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Does Iso-mechanical Power Lead to Iso-lung Damage?

An Experimental Study in a Porcine Model

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ABSTRACT

Background: Excessive tidal volume, respiratory rate, and positive end-expiratory pressure (PEEP) are all potential causes of ventilator-induced lung injury, and all contribute to a single variable: the mechanical power. The authors aimed to determine whether high tidal volume or high respiratory rate or high PEEP at iso-mechanical power produce similar or different ventilator-induced lung injury.

Methods: Three ventilatory strategies—high tidal volume (twice baseline functional residual capacity), high respiratory rate (40 bpm), and high PEEP (25 cm H_2O)—were each applied at two levels of mechanical power (15 and 30 J/min) for 48 h in six groups of seven healthy female piglets (weight: 24.2 ± 2.0 kg, mean ± SD).

Results: At iso-mechanical power, the high tidal volume groups immediately and sharply increased plateau, driving pressure, stress, and strain, which all further deteriorated with time. In high respiratory rate groups, they changed minimally at the beginning, but steadily increased during the 48 h. In contrast, after a sudden huge increase, they decreased with time in the high PEEP groups. End-experiment specific lung elastance was 6.5 ± 1.7 cm H_2O in high tidal volume groups, 10.1 ± 3.9 cm H_2O in high respiratory rate groups, and 4.5 ± 0.9 cm H_2O in high PEEP groups. Functional residual capacity decreased and extravascular lung water increased similarly in these three categories. Lung weight, wet-to-dry ratio, and histologic scores were similar, regardless of ventilatory strategies and power levels. However, the alveolar edema score was higher in the low power groups. High PEEP had the greatest impact on hemodynamics, leading to increased need for fluids. Adverse events (early mortality and pneumothorax) also occurred more frequently in the high PEEP groups.

Conclusions: Different ventilatory strategies, delivered at iso-power, led to similar anatomical lung injury. The different systemic consequences of high PEEP underline that ventilator-induced lung injury must be evaluated in the context of the whole body.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Ventilator-induced lung injury results from a complex interaction of physical variables involved in mechanical ventilation (tidal volume, respiratory rate [RR], positive end-expiratory pressure [PEEP], driving pressure, resistances, and flow).
- Although each variable has been previously studied in isolation, their overall effects within the recent construct of mechanical power (the product of change of lung volume and absolute pressure) delivered to the lung per unit of time (J/min) remains controversial.
- Previous animal studies have demonstrated mechanical power thresholds related to ventilator-induced lung injury, the adverse effects of high respiratory rate on low tidal volume ventilation in ventilator-induced lung injury, and the adverse effects of PEEP above a certain mechanical power threshold on ventilator-induced lung injury.

What This Article Tells Us That Is New

- The authors studied 42 healthy sedated pigs ventilated in the prone position for 48 h, controlling anesthetic level, hemodynamics, and temperature.
- Three ventilatory strategies (high tidal volume, high RR, or high PEEP) were studied at two levels of mechanical power (15 or 30 J/min, regulated by manipulating the other component variables). Measurements included hemodynamics, lung mechanics, gas exchange, lung histology, and lung weight.

What This Article Tells Us That Is New (Continued)

- High PEEP, as expected, had the greatest adverse hemodynamic impact.
- For all strategies, similar degrees of histologic lung injury and extravascular lung water accumulation occurred by 48 h, despite different time courses.
- Paradoxically, a greater degree of alveolar edema occurred at lower mechanical power, perhaps explained by different hemodynamic patterns that favored or reduced extravascular fluid accumulation.
- These data suggest that over time, the integrated effects resulting from high tidal volume, high RR, or high PEEP are more important than the direct and immediate consequence of any one of them alone. Ventilator-induced lung injury should be considered holistically in the context of whole-body physiology rather than as an isolated effect on the lung alone.

All primary components of mechanical ventilation, namely tidal volume (V_T),[1–4] driving pressure,[5] inspiratory flow,[6] respiratory rate (RR),[7] and positive end-expiratory pressure (PEEP),[8] have been recognized as potential contributors to ventilator-induced lung injury. Taken together, they are components of a "summary variable": the mechanical power.[9] The computation of mechanical power is based on the motion equation[10]: the total pressure present in the respiratory system at any given time is the sum of the pressure required to overcome the incremental elastic load (V_T · respiratory system elastance), the pressure required to move the gas through the respiratory system (flow · resistance), and the pressure stored in the respiratory system at end-expiration (PEEP). The sum of each of these pressures, multiplied by the V_T, equals the inflation energy spent during each breath. This inflation energy per cycle, multiplied by RR, determines the mechanical power, expressed in joules per minute (Supplemental Digital Content, http://links.lww.com/ALN/C261). While V_T and RR are unquestioned components of the mechanical power, more controversial has been the inclusion of PEEP in the mechanical power formula,[11] as no energy must be spent to maintain a given level of PEEP if the lung remains motionless. It must be pointed out, however, that to inflate the lung from a given level of PEEP requires an energy input *relative to its relaxed baseline* greater than the potential energy stored in the lung at that PEEP level. Indeed, the energy required equals the *absolute pressure* times the change in volume. In work specifically aimed to test PEEP as a component of mechanical power, we found a U-shaped relationship of PEEP to lung damage: harmful at zero end-expiratory pressure, harmless at 4 to 7 cm H_2O, and increasingly harmful over the range from 11 to 18 cm H_2O.[8]

The possible association between mechanical power and mortality/ventilator-induced lung injury has been found in critically ill patients receiving mechanical ventilation for at least 48 h[12] and in patients without acute respiratory distress syndrome (ARDS),[13] as well as in experimental animals with healthy[14] or diseased lungs.[15] Despite these promising signals of the usefulness of mechanical power as an indicator of damage risk, the relative weights of the mechanical power components in determining ventilator-induced lung injury has not been investigated. Indeed, the same value of mechanical power of inflation may be reached independently of the principal component variable being altered, V_T, RR, or PEEP. Yet within this framework of iso-mechanical power, it is unknown whether the overall lung damage inflicted by each component is similar, suggesting that the primary cause of ventilator-induced lung injury is the mechanical power *per se*, or whether ventilator-induced lung injury differs depending on the dominant component variable influencing power. The objective of this study was to answer this question by comparing in healthy piglets the individual effects of high V_T, high RR, and high PEEP, each delivered at two levels of mechanical power (15 and 30 J/min), on lung mechanics, hemodynamics, and gas exchange as well as on macroscopic and histologic lung anatomy.

Materials and Methods

The study, approved by local authorities (18/2795, LAVES, Oldenburg, Niedersachsen, Germany), included 42 healthy domestic piglets (body weight, mean ± SD, 24.2 ± 2.0 kg), which were maintained under total intravenous general anesthesia throughout the experiment (sufentanil, propofol, and midazolam). The animals were mechanically ventilated in volume-controlled mode, in prone position for 48 h at a constant inspired fraction of oxygen (0.40). They were instrumented with esophageal balloon, central venous, pulmonary artery, femoral artery, and urinary catheters. Crystalloids were infused as maintenance fluid, and norepinephrine and colloids were administered as needed to maintain a mean arterial pressure greater than 60 mmHg. Epinephrine was added to increase cardiac output if hemodynamic instability developed (for the details of experimental procedure see Supplemental Digital Content, http://links.lww.com/ALN/C261).

Experimental Design

We studied healthy animals so that whatever damage occurred could be attributed uniquely to mechanical ventilation. Forty-two pigs were allocated among six groups (seven pigs each) defined by two levels of mechanical power (high, approximately 30 J/min, or low, approximately 15 J/min) and three ventilatory strategies, in which the dominant mechanical power component was V_T, RR, or PEEP. We decided to apply 15 and 30 J/min of mechanical power to confirm the results of a previous study, in which 25 ± 1.7 J/min over 48 h discriminated between lower and higher degrees of lung damage. In high V_T groups, we set V_T equal to functional residual capacity (FRC) times 2.5 (approximately 30 to 35 ml/kg). To deliver this V_T at 15 or 30 J/min, we arbitrarily chose to keep the PEEP constant at 5 cm H_2O and to vary the RR from 7 to 15 bpm. This applied V_T is known to produce lung damage in similar sized healthy pigs ventilated over extended periods.[16] In the high RR

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group, we set the RR at 40 breaths/minute. To deliver this frequency at 15 or 30 J/min, we kept the PEEP constant at 5 cm H_2O, as the V_T was adjusted from 10 and 14 ml/kg. This frequency was arbitrarily chosen as a compromise to deliver potentially harmful RR, while minimizing the auto-PEEP. In the high PEEP groups, we set PEEP at 25 cm H_2O. We were obligated to use such a high level of PEEP so as to reach the targeted level of mechanical power, which increases only linearly with PEEP, instead of exponentially, as with V_T and RR.[9] To deliver a mechanical power of 15 and 30 J/min in this group while maintaining a nonharmful V_T in healthy lungs, we maintained 13 ml/kg of V_T and varied the frequency from 11 to 21 bpm. The ventilatory variables and the settings of the injurious ventilation are presented in figure 1 and detailed in table 1.

Experimental Procedure

The piglets were randomly allocated to one of the six groups and ventilated according to the predefined respiratory settings (V_T, RR, and PEEP) for 48 h. Every 6 h we measured ventilatory, hemodynamic, and gas exchange variables. We measured FRC every 12 h *via* multiple breath helium dilution in a closed system.[17] The animals were euthanized at the end of the experiment by injection of pentobarbital and potassium chloride. Autopsy was performed and lung weight and wet-to-dry ratios measured. Coded samples for histology were taken from apical, middle, and basal lung sectors, both in dependent and nondependent lung regions. The experimental procedures for sampling and analysis are detailed in the Supplemental Digital Content text and figure 1 (http://links.lww.com/ALN/C261).

Statistical Analysis

No *a priori* statistical power calculation was conducted; the sample size was based on our experience with previous experiments. For the sake of clarity, data are presented classifying the six groups either according to the mechanical power level, regardless of the ventilatory strategy, or according to the ventilatory strategy (high V_T *vs.* high RR *vs.* high PEEP), regardless of the mechanical power (30 J/min = higher power *vs.* 15 J/min = lower power; hereafter we will refer to these two levels as high and low, respectively). Data are presented as mean and SD; No. refers to the number of animals. We tested the normal distribution of the variables with the Shapiro–Wilk test. To evaluate differences in continuous variables at a given time point, we used

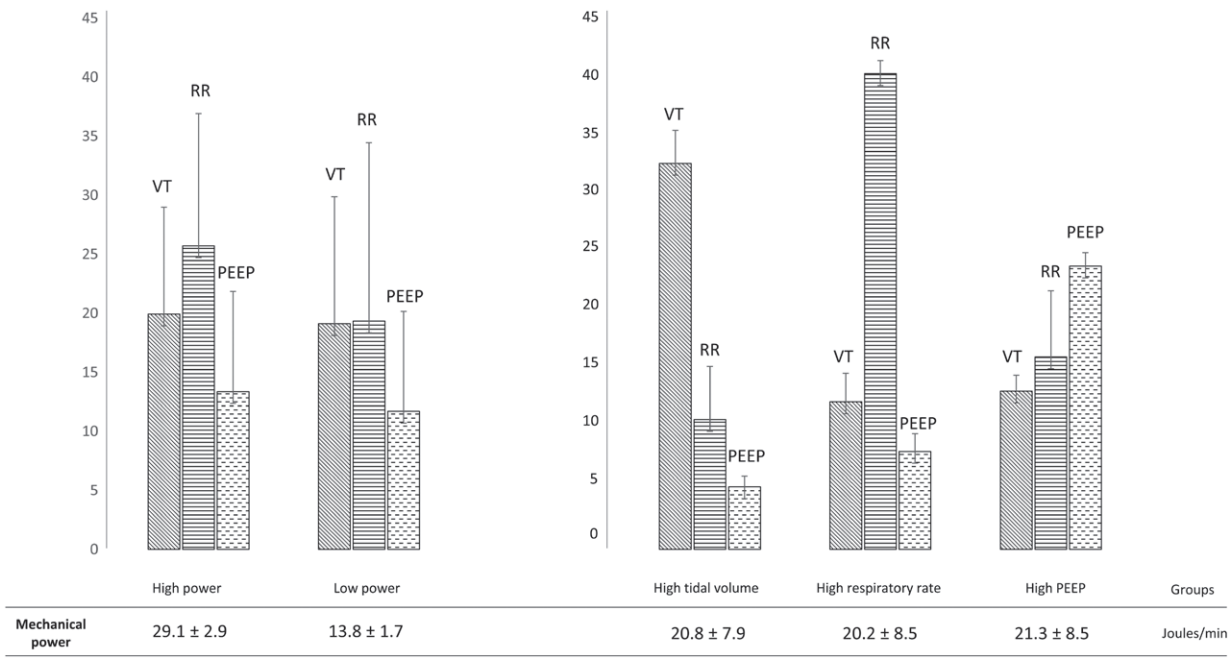

Fig. 1. (*Left*) Average values for tidal volume (V_T), respiratory rate (RR), and positive end-expiratory pressure (PEEP) in the higher mechanical power group (n = 21) and in the lower mechanical power group (n = 21). The individual components (V_T, RR, PEEP), were not statistically different between the two power categories. (*Right*) Average V_T, RR, and PEEP values in the high V_T group (n = 14), in the high RR group (n = 14), and in the high PEEP group (n = 14), as measured at the beginning of intervention protocol. The RR was significantly higher in the high PEEP group than in the high V_T group ($P < 0.001$), the V_T values were similar between the high respiratory rate group and the high PEEP group ($P = 0.645$), and the PEEP level was significantly higher in the high RR group than in the high V_T group ($P < 0.001$). Note that in the higher RR group, the set PEEP was 5 cm H_2O, while the actual end-expiratory pressure totaled ~8 to 10 cm H_2O (constant throughout the experiment), due to the auto-PEEP phenomenon.

Table 1. Experimental Ventilatory Settings

	High V_T		High RR		High PEEP	
Groups	L_P	H_P	L_P	H_P	L_P	H_P
Mechanical power (J/min)	13.6 ± 2.3	28.0 ± 2.7	14.3 ± 1.8	30.1 ± 2.9	13.4 ± 0.9	29.2 ± 3.0
	20.8 ± 7.9		22.2 ± 8.5		21.3 ± 8.5	
Energy per breath (J)	2.1 ± 0.8	1.9 ± 0.3	0.4 ± 0.1	0.7 ± 0.1	1.2 ± 0.1	1.4 ± 0.1
	2.0 ± 0.6		0.5 ± 0.2		1.3 ± 0.1	
V_T (ml/kg)	33.3 ± 5.2	32.2 ± 2.1	10.5 ± 1.2	14.5 ± 1.4	13.6 ± 1.1	13.1 ± 1.7
	32.7 ± 3.8		12.5 ± 2.4		13.4 ± 1.4	
RR (bpm)	7 ± 2	15 ± 2	40 ± 0	41 ± 2	11 ± 1	22 ± 1
	11 ± 5		40 ± 1		16 ± 6	
End-expiratory pressure (cm H_2O)	4.6 ± 0.5	5.9 ± 0.6	7.3 ± 0.8	9.4 ± 1.2	23.2 ± 0.6	24.8 ± 1.0
	5.3 ± 0.9		8.3 ± 1.5		24.0 ± 1.1	
Driving pressure (cm H_2O)	29.1 ± 6.1	26.1 ± 3.1	9.4 ± 1.1	13.1 ± 2.5	25.6 ± 2.4	30.9 ± 5.5
	27.6 ± 4.9		11.3 ± 2.7		28.3 ± 4.9	
Minute ventilation (l/min)	5.6 ± 0.6	11.5 ± 1.1	9.7 ± 0.9	14.4 ± 0.8	3.5 ± 0.3	6.9 ± 0.6
	8.6 ± 3.2		12.1 ± 2.6		5.2 ± 1.8	
Mean airway pressure (cm H_2O)	10.1 ± 1.2	14.9 ± 1.7	11.6 ± 0.8	15.4 ± 0.8	30.1 ± 1.8	37.6 ± 3
	12.5 ± 2.8		13.5 ± 2.1		33.9 ± 4.5	
Inspiratory flow (l/s)	35.3 ± 11.5	41.6 ± 12.1	31.4 ± 2.9	46.1 ± 4.8	13.0 ± 3.5	17.9 ± 3.0
	38.4 ± 11.8		38.8 ± 8.5		15.4 ± 4.0	
Inspiratory/ expiratory ratio	0.5 ± 0.4	0.7 ± 0.3	0.7 ± 0.2	0.7 ± 0.1	0.6 ± 0.3	0.9 ± 0.2
	0.6 ± 0.3		0.7 ± 0.1		0.7 ± 0.3	
Plateau airway pressure (cm H_2O)	33.7 ± 5.9	32.0 ± 2.8	16.6 ± 1.6	22.5 ± 1.8	48.9 ± 2.7	55.7 ± 5.4
	32.8 ± 4.5		19.6 ± 3.4		52.3 ± 5.4	
Resistive pressure (cm H_2O)	6.9 ± 3.2	7.2 ± 2	3.5 ± 0.6	6.0 ± 0.6	3.8 ± 1.7	4.3 ± 1.1
	7.0 ± 2.6		4.8 ± 1.5		4.1 ± 1.4	

Ventilatory parameters of the six experimental groups at the beginning of injurious ventilation. Values are expressed as mean ± SD. Groups are defined according to the principal component variable determining the mechanical power and according to the level of mechanical power. The ventilatory parameters are presented either referring to the six groups (seven pigs each), defined by two variables (principal component and power level, *lateral columns*) or referring to the three groups defined by one variable, the principal component, regardless of mechanical power (14 pigs per group, *central columns*). Of note, the set PEEP was 25 cm H_2O in the high PEEP groups and 5 cm H_2O in the other groups; however, the end-expiratory pressure could differ from the set PEEP due to air trapping (auto-PEEP). H_P, higher power; L_P, lower power; PEEP, positive end-expiratory pressure; RR, respiratory rate; V_T, tidal volume.

a two-sample independent *t* test for mechanical power level comparisons and independent sample one-way ANOVA for ventilatory strategy comparisons, Fisher's exact test was used to compare categorical variables. To evaluate the different time courses of mechanics, hemodynamics, and gas exchange variables among groups (repeated measures, excluding baseline values), we used a linear mixed model: the fixed effects are the ventilatory strategy (high V_T, high RR, high PEEP groups), the mechanical power (high and low groups), and the interactions between each of them and time, while the animals are the random effect. This model ignores the missing data, but produces outputs with the same numbers of observations compared with the original dataset. This model allowed detection if the time course of the given variable was significantly different among the power levels and ventilatory strategies. A linear regression was used to follow the changes of a given variable within a ventilatory strategy with time. *Post hoc* comparisons were conducted using Tukey's test. A *P* value less than 0.05 was considered statistically significant (two-tailed testing). Outliers were not excluded from the analyses. The end-experiment variables were the ones measured after 48 h (34 pigs) and the last measured before death in the pigs that died during the experimental procedure. Analyses were performed with R software version 3.5.2 (R Foundation for Statistical Computing, Austria, libraries Rcmdr, nlme, emmeans).

Results

Mechanical, hemodynamic, and gas exchange variables differed strikingly among the three ventilatory strategies, primarily due to the setting applied. Their time courses throughout the experiment are reported in detail in the Supplemental Digital Content, figures 2 to 25 (http://links.lww.com/ALN/C261).

High V_T Group

Mechanics. Altered mechanics were characterized by the obviously sudden increases of plateau pressure (from 14.0 ± 1.4 to 32.8 ± 4.5 cm H_2O), driving pressure (8.9 ± 1.4 to 27.6 ± 4.9 cm H_2O), and lung stress (6.8 ± 2.7 to 17.2 ± 4.7 cm H_2O). With time, all these variables worsened further. Indeed, the plateau pressure rose up to 37.8 ± 12.9 cm H_2O ($P = 0.025$; Supplemental Digital Content fig. 2, http://links.lww.com/ALN/C261), the driving pressure increased up to 32.5 ± 12.6 cm H_2O ($P = 0.037$;

Supplemental Digital Content fig. 3, http://links.lww.com/ALN/C261), and the lung stress reached 22.2 ± 9.8 cm H_2O (P = 0.003; Supplemental Digital Content fig. 4, http://links.lww.com/ALN/C261). The baseline lung elastance was 19.4 ± 6.7 cm H_2O/l and rose to 24.9 ± 11.5 cm H_2O/l over the 48-h period (P = 0.002; Supplemental Digital Content fig. 5, http://links.lww.com/ALN/C261). Of note, all of these variables were worse when ventilated at 30 J/min compared to 15 J/min, although they did not reach statistical significance (Supplemental Digital Content figs. 2 to 5, http://links.lww.com/ALN/C261). The strain immediately rose from 0.9 ± 0.2 to 2.5 ± 0.3 and increased over time up to 3.4 ± 1.0 (P < 0.001; Supplemental Digital Content fig. 6, http://links.lww.com/ALN/C261). Interestingly, the specific lung elastance remained nearly constant throughout the experiment from 7.2 ± 2.4 cm H_2O to 6.5 ± 1.7 cm H_2O (P = 0.839; Supplemental Digital Content fig. 7, http://links.lww.com/ALN/C261). The FRC steadily decreased over time from 385 ± 69 to 294 ± 75 ml (P = 0.001; Supplemental Digital Content fig. 8, http://links.lww.com/ALN/C261).

Hemodynamics. The cardiac output significantly decreased from 4.4 ± 0.8 to 3.3 ± 0.8 l/min (P = 0.001; Supplemental Digital Content fig. 12, http://links.lww.com/ALN/C261). The mean arterial pressure slightly but significantly decreased (from 76 ± 8 to 61 ± 9 mmHg, P = 0.001; Supplemental Digital Content fig. 13, http://links.lww.com/ALN/C261), pulmonary artery (Supplemental Digital Content fig. 14, http://links.lww.com/ALN/C261) and wedge pressures (Supplemental Digital Content fig. 15, http://links.lww.com/ALN/C261) remained unmodified, and central venous pressures slightly but significantly increased (Supplemental Digital Content fig. 16, http://links.lww.com/ALN/C261). No statistical differences were found in the time course of these variables, whether delivered either at 30 or at 15 J/min. The end-experiment fluid balance, however, was approximately 57% higher in the high-power group compared to the low-power group (8.2 ± 2.5 *vs.* 5.3 ± 2.8 l; Supplemental Digital Content fig. 17, http://links.lww.com/ALN/C261; P < 0.001). The difference of norepinephrine infusion between the high and low groups did not reach the statistical significance (Supplemental Digital Content fig. 18, http://links.lww.com/ALN/C261). This hemodynamic setting and this fluid strategy were associated with a linear increase of extravascular lung water from 289 ± 45 to 441 ± 112 ml (P < 0.001; Supplemental Digital Content fig. 19, http://links.lww.com/ALN/C261).

Gas Exchange. At the setting of the injurious ventilation, Pao_2 (Supplemental Digital Content fig. 21, http://links.lww.com/ALN/C261) remained high, while the partial pressure of CO_2 rapidly decreased to about 25 mmHg in the low-power group and about 15 mmHg in the high-power group (Supplemental Digital Content fig. 22, http://links.lww.com/ALN/C261) with proportional rises in pH (Supplemental Digital Content fig. 23, http://links.lww.com/ALN/C261). The physiologic dead space fraction significantly decreased from 50 to 30% (P < 0.001; Supplemental Digital Content fig. 24, http://links.lww.com/ALN/C261). Over time, the $Paco_2$ remained constant (P = 0.420), while the pH tended to normalize (P < 0.001). The Pao_2 was always greater than 200 mmHg, but slightly decreased over time (P = 0.005). The shunt fraction held near constant throughout the experiment at approximately 5% (Supplemental Digital Content fig. 25, http://links.lww.com/ALN/C261).

High RR Groups

Mechanics. After the application of the experimental ventilatory settings, the baseline plateau pressure (14.9 ± 1.4 cm H_2O), driving pressure (9.7 ± 1.2 cm H_2O), and lung stress (7.2 ± 2.1 cm H_2O) values immediately increased slightly, due to the appearance of auto-PEEP (up to 19.6 ± 3.4 cm H_2O, 11.3 ± 2.7 cm H_2O, and 7.3 ± 1.7 cm H_2O, respectively). Throughout the following 48 h, each of these variables sharply increased (P < 0.001 for all): plateau pressure up to 27.7 ± 7.0 cm H_2O (Supplemental Digital Content fig. 2, http://links.lww.com/ALN/C261), driving pressure up to 17.9 ± 5.0 cm H_2O (Supplemental Digital Content fig. 3, http://links.lww.com/ALN/C261), and lung stress up to 14.0 ± 4.7 cm H_2O (Supplemental Digital Content fig. 4, http://links.lww.com/ALN/C261). Lung elastance doubled over time from 22.2 ± 5.7 to 42.2 ± 18.7 cm H_2O (P < 0.001; Supplemental Digital Content fig. 5, http://links.lww.com/ALN/C261). The lung strain underwent a modest but significant increase from 1.0 ± 0.1 to 1.6 ± 1.0 after 48 h (P = 0.002; Supplemental Digital Content fig. 6, http://links.lww.com/ALN/C261). The specific lung elastance sharply increased after 24 h from a baseline value of 7.7 ± 2.6 up to 10.1 ± 3.9 cm H_2O (P < 0.001; Supplemental Digital Content fig. 7, http://links.lww.com/ALN/C261). The FRC significantly decreased with time (P < 0.001), similar to what was observed with the high V_T groups (Supplemental Digital Content fig. 8, http://links.lww.com/ALN/C261). Each of these variables behaved similarly at 15 and 30 J/min, with the exception of plateau pressure, which was higher in the high-power high RR group.

Hemodynamics. The cardiac output slightly decreased from 3.8 ± 0.7 to 3.2 ± 0.7 l/min (P = 0.054; Supplemental Digital Content fig. 12, http://links.lww.com/ALN/C261), as well as the mean arterial pressure (P < 0.001; Supplemental Digital Content fig. 13, http://links.lww.com/ALN/C261). In contrast, pulmonary artery (Supplemental Digital Content fig. 14, http://links.lww.com/ALN/C261), wedge (Supplemental Digital Content fig. 15, http://links.lww.com/ALN/C261), and central venous pressures (Supplemental Digital Content fig. 16, http://links.lww.com/ALN/C261) slightly but significantly increased (P = 0.008, 0.041, and 0.002 respectively). The

fluid balance and norepinephrine infusion rate were similar to the high V_T groups (Supplemental Digital Content figs. 17 and 18, http://links.lww.com/ALN/C261). The extravascular lung water increased at lower pace compared to the high V_T groups, but after 48 h reached similar values (rising from 264 ± 35 to 423 ± 184 ml, $P < 0.001$; Supplemental Digital Content fig. 19, http://links.lww.com/ALN/C261).

Gas Exchange. Pao_2 (Supplemental Digital Content fig. 21, http://links.lww.com/ALN/C261) remained constant throughout the experiment ($P = 0.938$), while arterial partial pressure of CO_2 (Supplemental Digital Content fig. 22, http://links.lww.com/ALN/C261) and pH (Supplemental Digital Content fig. 23, http://links.lww.com/ALN/C261) decreased, similar to the high V_T groups. The dead space fraction was significantly higher throughout the experiment than in high V_T groups (48.1 ± 7.6 *vs.* 31.8 ± 11.7%; Supplemental Digital Content fig. 24, http://links.lww.com/ALN/C261), while the shunt fraction (Supplemental Digital Content fig. 25, http://links.lww.com/ALN/C261) remained similarly constant at 5%.

High PEEP Groups

Mechanics. After applying 25 cm H_2O of PEEP, the plateau pressure sharply and immediately increased from 15.4 ± 2.4 up to 52.3 ± 5.4 cm H_2O, and the driving pressure rose from 10.2 ± 2.6 to 28.3 ± 4.9 cm H_2O, while the lung stress increased from 7.8 ± 2.8 to 32.1 ± 7.7 cm H_2O. No significant differences in these variables were found between higher- and lower-power categories. In contrast to the other two strategies, however, plateau pressure (Supplemental Digital Content fig. 2, http://links.lww.com/ALN/C261), driving pressure (Supplemental Digital Content fig. 3, http://links.lww.com/ALN/C261), and lung stress (Supplemental Digital Content fig. 4, http://links.lww.com/ALN/C261) progressively decreased until the end of the experiment, down to 44.8 ± 3.0, 20.3 ± 2.9, and 22.9 ± 5.7 cm H_2O, respectively ($P < 0.001$ for all). The lung elastance (Supplemental Digital Content fig. 5, http://links.lww.com/ALN/C261) immediately increased after the application of the high PEEP setting from 24.3 ± 8.2 to 64.4 ± 18.8 cm H_2O but later decreased down to 38.6 ± 14.1 cm H_2O ($P < 0.001$). The lung strain rose immediately from 1.0 ± 0.2 to 3.8 ± 0.6 after PEEP application, increased to a maximum of 5.7 ± 1.4 after 30 h, and stabilized to 5.2 ± 1.6 near the end of the experiment (Supplemental Digital Content fig. 6, http://links.lww.com/ALN/C261). The baseline specific lung elastance (7.8 ± 2.4 cm H_2O) after 24 h sharply decreased compared to the other ventilatory strategies, reaching a minimum of 4.5 ± 0.9 cm H_2O by the end of the experiment ($P < 0.001$; Supplemental Digital Content fig. 7, http://links.lww.com/ALN/C261). The FRC decreased earlier than in the other ventilatory strategies due to the low FRC recorded in the three pigs that developed pneumothorax; nonetheless, its values at the end of the experiment were similar to those of the other groups (from 351 ± 35 to 292 ± 67 ml; Supplemental Digital Content fig. 8, http://links.lww.com/ALN/C261).

Hemodynamics. The hemodynamic pattern in this group was sharply different from the two other ventilatory strategies: indeed, in pigs exposed to high mechanical power, the cardiac output remained remarkably constant from 3.9 ± 0.6 to 3.9 ± 1.0 l, whereas it rose from 4.1 ± 0.5 to 5.8 ± 1.9 l in pigs ventilated at lower mechanical power ($P < 0.001$; Supplemental Digital Content fig. 12, http://links.lww.com/ALN/C261). The average arterial pressure (Supplemental Digital Content fig. 13, http://links.lww.com/ALN/C261) was slightly but significantly lower in this group compared to the other ventilatory strategies (67 ± 9 mmHg *vs.* 73 ± 11 in high V_T strategy, $P = 0.017$, and 73 ± 11 mmHg in high RR strategy, $P = 0.013$). In contrast, pulmonary artery (Supplemental Digital Content fig. 14, http://links.lww.com/ALN/C261), wedge (Supplemental Digital Content fig. 15, http://links.lww.com/ALN/C261), and central venous pressures (Supplemental Digital Content fig. 16, http://links.lww.com/ALN/C261) were significantly 54%, 60%, and 60% higher than in the other two groups ($P < 0.001$). The fluid balance associated with this hemodynamic pattern was significantly greater than with the other two strategies (10.5 ± 1.6 l *vs.* 6.2 ± 1.2 l in the high V_T groups and 6.4 ± 1.5 l in the high RR groups, $P < 0.001$), but not statistically different between higher and lower power (Supplemental Digital Content fig. 17, http://links.lww.com/ALN/C261). In contrast, norepinephrine was given in significantly greater amounts only in the group with high PEEP delivered at low power (Supplemental Digital Content fig. 18, http://links.lww.com/ALN/C261). Epinephrine was needed in all the animals of this high PEEP group (Supplemental Digital Content fig. 20, http://links.lww.com/ALN/C261). The extravascular lung water increased similarly to the other two types of power-altering strategies (from 307 ± 55 to 415 ± 65 ml, $P < 0.001$; Supplemental Digital Content fig. 19, http://links.lww.com/ALN/C261).

Gas Exchange. Due to the ventilatory protocol, the partial pressure of CO_2 (Supplemental Digital Content fig. 22, http://links.lww.com/ALN/C261) was higher and the pH was lower (Supplemental Digital Content fig. 23, http://links.lww.com/ALN/C261) in this high PEEP strategy, particularly in the low-power group, where 25 cm H_2O of PEEP was associated with 0.32 l V_T at a RR of 11/min *versus* 0.32 l at a RR of 22/min. The Pao_2 was significantly lower in the low-power group compared to all the other groups, independent of strategy ($P = 0.001$; Supplemental Digital Content fig. 21, http://links.lww.com/ALN/C261). The dead space was significantly higher in the high-power group compared to the low-power group ($P = 0.002$; Supplemental Digital Content fig. 24, http://links.lww.com/ALN/C261). In general, dead space fraction was similar to that measured in high RR groups and significantly higher than measured in the high V_T groups.

The average shunt fraction (Supplemental Digital Content fig. 25, http://links.lww.com/ALN/C261) was significantly higher in the high PEEP, low-power group than high PEEP, high-power group (8.1 ± 5.3 *vs.* 3.7 ± 2.1, $P = 0.002$).

End-experiment Variables

No significant differences were found in lung weight among the three ventilatory strategies delivered at iso-mechanical power (fig. 2, right panel), averaging 26.6 ± 6.3, 23.7 ± 5.7, and 26.3 ± 4.9 g/kg in the high V_T, RR, and PEEP groups, respectively ($P = 0.341$). Similarly, the end-experiment lung weights were similar in pigs treated with high or low mechanical power, regardless of the ventilatory strategy, averaging 26.1 ± 6.3 and 24.9 ± 5.1 g/kg of body weight, respectively ($P = 0.508$; fig. 2, left panel). In table 2 we report lung, liver, bowel, kidney, and muscle wet-to-dry ratio, body weight gain, end-experiment fluid balance, pneumothorax, and death according to mechanical power level and ventilatory strategy. As shown, the wet-to-dry ratios of lungs, liver, bowel, and muscle were similar across the three ventilatory strategies, with the exception of the kidney wet-to-dry ratio, which was significantly greater in the high PEEP groups. No significant differences were found between high- and low-power groups. Notably, the animals treated with high PEEP had a body weight gain and cumulative fluid balance nearly double compared to the other groups. The composite adverse event markers (pneumothorax and death) were significantly worse in the high PEEP groups than in those of the other ventilatory strategies (Fisher exact test $P = 0.045$). In figure 3, upper panel, we summarize the histologic findings according to lung mechanical power: overall, no differences were found between mechanical power levels, with the exception of alveolar edema, which was significantly greater in the lower power groups. Similarly, no significant histologic differences were found among the three ventilatory strategies (fig. 3, lower panel). In figure 4, we report a representative histologic pattern we found with each ventilatory strategy delivered at different mechanical power. Histologic patterns that ranged from near-normal to near complete destruction of the lung structure coexisted in the same lung, regardless of the mechanical power or the ventilatory strategy (Supplemental Digital Content fig. 26, http://links.lww.com/ALN/C261).

Discussion

The main findings of this paper were as follows: (1) different ventilatory strategies produced different time courses of mechanical, hemodynamic, and gas exchange variables, partly influenced by the mechanical power level; (2) at

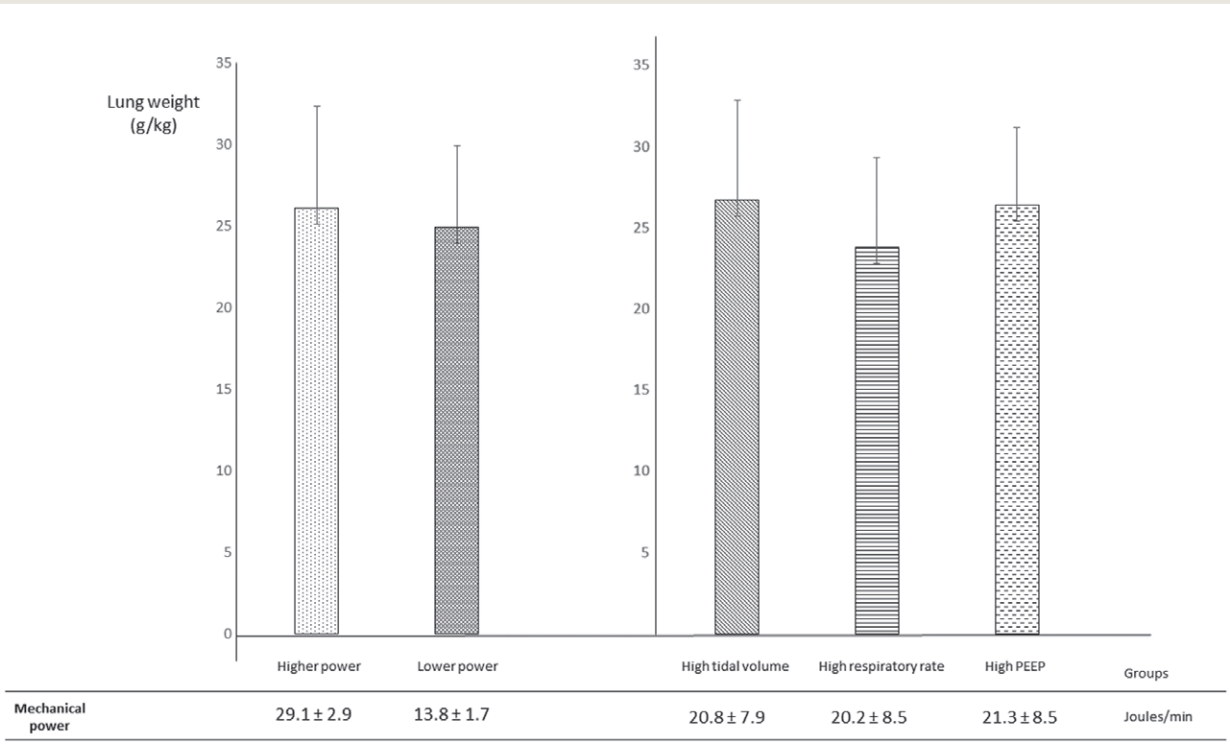

Fig. 2. (*Left*) Lung weight measured at the end of the experiment in the group of pigs treated with 30 J/min of mechanical power (n = 21) and the group of pigs treated with 15 J/min mechanical power (n = 21). (*Right*) The lung weights measured in the 14 pigs treated with a high tidal volume, high respiratory rate, and high positive end-expiratory pressure (PEEP). These three different ventilatory strategies were applied at an iso-mechanical power of ~21 J/min.

Table 2. Anatomical and Outcome Variables in the Experimental Groups

	Low Power (n = 21)	High Power (n = 21)	*P* Value	High V_T (n = 14)	High RR (n = 14)	High PEEP (n = 14)	*P* Value
Lung wet-to-dry ratio	6.7 ± 0.9	7.2 ± 1.3	0.215	7.4 ± 1.6	6.7 ± 0.6	6.7 ± 0.7	0.116
Liver wet-to-dry ratio	4.1 ± 0.5	4.1 ± 0.5	0.920	4.3 ± 0.6	4.0 ± 0.5	4.0 ± 0.4	0.138
Kidney wet-to-dry ratio	5.1 ± 1.2	5.5 ± 0.6	0.142	5.3 ± 0.9	4.8 ± 1.0	5.9 ± 0.7	0.012
Bowel wet-to-dry ratio	5.7 ± 0.9	5.6 ± 1.2	0.587	5.6 ± 0.6	5.9 ± 1.1	5.5 ± 1.3	0.541
Muscle wet-to-dry ratio	3.6 ± 0.7	3.8 ± 0.4	0.253	3.5 ± 0.5	3.9 ± 0.7	3.6 ± 0.5	0.359
Body weight gain (kg)	5.3 ± 2.9	6.0 ± 2.5	0.460	4.2 ± 1.9	4.4 ± 1.7	8.4 ± 2.0	<0.001
Fluid balance (l)	7.0 ± 2.6	7.7 ± 2.6	0.437	5.8 ± 2.2	6.4 ± 1.5	9.7 ± 2.1	<0.001
Pneumothorax	2	3	1	1	1	3	0.591
Death	3	5	0.697	3	0	5	0.068

Wet-to-dry ratios of lung, liver, kidney, bowel, and muscle. Body weight gain, fluid balance, pneumothorax and deaths in the 21 pigs each treated with higher mechanical power (30 J/min) and lower mechanical power (15 J/min). Wet-to-dry ratios of lung, liver, kidney, bowel, and muscle. Body weight gain, fluid balance, pneumothorax and deaths in group of 14 pigs each treated with high tidal volume (V_T), high respiratory rate (RR), and high positive end-expiratory pressure (PEEP) at iso-mechanical power (~21 J/min).

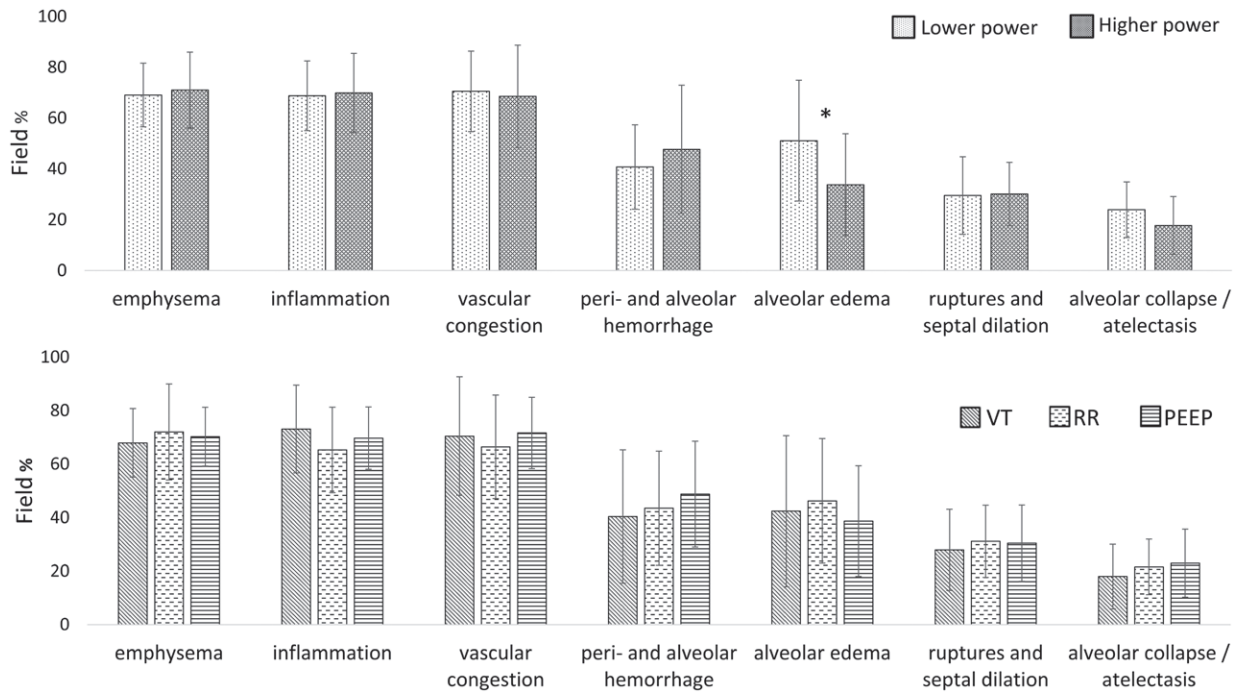

Fig. 3. Elementary histologic lesions according to applied mechanical power level (*top*) and ventilatory strategy (*bottom*). As shown, there were no statistically significant differences among groups, with the exception of alveolar edema, which was more extensive in the lower power groups ($P = 0.016$). PEEP, positive end-expiratory pressure; RR, respiratory rate; V_T, tidal volume.

iso-mechanical power, the anatomical lung damage caused by high V_T, high RR, or high PEEP interventions were indistinguishable.

Ventilatory Strategies

High V_T. The application of high V_T immediately elevated stress and strain, proportional to the level of mechanical power. Alterations of lung structure and inflammatory reaction accounted for the increase in extravascular lung water and decreased FRC. Interestingly, the specific lung elastance remained constant in this group, as found in patients with ARDS, where the "baby lung" maintains relatively normal intrinsic elastic properties.[18] In summary, the high V_T group showed the typical time course of ventilator-induced lung injury.

High RR. The ventilatory setting in this group was a combination of RR, V_T, and PEEP, which may be encountered in

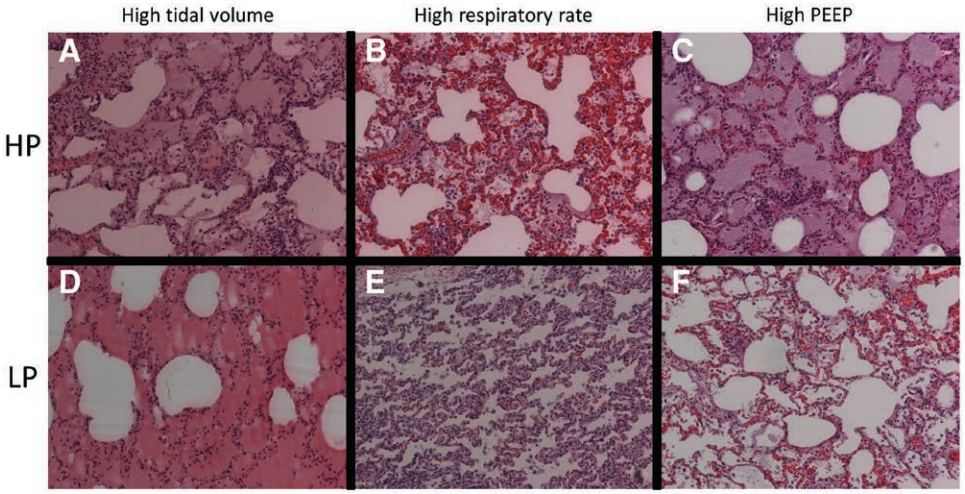

Fig. 4. Photomicrographs from each experimental group (*from right to left, from upper to lower*): (*A*) High tidal volume, high power (HP): pulmonary edema, with foci of emphysema and inflammatory alveolitis, focal microhemorrhages. (*B*) High respiratory rate, high power: emphysema and sparse foci of edema, intense perialveolar hyperemia with intraalveolar microhemorrages, extensive alveolitis with leukocytes, and epithelial cell sloughing. (*C*)High positive end-expiratory pressure (PEEP), high power: diffuse severe edema and sparse foci of emphysema; severe perialveolar hyperemia, intraalveolar inflammatory infiltrates with polynucleated neutrophils, focal intraalveolar hemorrhages. (*D*) High tidal volume, low power (LP): severe alveolar edema and foci of emphysema. Some alveoli show mild inflammation with alveolar cell sloughing and red cells lysis. (*E*) High respiratory rate, low power: moderate focal alveolar collapse, moderate perialveolar hyperemia, sparse intraalveolar cells, possibly from bronchial or alveolar sloughing. (*F*) High PEEP, low power: marked perialveolar hyperemia, diffuse emphysema, focal residues of edema, intralveolar inflammatory reaction, and cells from sloughing.

ARDS patients. The only immediate change of mechanical properties was attributable to an increase of 3 to 5 cm H_2O of auto-PEEP. All mechanical variables, however, sharply deteriorated thereafter, ending up with extravascular lung water and lung weight similar to that observed in the high V_T groups. After 24 h of treatment, the increase of specific lung elastance suggested a stiffening of the ventilatable lung, possibly due to the increased rate of stress and strain application and/or impaired surfactant functioning.[19,20]

High PEEP Groups. The application of high PEEP with two levels of mechanical power induced tremendous stress and strain. All pressures and lung elastance decreased with time, as did specific lung elastance, suggesting a progressive relaxation of the lung structural framework. Relaxation was also indicated by the increased strain, despite decreased stress.

In summary, the mechanics of the high V_T groups were characterized by decreased lung volume with normal intrinsic elastic properties; the high RR groups by decreased lung volume with stiffening of the lung structure; and high PEEP groups by decreased lung volume with structural relaxation of the lung. Whatever the ventilatory strategy, the trigger of ventilator-induced lung injury must be the "fracture" of molecular bonds in the extracellular matrix in excess of repair capability[21–23] with consequent inflammatory edema.[24] We may then wonder how such different ventilatory strategies might lead to the structural changes of the extracellular matrix. No doubt that extremely high V_T, as used in this work, may be accompanied by sufficient energy to induce rupture, particularly at the interface of lung regions with different elasticity (stress risers).[25–27] The injuring mechanism of low-level repeated stresses at high frequency might arise from a sort of progressive structural fatigue, in which cumulative stress may result in molecular breakdown of matrix elements. High PEEP applies an increased baseline stress to the extracellular matrix. A further stress added by the V_T may require energy sufficient to fracture the molecular bonds of the polymers in the matrix. Therefore, although the mechanism by which a critical energy over time is delivered to the extracellular matrix may differ among the ventilatory strategies we tested, it is not entirely surprising that a similar amount of energy would eventually lead to similar lung damage. Actually, the histologic findings, which documented the regional heterogeneity of damage, were indistinguishable within the ventilatory strategies.

The functional/structural alterations of the extracellular matrix unavoidably lead to alterations of the capillary/alveolar barrier anchored to it. Indeed, edema is the most widely used variable to quantify ventilator-induced lung injury. We must consider, however, that for edema to develop, structural/functional alteration of capillary/alveolar barrier alone does not act in isolation; hemodynamics may be as crucial as the structural lung damage itself. At the two extremes, edema may develop without any anatomical alterations

simply due to hydrodynamics,[28] while little or no edema would develop despite structural alteration if the capillary flow were reduced to near zero, as we have shown in experiments of regional perfusion block.[29] Accordingly, the ventilator-induced lung injury estimated by lung weight cannot be precisely interpreted without simultaneously considering the hemodynamic pattern. In this study we found a similar lung weight when the three ventilatory strategies were delivered at higher or lower levels of mechanical power. This unexpected finding indicates at first sight that 15 J/min are equally as damaging as 30 J/min. Alternatively, it is possible that more severe structural lung lesions induced by 30 J/min are associated with hemodynamic patterns less favorable to edema formation. The higher wedge pressure recorded at higher mechanical power (favoring edema formation, Supplemental Digital Content fig. 15, http://links.lww.com/ALN/C261) was associated with higher mean airway pressure (impeding edema formation, Supplemental Digital Content fig. 11, http://links.lww.com/ALN/C261). This combination may account for the greater extent of edema found in low-power groups, characterized by lower mean airway pressure. Also, the differences between this study and our previous one on mechanical power[8] may be discussed in the framework lung structure/hemodynamic interaction. In that earlier study, despite higher mechanical power (26.6 ± 12.1 *vs.* 21.8 ± 8.3 J/min, $P = 0.049$), the lung weight was lower (15.6 ± 5.2 *vs.* 25.5 ± 5.7 g/kg, $P < 0.001$). In the current study, however, increased fluid administration was needed to keep the animals alive (10.1 ± 2.3 *vs.* 4.2 ± 0.9 l). Several factors may account for this, primarily a different study design. Indeed, by protocol, in this study we applied significantly greater stress and strain. Moreover, due to a change of institutional policy for animal management, the average dose of propofol was increased in the current experiment (10.7 ± 2 *vs.* 8.2 ± 3.3 $mg \cdot kg^{-1} \cdot h^{-1}$ $P < 0.001$). Summarizing, while 15 and 30 J/min of mechanical power might induce different degrees of structural lung damage, the end result of structure/hemodynamic interactions occurring during management is ultimately similar. Therefore, 15 J/min of mechanical power is still far from being a safe "threshold" for ventilator-induced lung injury in this model.

Of particular interest regarding the lung structure/hemodynamic interaction is the ventilator-induced lung injury induced by high PEEP. In our study, the end-inspiratory lung volumes exceeded baseline total lung capacity (3 × FRC), potentially overcoming the physical limits of the lung's supporting architecture. Simultaneously, the animals of the high PEEP groups presented the most severe hemodynamic impairment and needed the greatest amount of fluid and cardiovascular support. The combination of higher fluid delivery and higher norepinephrine and epinephrine dosing led in this group to a hemodynamic pattern sharply different from the other two, characterized by higher cardiac output, lower systemic vascular resistances, and higher pulmonary artery and wedge pressures. It is likely that this distortion of normal hemodynamic profile accounts in part for the observed lung edema, extrapulmonary organ alterations (*e.g.*, higher kidney wet-to-dry ratio) and worsened outcomes observed in this group of animals.

Limitations

Apart from the concerns already expressed, we acknowledge that our model involved initially healthy pigs managed in their natural prone position. Our findings may well have differed if ventilation were applied to animals with preexisting acute lung injury or to those managed in the supine position. We believe that the greatest limitation, however, is that our study cannot elucidate two aspects of mechanical power, which are likely of paramount importance, *i.e.*, its distribution in time and space. At the same mean power, its damaging intensity could be concentrated at different times of the respiratory cycle[30] and, in injured lungs, at the interface of lung units with different elastic properties (stress risers).[22,31] Moreover, as our findings suggest, using one high iso-power strategy might initiate injury of a different kind or at a different pace than another, but over extended time, their end results may be indistinguishable.

Conclusions and Possible Clinical Implications

Conclusions drawn from experimental work designed to investigate mechanisms do not translate directly to the clinical scenario, as the interventions applied to prove or disprove our hypothesis were deliberately exaggerated. Few thoughtful physicians would routinely apply a V_T twice the FRC, 25 cm H_2O of PEEP, or a RR of 40 breaths per minute—especially not to nearly normal lungs. However, our results do provide key messages of clinical interest and potential impact: (1) that each major component of the ventilatory cycle may contribute impressively to lung damage; (2) that hemodynamics play a key role in the manifestations of ventilator-induced lung injury; and (3) that RR may strongly influence injury.

When discussing each of the variables separately, the unavoidable risk is to obscure the most important finding of the study: ventilator-induced lung injury primarily arises from a *combination* of variables and not from just one. Indeed, if we were to consider the single variables in isolation, from this study we should conclude that V_T values of 35 ml/kg and 10 ml/kg are equally dangerous, or (if one ignores the striking role of RR) that a driving pressure of 27 cm H_2O produces the same effects as a driving pressure of 10 cm H_2O. Our data strongly suggest that what really matters is the context in which the single variable operates, that all the variables must be considered together, and that their combined risk might be best quantified as mechanical power.

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Competing Interests

The authors declare no competing interests.

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References

1. Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000; 342:1301–8
2. Tsuno K, Prato P, Kolobow T: Acute lung injury from mechanical ventilation at moderately high airway pressures. J Appl Physiol (1985) 1990; 69:956–61
3. Kolobow T, Moretti MP, Fumagalli R, Mascheroni D, Prato P, Chen V, Joris M: Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. Am Rev Respir Dis 1987; 135:312–5
4. Protti A, Cressoni M, Santini A, Langer T, Mietto C, Febres D, Chierichetti M, Coppola S, Conte G, Gatti S, Leopardi O, Masson S, Lombardi L, Lazzerini M, Rampoldi E, Cadringher P, Gattinoni L: Lung stress and strain during mechanical ventilation: Any safe threshold? Am J Respir Crit Care Med 2011; 183:1354–62
5. Amato MB, Meade MO, Slutsky AS, Brochard L, Costa EL, Schoenfeld DA, Stewart TE, Briel M, Talmor D, Mercat A, Richard JC, Carvalho CR, Brower RG: Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372:747–55
6. Protti A, Maraffi T, Milesi M, Votta E, Santini A, Pugni P, Andreis DT, Nicosia F, Zannin E, Gatti S, Vaira V, Ferrero S, Gattinoni L: Role of strain rate in the pathogenesis of ventilator-induced lung edema. Crit Care Med 2016; 44:e838–45
7. Hotchkiss JR Jr, Blanch L, Murias G, Adams AB, Olson DA, Wangensteen OD, Leo PH, Marini JJ: Effects of decreased respiratory frequency on ventilator-induced lung injury. Am J Respir Crit Care Med 2000; 161(2 pt 1):463–8
8. Collino F, Rapetti F, Vasques F, Maiolo G, Tonetti T, Romitti F, Niewenhuys J, Behnemann T, Camporota L, Hahn G, Reupke V, Holke K, Herrmann P, Duscio E, Cipulli F, Moerer O, Marini JJ, Quintel M, Gattinoni L: Positive end-expiratory pressure and mechanical power. ANESTHESIOLOGY 2019; 130:119–30
9. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, Protti A, Gotti M, Chiurazzi C, Carlesso E, Chiumello D, Quintel M: Ventilator-related causes of lung injury: The mechanical power. Intensive Care Med 2016; 42:1567–75
10. Rohrer JJ: Der Zusammenhang der Atemkräfte und ihre Abhängigkeit von Dehnungszustand der Atmungsorgane [The relationship among respiratory variables and their dependence on the expansion of the respiratory system]. Pflügers Archiv- European Journal of Physiology 1916; 165:419–44
11. Huhle R, Serpa Neto A, Schultz MJ, Gama de Abreu M: Is mechanical power the final word on ventilator-induced lung injury?-No. Ann Transl Med 2018; 6:394
12. Serpa Neto A, Deliberato RO, Johnson AEW, Bos LD, Amorim P, Pereira SM, Cazati DC, Cordioli RL, Correa TD, Pollard TJ, Schettino GPP, Timenetsky KT, Celi LA, Pelosi P, Gama de Abreu M, Schultz MJ; PROVE Network Investigators: Mechanical power of ventilation is associated with mortality in critically ill patients: An analysis of patients in two observational cohorts. Intensive Care Med 2018; 44:1914–22
13. Fuller BM, Page D, Stephens RJ, Roberts BW, Drewry AM, Ablordeppey E, Mohr NM, Kollef MH: Pulmonary mechanics and mortality in mechanically ventilated patients without acute respiratory distress syndrome: A cohort study. Shock 2018; 49:311–6
14. Cressoni M, Gotti M, Chiurazzi C, Massari D, Algieri I, Amini M, Cammaroto A, Brioni M, Montaruli C, Nikolla K, Guanziroli M, Dondossola D, Gatti S, Valerio V, Vergani GL, Pugni P, Cadringher P, Gagliano N, Gattinoni L: Mechanical power and development of ventilator-induced lung injury. ANESTHESIOLOGY 2016; 124:1100–8
15. Araos J, Alegria L, Garcia P, Cruces P, Soto D, Erranz B, Amthauer M, Salomon T, Medina T, Rodriguez F, Ayala P, Borzone GR, Meneses M, Damiani F, Retamal J, Cornejo R, Bugedo G, Bruhn A: Near-apneic ventilation decreases lung injury and fibroproliferation in an acute respiratory distress syndrome model with extracorporeal membrane oxygenation. Am J Respir Crit Care Med 2019; 199:603–12

16. Protti A, Andreis DT, Milesi M, Iapichino GE, Monti M, Comini B, Pugni P, Melis V, Santini A, Dondossola D, Gatti S, Lombardi L, Votta E, Carlesso E, Gattinoni L: Lung anatomy, energy load, and ventilator-induced lung injury. Intensive Care Med Exp 2015; 3:34
17. Damia G, Mascheroni D, Croci M, Tarenzi L: Perioperative changes in functional residual capacity in morbidly obese patients. Br J Anaesth 1988; 60:574–8
18. Gattinoni L, Pesenti A: The concept of "baby lung". Intensive Care Med 2005; 31:776–84
19. Jorba I, Beltrán G, Falcones B, Suki B, Farré R, García-Aznar JM, Navajas D: Nonlinear elasticity of the lung extracellular microenvironment is regulated by macro-scale tissue strain. Acta Biomater 2019; 92:265–76
20. Suki B, Bates JH: A nonlinear viscoelastic model of lung tissue mechanics. J Appl Physiol (1985) 1991; 71:826–33
21. Tonetti T, Vasques F, Rapetti F, Maiolo G, Collino F, Romitti F, Camporota L, Cressoni M, Cadringher P, Quintel M, Gattinoni L: Driving pressure and mechanical power: New targets for VILI prevention. Ann Transl Med 2017; 5:286
22. Marini JJ, Gattinoni L: Energetics and the root mechanical cause for ventilator-induced lung injury. Anesthesiology 2018; 128:1062–4
23. Marini JJ, Rocco PRM, Gattinoni L: Static and dynamic contributors to VILI in clinical practice: Pressure, energy, and power. Am J Respir Crit Care Med 2019 (Epub ahead of print)
24. O'Neill LA: TLRs play good cop, bad cop in the lung. Nat Med 2005; 11:1161–2
25. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 1970; 28:596–608
26. Cressoni M, Cadringher P, Chiurazzi C, Amini M, Gallazzi E, Marino A, Brioni M, Carlesso E, Chiumello D, Quintel M, Bugedo G, Gattinoni L: Lung inhomogeneity in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2014; 189:149–58
27. Cressoni M, Chiurazzi C, Gotti M, Amini M, Brioni M, Algieri I, Cammaroto A, Rovati C, Massari D, di Castiglione CB, Nikolla K, Montaruli C, Lazzerini M, Dondossola D, Colombo A, Gatti S, Valerio V, Gagliano N, Carlesso E, Gattinoni L: Lung inhomogeneities and time course of ventilator-induced mechanical injuries. Anesthesiology 2015; 123:618–27
28. Guyton AC, Lindsey AW: Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema. Circ Res 1959; 7:649–57
29. Cambiaghi B, Vasques F, Mörer O, Ritter C, Mauri T, Kunze-Szikszay N, Holke K, Collino F, Maiolo G, Rapetti F, Schulze-Kalthoff E, Tonetti T, Hahn G, Quintel M, Gattinoni L: Effects of regional perfusion block in healthy and injured lungs. Intensive Care Med Exp 2017; 5:46
30. Schumann S, Goebel U, Haberstroh J, Vimlati L, Schneider M, Lichtwarck-Aschoff M, Guttmann J: Determination of respiratory system mechanics during inspiration and expiration by FLow-controlled EXpiration (FLEX): A pilot study in anesthetized pigs. Minerva Anestesiol 2014; 80:19–28
31. Santos RS, Maia LA, Oliveira MV, Santos CL, Moraes L, Pinto EF, Samary CDS, Machado JA, Carvalho AC, Fernandes MVS, Martins V, Capelozzi VL, Morales MM, Koch T, Gama de Abreu M, Pelosi P, Silva PL, Rocco PRM: Biologic impact of mechanical power at high and low tidal volumes in experimental mild acute respiratory distress syndrome. Anesthesiology 2018; 128:1193–206