://links.lww.com/

Table 1. Lung Weights and Wet-to-Dry Values

PEEP	Lower PEEP			Higher PEEP			P Value
	0	4	7	11	14	18	
End lung weight/ initial pig weight, %	1.4±0.14 (n = 6)	1.43±0.46 (n = 6)	1.7±0.67 (n = 6)	1.84±0.53 (n = 6)	1.61±0.49 (n = 6)	1.66±0.32 (n = 6)	0.562
	1.5±0.45			1.7±0.44			0.18
Wet-to-dry lung index	5.9±0.3 (n = 6)	6±0.7 (n = 6)	6.6±0.7 (n = 6)	6.5±0.4 (n = 6)	6.8±0.9 (n = 6)	10.3±4.8 (n = 6)	0.006
	6.2±0.6			7.9±3.2			0.03
Wet-to-dry liver index	3.9±0.3 (n = 3)	3.7±0.2 (n = 3)	3.6±0.3 (n = 4)	4.4±0.5 (n = 3)	4.8±1.5 (n = 4)	7.0±4.2 (n = 4)	0.25
	3.7±0.3			5.5±2.7			0.06
Wet-to-dry kidney index	4.7±1.2 (n = 3)	4.3±1.1 (n = 3)	4.9±0.8 (n = 4)	5.4±0.2 (n = 3)	6.0±1.4 (n = 4)	9.5±4.5 (n = 4)	0.135
	4.7±0.9			7.1±3.6			0.06
Wet-to-dry muscle index	3.8±0.5 (n = 3)	4.7±0.6 (n = 3)	4.0±0.7 (n = 4)	4.1±0.3 (n = 3)	4.4±1.0 (n = 4)	6.5±2.4 (n = 4)	0.09
	4.1±0.7			5.3±1.8			0.14
Wet-to-dry bowel index	5.5±0.5 (n = 3)	5.6±0.3 (n = 3)	5.6±0.9 (n = 4)	5.2±0.2 (n = 3)	6.0±1.4 (n = 4)	8.5±4.2 (n = 4)	0.31
	5.6±0.6			6.7±2.8			0.24

Lung weights and wet-to-dry values are reported as mean ± SD. In the first line, comparison was made across the positive end-expiratory pressure (PEEP) group using the ANOVA test. In the second line, comparison was made between lower and higher PEEP groups using the Student's *t* test.
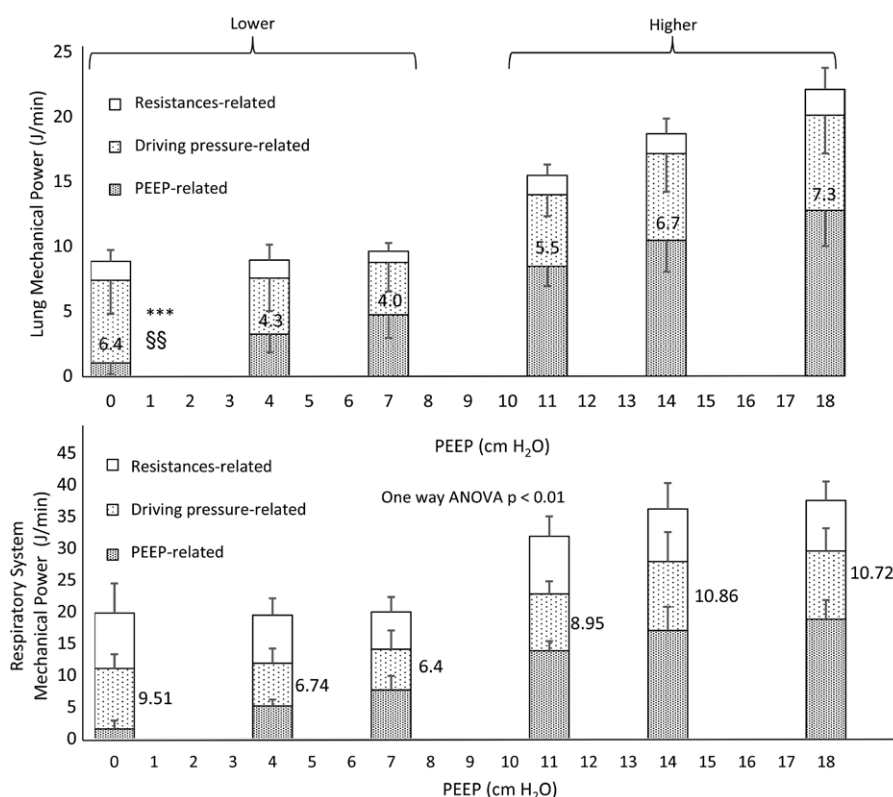

Fig. 1. Column chart showing the mechanical power applied to the respiratory system (*top*) and to the lung (*bottom*) at set positive end-expiratory pressure (PEEP) values of 0, 4, 7, 11, 14, and 18 cm H_2O. Note that power is scaled differently for respiratory system (0 to 45 J/min) and the lung (0 to 25 J/min). ***P <0.001, driving pressure related power PEEP 0 *vs.* PEEP 4. §§P <0.05, driving pressure related lung power PEEP 0 *versus* PEEP 7.

ALN/B790). Of the 36 animals, 5 died during the experiment from either tension pneumothorax (n = 1; PEEP 18 cm H_2O) or hemodynamic collapse (n = 2, PEEP 14 cm H_2O; n = 2, PEEP 18 cm H_2O). The difference in mortality among the PEEP groups was significant ($P = 0.012$; fig. S3, Supplemental Digital Content, http://links.lww.com/ALN/B790).

PEEP Effects on Lung Mechanics

At baseline (time 0), plateau airway pressure, driving airway pressure, and driving transpulmonary pressure were all correlated with the end-expiratory lung volume (FRC + PEEP volume; $P < 0.001$; r^2 plateau airway pressure, 0.85; r^2 driving airway pressure, 0.50; r^2 driving transpulmonary pressure, 0.24; data not shown). The time course of these variables is displayed in fig. S4, Supplemental Digital Content, http://links.lww.com/ALN/B790). As shown, they all increased in every group, especially after 24 to 30 h. Of note, the greatest deteriorations of both airway and transpulmonary driving pressures were observed in the ZEEP group (see also table S1, Supplemental Digital Content, http://links.lww.com/ALN/B790).

These increases in pressure were uniquely due to the worsening of lung elastance, which accounted for an overall increase in the respiratory system elastance despite a small decrease in the chest wall elastance (fig. 2). All baseline elastance values were positively correlated with the baseline end-expiratory lung volume ($P < 0.001$; r^2 lung elastance, 0.368; r^2 respiratory system elastance, 0.523; r^2 chest-wall elastance, 0.285; data not shown), and the greatest worsening of lung elastance was observed in the six animals treated at ZEEP (from 23 ± 4.8 to 46 ± 23 cm H_2O/l; $P = 0.044$; fig. 2B). Lung stress at baseline was significantly higher in the groups with higher PEEP (table S1) and tended to increase during the experiment, particularly after 24 to 30 h (fig. S5, Supplemental Digital Content, http://links.lww.com/ALN/B790). In contrast, the associated strain did not change significantly throughout the experiment. Consequently, the specific elastance, which is the proportionality constant between stress and strain that reflects the intrinsic elasticity of lung parenchyma, worsened with time both in the lower and the higher PEEP groups. The time courses of these variables are presented in figure S5 in the Supplemental Digital Content (see also table S1, Supplemental Digital Content, http://links.lww.com/ALN/B790).

PEEP Effects on Gas Exchange

The P_{AO_2}/F_{IO_2} ratio was different among the PEEP groups and decreased slightly but significantly over the course of the experiment ($P < 0.001$), especially at ZEEP (from 632 ± 59 to 505 ± 106 mmHg; $P = 0.028$). The P_{AO_2}/F_{IO_2} ratio paralleled the shunt fraction behaviors (fig. S6, Supplemental Digital Content, http://links.lww.com/ALN/B790, for the time course). The ventilatory protocol led to hypocapnia in all animals, both at baseline and during the course of the experiment (fig. S6C, Supplemental Digital Content, http://links.lww.com/ALN/B790). Dead space increased in all groups, especially in the PEEP 18 cm H_2O group ($P < 0.001$; fig. S6D, Supplemental Digital Content, http://links.lww.com/ALN/B790). Base excess and pH were similar at baseline in all groups and steadily decreased in every group during the course of the experiment, even though lactate levels remained more or less constant. The time course of arterial base excess and pH is shown in figure S7, Supplemental Digital Content (see also table S2, Supplemental Digital Content, http://links.lww.com/ALN/B790).

Hemodynamics

As shown in figure 3 and table S3 (Supplemental Digital Content, http://links.lww.com/ALN/B790), cardiac output (fig. 3A) was similar at baseline in all groups and decreased significantly over time ($P < 0.001$). Mean arterial pressure (fig. 3B) differed significantly between the PEEP groups at
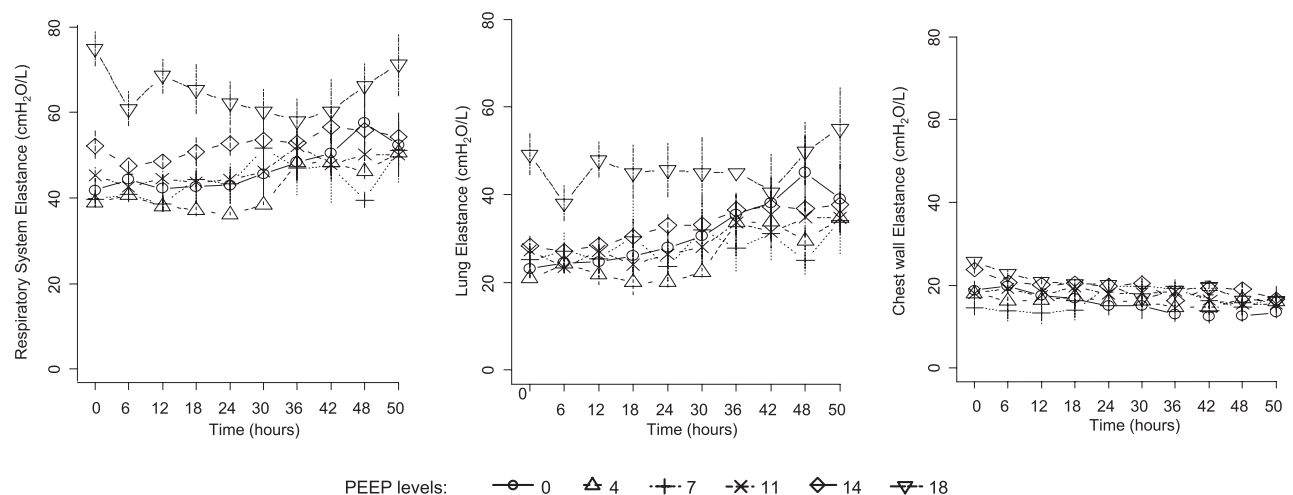

PEEP levels: —○— 0   —△— 4   ·+· 7   ·×· 11   —◇— 14   —▽— 18

Fig. 2. Time course of respiratory system elastance (linear mixed effects model: time, $P < 0.001$; positive end-expiratory pressure [PEEP], $P < 0.001$; PEEP:time interaction, $P = 0.445$; *left*), lung elastance (linear mixed effects model: time, $P < 0.001$; PEEP, $P = 0.002$; PEEP:time interaction, $P = 0.499$; *middle*), and chest wall elastance (linear mixed effects model: time, $P = 0.005$; PEEP, $P = 0.103$; PEEP:time interaction, $P = 0.125$; *right*) in the different PEEP groups.
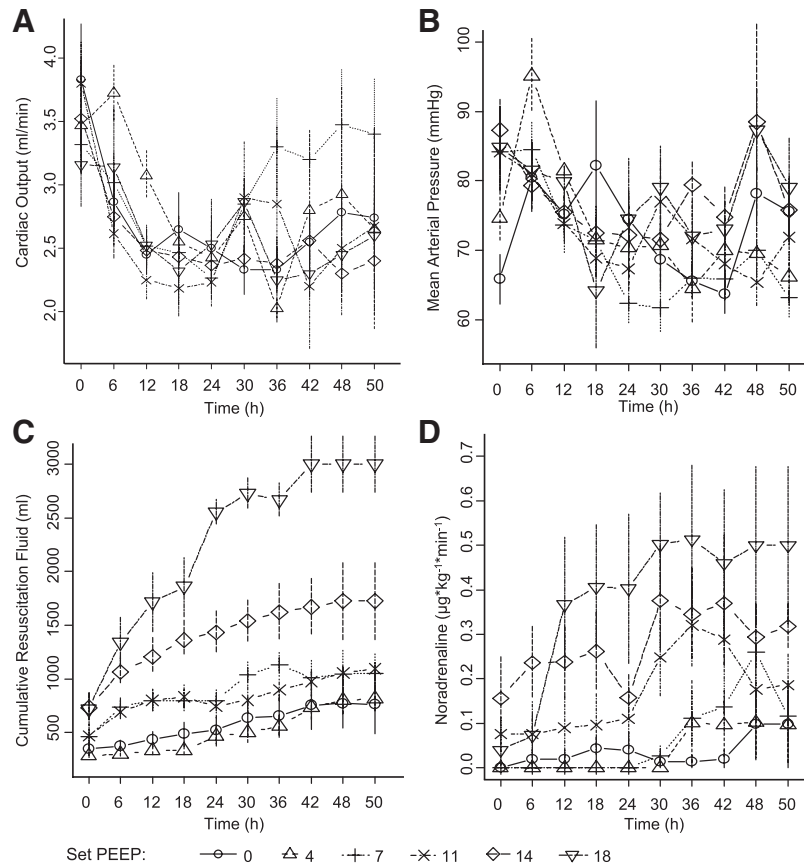
Fig. 3. Time course of cardiac output (linear mixed effects model: time, $P < 0.001$; positive end-expiratory pressure [PEEP], $P = 0.684$; PEEP:time interaction, $P = 0.315$; A), mean arterial pressure (linear mixed effects model: time, $P < 0.001$; PEEP, $P = 0.543$; PEEP:time interaction, $P = 0.011$; B), cumulative resuscitation fluids (linear mixed effects model: time, $P < 0.001$; PEEP, $P < 0.001$; PEEP:time interaction, $P < 0.001$; C), and noradrenaline (linear mixed effects model: time, $P < 0.001$; PEEP $P = 0.001$; PEEP:time interaction, $P = 0.003$; D) in the different PEEP groups.

baseline ($P = 0.045$). It decreased significantly over time, but there was no identifiable pattern associated with the PEEP levels. On the other hand, the volume of infused fluids required to maintain perfusion was proportional to the level of PEEP at baseline and throughout the experiment (fig. 3C). The noradrenaline infusion rate required to maintain arterial pressure was proportional to the PEEP level, but little was needed in the ZEEP and the 4 cm H_2O PEEP groups (fig. 3D).

Mean pulmonary pressure and wedge pressures increased both with increasing PEEP and over time (fig. S8, Supplemental Digital Content, http://links.lww.com/ALN/B790). Similar changes were seen in the fluid balance (fig. S9, Supplemental Digital Content, http://links.lww.com/ALN/B790). Arterial lactate levels slightly increased over time but were not different among the treatment groups (see also fig. S10 and table S3, Supplemental Digital Content, http://links.lww.com/ALN/B790).

PEEP and Edema
Table 1 (see also fig. S11, Supplemental Digital Content, http://links.lww.com/ALN/B790) displays the lung weight at the end of the experiment as well as the wet-to-dry indexes of lung, liver, bowel, kidney, and skeletal muscle.

The average lung weight in these 36 piglets was significantly higher than the normal lung weight we previously measured by computed tomography scan in 73 healthy piglets of the same body weight (371 ± 105 g vs. 321 ± 40 g; $P < 0.001$),[5] and it did not differ significantly between the groups. However, the wet-to-dry index, which accounts for the experimental duration, slightly increased with rising PEEP, reaching statistical significance ($P = 0.006$). The wet-to-dry index of all studied organs was higher among animals ventilated with higher PEEP, although the difference was only statistically significant for the lungs. This may have been due to an inadequate statistical power because of the small number of samples available for measuring the wet-to-dry index of liver, kidney, bowel, and muscle (11 and 10 in the higher and lower PEEP groups, respectively).

Lung Histology
We found no differences, either between left and right lungs or among different lung regions, *i.e.*, apex, middle, and basal. The lesions in these prone animals were also uniformly distributed between dependent and nondependent regions. We therefore analyzed these histologic findings

together, regardless of their anatomical position. A representative overview of the macroscopic aspect of the lungs in different PEEP groups is available in supplemental figure S12 (Supplemental Digital Content, http://links.lww.com/ALN/B790). Histologic data are reported in figure 4 and supplemental figure S13 (Supplemental Digital Content, http://links.lww.com/ALN/B790). As shown in the upper panel of figure 4, the most frequent finding was vascular congestion, followed by inflammatory cell infiltration, alveolar collapse/atelectasis, and septal dilatation/rupture. A similar pattern recurred with each of these lesions. Indeed, most of them were highly represented at ZEEP. They all decreased in the animals treated at 4 cm H_2O but increased at higher PEEP levels. The decrease from ZEEP to PEEP 4 was significant for vascular congestion ($P < 0.001$), inflammation ($P < 0.001$), atelectasis ($P < 0.001$), septal rupture ($P = 0.041$), emphysema-like lesions ($P < 0.001$), and intravascular thrombi ($P < 0.001$). The incidence of vascular congestion, inflammation, atelectasis, and septal rupture increased significantly from PEEP 4 to PEEP 14 to 18 cm H_2O ($P < 0.001$). The behavior of the other, less frequent lesions is reported in the supplement (fig. S13, Supplemental Digital Content, http://links.lww.com/ALN/B790). Briefly, at higher PEEP (14 to 18 cm H_2O), alveolar edema was lower, and alveolar hemorrhage was higher than at lower PEEP. No hyaline membranes were observed.

PEEP and Mechanical Power Thresholds

The variables suggestive of lung damage are presented in table 2. The measures obtained in all piglets—regardless of allocation group—were pooled, and their median values were computed. We then computed—as "threshold"—the mechanical power associated with the median value of each variable. Therefore, this threshold represents the mechanical power that is associated with a damage greater or lower than the 50% median value. As shown, the mechanical power thresholds averaged were 13 ± 1 J/min for the lung and 25 ± 1.7 J/min for the respiratory system. We introduced into a logistic regression model the lung-specific elastance, dead space, wet-to-dry index, noradrenaline requirement, and pulmonary artery mean pressure. These variables were selected as representative of lung mechanics, gas exchange, anatomy, and hemodynamics. The specific elastance odds ratio was 1.83 (CI, 1.6 to 2.2), the pulmonary artery pressure odds ratio was 1.13 (CI, 1.1 to 1.2), and the noradrenaline odds ratio was 565 (CI, 66 to 7,749). These three variables were significantly related to the lung mechanical power threshold of 13 J/min ($P < 0.001$ for all). The dead space and the wet-to-dry index were not significantly related with the mechanical power threshold.

Summary of Results

The mean values ($\pm$ SDs) of each of the variables considered above are reported for each group in the supplement:
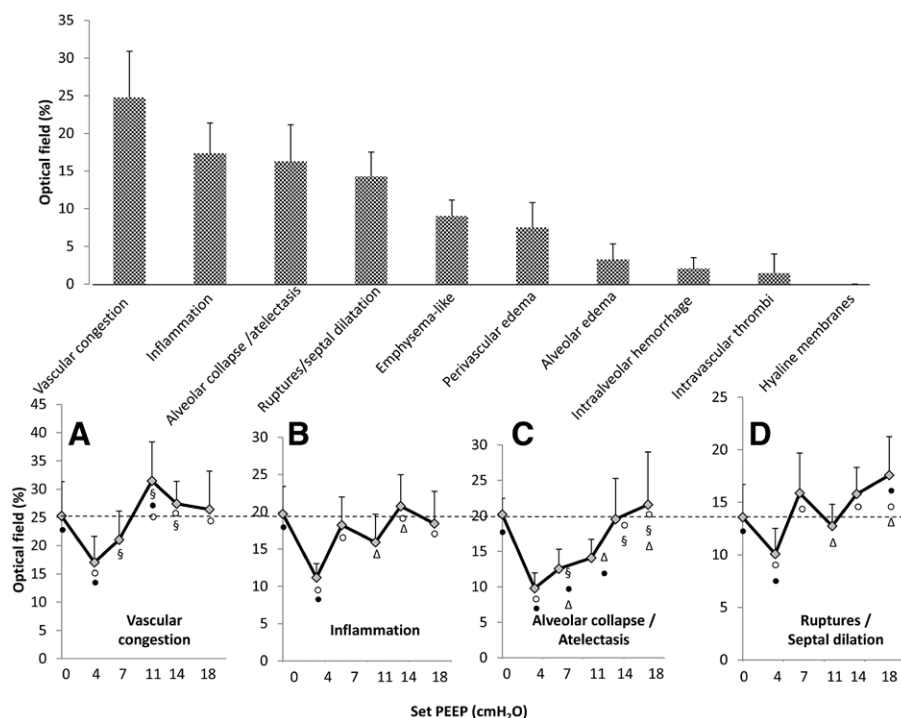

Fig. 4. (*Upper*) Column chart showing the percentage of optical field affected by the different histopathologic lesions in all the experimental animals. (*Lower*) Percentages of optical field with vascular congestion (*A*), inflammatory infiltrates (*B*), alveolar collapse/atelectasis (*C*), and septal dilations/ruptures (*D*) as a function of experimental positive end-expiratory pressure (PEEP) groups. Significant statistical differences are indicated by *black circles* (zero end-expiratory pressure), *white circles* (4 cm H_2O), *section signs* (§) (7 cm H_2O), and *white triangles* (11 cm H_2O).

Table 2. Summary of Findings of the Receiver Operating Characteristic Curves

Variable	Median Value	Lung Mechanical Power, J/min	Lung AUC (ROC) CI	Respiratory System Mechanical Power, J/min	Respiratory System AUC (ROC) CI
Wet-to-dry lung index	6.45	12.1	0.78 (0.61–0.92)	22.7	0.71 (0.53–0.88)
Pathology total	97	13	0.59 (0.4–0.78)	27.9	0.58 (0.39–0.77)
Lung elastance, cm H_2O/l	28.6	13.2	0.84 (0.8–0.88)	25.8	0.69 (0.63–0.75)
Specific lung elastance, cm H_2O	10.1	13.1	0.9 (0.87–0.93)	25.3	0.8 (0.75–0.84)
Dead space, %	40	13.4	0.62 (0.56–0.68)	25.6	0.57 (0.5–0.63)
Driving pressure, cm H_2O	16.4	13	0.91 (0.87–0.94)	25.3	0.84 (0.8–0.88)
PEEP, cm H_2O	8.7	11.7	0.91 (0.88–0.94)	22.0	0.91 (0.88–0.94)
Driving transpulmonary, cm H_2O	8.12	15.51	0.76 (0.71–0.8)	25.16	0.64 (0.58–0.69)
PAP mean, mmHg	23	12.6	0.86 (0.82–0.90)	24.9	0.87 (0.81–0.93)
Mean		13 ± 1		25 ± 1.7	

Shown is a summary of findings of the receiver operating characteristic (ROC) curves that we constructed using the medians of the various variables as cutoffs to identify the mechanical power that best discriminates between more and less severe conditions. AUC, area under the curve; PAP, pulmonary artery pressure; PEEP, positive end-expiratory pressure.

lung and respiratory system mechanics variables (Table S1, Supplemental Digital Content, http://links.lww.com/ALN/B790), gas exchange variables (table S2, Supplemental Digital Content, http://links.lww.com/ALN/B790), hemodynamic variables (table S3, Supplemental Digital Content, http://links.lww.com/ALN/B790), and intergroup comparisons (table S4, Supplemental Digital Content, http://links.lww.com/ALN/B790).

Discussion

If we strictly consider the effects of the presence of positive pressure at end expiration (isolating PEEP itself as a potentially damaging contributor), this study shows that its increase from 4 to 7, 11, 14, and 18 cm H_2O is associated with proportionally greater damage to the previously healthy lung, whether considering gross anatomy, histology, hemodynamics, or the overall clinical scenario. Indeed, the total energy per cycle required to overcome the presence of PEEP contributed to the lung damage. On the other hand, under unchanging ventilating conditions, it is evident that, over time, the complete absence of PEEP harmed the initially healthy lungs of these anesthetized animals. Although such damages were almost fully prevented at 4 cm H_2O PEEP and partially prevented at 7 cm H_2O, they were similar and even higher than at ZEEP at PEEP values of 11, 14, or 18 cm H_2O (fig. 4).

In keeping constant the tidal volume and the respiratory rate, the total mechanical power theoretically should have increased linearly with PEEP.[1] However, we found it similar at 0, 4, and 7 cm H_2O because of the improving respiratory system elastance over that range. Indeed, up to 7 cm H_2O, the increases in the PEEP component of delivered mechanical power were offset by parallel decreases of the driving pressure component. We may envisage several hypotheses for the presence of damage of different extents at the same total mechanical power level. First, it is possible that, for the same "package" of mechanical power, the contribution of its components does not carry the same weight in inducing damage. A possible explanation could be that the higher driving pressure at ZEEP could have played a greater role than the PEEP increase. Alternatively, staying more strictly within the mechanical power hypothesis, it is possible that the decrease in FRC at ZEEP caused by anesthesia and paralysis (prevented by PEEP) resulted in an increased *specific* power, *i.e.*, the power normalized for the dimension of the lung to which it is applied. In addition, it is possible that the power focused at the interface between units undergoing collapse and decollapse is far greater than in the remaining lung parenchyma.

Indeed, in the ZEEP animals, lung damage manifested as decreased FRC, increased atelectasis, and inflammatory infiltrates, as well as increased lung elastance and specific elastance. Of note, the ZEEP animals had the lowest lung weight and wet-to-dry index, noradrenaline infusion rates, and resuscitation fluid volumes, whereas the mean pulmonary artery and wedge pressures were similar to the ones measured in piglets treated at PEEP 4 or 7 cm H_2O. The bulk of data suggests that, at ZEEP, atelectrauma with increased driving pressure/increased focused mechanical power is the most relevant cause of lung damage in our model, occurring without major hemodynamic impairment.

By increasing PEEP from 4 to 11, 14, or 18 cm H_2O, we observed progressively greater damage, and we measured a substantial increase in lung mechanical power. This increase was mainly related to the increase in the PEEP-related power component, whereas the component related selectively to driving pressure (excluding PEEP) was similar to that applied at ZEEP. Some of the damages observed at ZEEP, such as increased lung weight, histologic atelectasis, and inflammatory infiltrates, were not prevented by these higher levels of PEEP, whereas other indicators, namely stress, strain, lung elastance, and specific lung elastance, even increased significantly by 40 to 70%. Furthermore, new alterations manifested at these higher PEEP levels, such as a striking

increase in mean pulmonary artery pressure (by 40%), additional fluid requirements (by 145%), and greater needs for noradrenaline infusion (by 100%). Finally, the death of five animals treated at 14 to 18 cm H_2O PEEP was clearly attributable to hemodynamic impairment; one of these deaths was attributable to tension pneumothorax. Indeed, increasing PEEP above 7 cm H_2O did not prevent lung damage and added a relevant burden of hemodynamic instability that led to significantly increased damage and mortality.

In these experiments, we identified a threshold level of lung mechanical power of 13 J/min that split anatomical, mechanical, gas exchange, and hemodynamic damage variables at their median values. This is similar to the threshold value of 12.5 J/min that we found in a different experimental setting, where the mechanical power was modified by changing the respiratory frequency while keeping the tidal volume constant at ZEEP.[3] It must be pointed out, however, that such a threshold should be considered only as the limit above which mechanical ventilation may be lethal and not as the limit below which mechanical ventilation will safely maintain the lungs normally. Actually, we observed lung damages in all PEEP groups, likely because the applied ventilation was deleterious, regardless of the PEEP level.

One of the main conceptual challenges of this experiment was how to assess ventilator-induced lung injury. Ventilator-induced lung injury encompasses a variety of anatomical, physiologic, and clinical signs.[9,10] Experimentally, the most common findings of atelectrauma are increased lung weight (edema), shunt, dead space, and elastance, as well as histologic atelectasis and inflammatory infiltrates.[10] The most typical feature of volutrauma, however, is hyperinflation, with its effects on lung mechanics and hemodynamics. In our study, atelectrauma was the most likely cause of damage manifested at ZEEP, even though edema was not an important feature, probably because mean airway pressure was sufficiently high to prevent it.[11–13] Increasing PEEP moved the pattern toward volutrauma, with its typical effects on lung mechanics, hemodynamics, and mortality, but without gas exchange impairment or relevant edema, as indicated by less alveolar and perivascular edema observed at the highest PEEP levels (fig. S13, B and C, fig. S13, Supplemental Digital Content, http://links.lww.com/ALN/B790). Of note, the putative increase or decrease of ventilator-induced lung injury in clinical trials is measured as increased or decreased mortality rate,[14–18] although the mortality attributable to mechanical ventilation or ventilator-induced lung injury *per se* is far from defined. In contrast, in our model, all negative effects, including mortality, could be solely attributed to the consequences of mechanical ventilation, because the experiment started with healthy lungs of animals supported in their naturally prone position.

In this study, we wanted to investigate the role of PEEP as a component of mechanical power. Unfortunately, it is not possible (without artificial lungs) to increase the mechanical power actually applied selectively by PEEP, *i.e.*, without

accompanying changes in some of the other contributing components. In our model that mandated constant tidal volume and frequency, an increase in PEEP unavoidably may result in linear increases in plateau and driving pressures while tracking along the straight part of the volume–pressure curve, but in their exponential increases while tracking along the uppermost portion of that curve. The issue, however, is not whether PEEP or tidal volume or driving pressure or frequency is a greater or lesser inducer of ventilator-induced lung injury but rather how to consider them together, because ventilator-induced lung injury depends on how *all* these variables are set when ventilating a given patient. We believe that, at this stage, the mechanical power is a unifying tool that reminds us that all its components should be considered when attempting to prevent ventilator-induced lung injury. Indeed, PEEP may be an important determinant of damage in some settings (as explored in this study), whereas in others it would be expected to be a minor contributor compared with the dominating influence of the driving pressure,[19] respiratory frequency,[3] or their combination[20] (depending on their magnitudes and interactions).

Limitations

Our experiments have several limitations, because they did not answer some fundamental questions related to power. First, as discussed above, the increase in PEEP at the same tidal volume is associated with increase in plateau pressure and driving pressure, in a sense making arbitrary the interpretation of the results. Second, we do not know how to best normalize the mechanical power. This is not really relevant in our experiment, because the inherent normalization was provided by the use of healthy animals of similar weight and age. The normalization would be of paramount importance when comparing different species. The influence of species on damaging power threshold for the lung is also unknown, and the threshold value of 13 J/min that we found here and previously in piglets cannot be translated with quantitative certainty to the human being. We should consider, in addition, that stresses related to PEEP levels of 4 and 7 cm H_2O in piglets are roughly equivalent to 8 and 14 cm H_2O in humans, because of the differences in specific lung elastance (~6 *vs.* ~12 cm H_2O).[5] Furthermore, we do not clearly know how mechanical power is distributed in space, (*i.e.*, "baby lung" size and stress-raising inhomogeneity[21]), and in time, *i.e.*, within the phases of the respiratory cycle (inspiration *vs.* expiration). We also do not know whether all "packages" of mechanical power result in equivalent damage or whether power-related damage depends critically upon the composition of its determinants, as suggested by the comparison of ZEEP and 4 to 7 cm H_2O PEEP. Obviously, if a mechanical power threshold for damage were to be identified in humans, it would represent a boundary limit beyond which the applied pattern of mechanical ventilation is not acceptable and therefore represent a key indicator of the need for alternative methods of ventilatory support.

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