Mechanical Power and Development of Ventilator-induced Lung Injury

Massimo Cressoni, M.D., Miriam Gotti, M.D., Chiara Chiurazzi, M.D., Dario Massari, M.D., Ilaria Algieri, M.D., Martina Amini, M.D., Antonio Cammaroto, M.D., Matteo Brioni, M.D., Claudia Montaruli, M.D., Klodiana Nikolla, M.D., Mariateresa Guanziroli, M.D., Daniele Dondossola, M.D., Stefano Gatti, M.D., Vincenza Valerio, Ph.D., Giordano Luca Vergani, M.D., Paola Pugni, M.D., Paolo Cadringher, M.Sc., Nicoletta Gagliano, Ph.D., Luciano Gattinoni, M.D., F.R.C.P.

ABSTRACT

Background: The ventilator works mechanically on the lung parenchyma. The authors set out to obtain the proof of concept that ventilator-induced lung injury (VILI) depends on the mechanical power applied to the lung.

Methods: Mechanical power was defined as the function of transpulmonary pressure, tidal volume (TV), and respiratory rate. Three piglets were ventilated with a mechanical power known to be lethal (TV, 38 ml/kg; plateau pressure, 27 cm H_2O; and respiratory rate, 15 breaths/min). Other groups (three piglets each) were ventilated with the same TV per kilogram and transpulmonary pressure but at the respiratory rates of 12, 9, 6, and 3 breaths/min. The authors identified a mechanical power threshold for VILI and did nine additional experiments at the respiratory rate of 35 breaths/min and mechanical power below (TV 11 ml/kg) and above (TV 22 ml/kg) the threshold.

Results: In the 15 experiments to detect the threshold for VILI, up to a mechanical power of approximately 12 J/min (respiratory rate, 9 breaths/min), the computed tomography scans showed mostly isolated densities, whereas at the mechanical power above approximately 12 J/min, all piglets developed whole-lung edema. In the nine confirmatory experiments, the five piglets ventilated above the power threshold developed VILI, but the four piglets ventilated below did not. By grouping all 24 piglets, the authors found a significant relationship between the mechanical power applied to the lung and the increase in lung weight (r^2 = 0.41, P = 0.001) and lung elastance (r^2 = 0.33, P < 0.01) and decrease in Pa_{O_2}/F_{IO_2} (r^2 = 0.40, P < 0.001) at the end of the study.

Conclusion: In piglets, VILI develops if a mechanical power threshold is exceeded. **(Anesthesiology 2016; 124:1100-8)**

VENTILATOR-INDUCED lung injury (VILI) has been described in various clinical[1] and experimental settings,[2] and several factors have been considered as possible triggers for VILI. Tidal volume (TV) and plateau pressure[2] have been studied most as surrogates of strain and stress, respectively.[3] Strain is the TV related to the lung size capable of being ventilated. Stress is the pressure that develops in the lung structure when a force is applied and is equal to the transpulmonary pressure applied to the lung. Other factors such as temperature,[4] respiratory rate,[5–7] and flow[8,9] have been described as cofactors for VILI. All these factors together generate the energy applied to the respiratory system, which, expressed per minute, is the mechanical power. Mechanical power acts directly on the lung skeleton, that is, the extracellular matrix, deforming the epithelial and endothelial cells anchored to it.[10] Depending on the amount of mechanical power, the alterations to the lung parenchyma may range from mechanical rupture[11,12] to an inflammatory reaction due to activation of macrophages,[13] neutrophils,[14] and endothelial and epithelial cells.[15,16]

What We Already Know about This Topic

- To minimize ventilator-associated lung injury, we avoid high tidal volume or driving pressure; however, the role of "power" (work applied to the lung per unit time) is uncertain.

What This Article Tells Us That Is New

- Twenty-four anesthetized piglets ventilated with a range of tidal volume and respiratory rate developed widespread lung injury above a threshold of 12 J/min. This finding suggests that mechanical power applied may be taken into account for ventilator-induced lung injury prevention.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication July 31, 2015. Accepted for publication January 20, 2016. From the Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy (M.C., M.G., C.C., D.M., I.A., M.A., A.C., M.B., C.M., K.N., M.G., G.L.V., P.P., P.C.); Centro di Ricerche Precliniche, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy (D.D., S.G.); Department of Anesthesiology and Intensive Care Medicine, Georg-August-University Goettingen, Goettingen, Germany (L.G.); and Dipartimento di Scienze Biomediche per la Salute, Università degli Studi di Milano, Milan, Italy (V.V., N.G.).

 Anesthesiology 2016; 124:1100-8

<zdoi;10.1097/ALN.0000000000001056>

In this study, we varied the power applied to the respiratory system by changing the respiratory rate while keeping the TV (strain) and transpulmonary pressure (stress) constant, which we knew was lethal at 15 breaths/min.[17–19] Our aim was to identify a power threshold for VILI. In a further series of experiments, we tested the power threshold hypothesis by applying power above and below the threshold and using computed tomography (CT) scans to measure VILI.[19]

Materials and Methods

Experimental Setting

We studied 24 healthy female piglets (21 ± 2 kg), using 15 piglets to investigate the power threshold for VILI and 9 for confirmatory experiments. This study was approved by the Italian Board of Health (Rome, Italy) and complied with international recommendations.[20] The piglets were instrumented with a tracheal tube, esophageal balloon, central venous catheter, arterial line, and urinary catheter (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259, for details).

Study Protocol

Power Threshold. Five groups of piglets (three piglets per each group) were ventilated in prone-Trendelenburg position[21] at the respiratory rates of 3, 6, 9, 12, or 15 breaths/min. Other respiratory variables were identical in all groups: namely, the inspiratory oxygen fraction (50%), the TV (38 ml/kg—strain greater than 2.5,[17] which had been previously shown to be lethal in 54 h[17–19]), the inspiratory:expiratory ratio (1:2), and end-expiratory pressure at 0 cm H_2O. This ventilatory setting generates inspiratory flows ranging from a minimum of 0.11 ± 0.02 l/s in piglets ventilated at 3 breaths/min to a maximum of 0.57 ± 0.08 l/s in piglets ventilated at 15 breaths/min. In these experiments, we did not attempt to control arterial carbon dioxide tension or pH because we had previously shown that these did not change the volume/strain threshold for VILI in this model.[17]

Confirmatory Experiments. After computing the possible mechanical power threshold for VILI (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259), we performed a second series of nine experiments with mechanical power below (four piglets) and above (five piglets) the threshold. In order to exclude any main effect of the respiratory rate on VILI development, we set the respiratory rate at 35 breaths/min in all the confirmatory experiments. In five of these confirmatory experiments (three above and two below the mechanical power threshold), we kept the $Paco_2$ in the physiological range by using an external supply. The four piglets treated with mechanical power below the threshold (8 ± 2 J/min) were ventilated for 54 h with F_{IO_2} 0.5, TV 11 ± 0.22 ml/kg, and respiratory rate 35 breaths/min. The five piglets treated with mechanical power above the threshold (22 ± 5 J/min) were ventilated with F_{IO_2} 0.5, TV 22 ± 4 ml/kg, and respiratory rate 35 breaths/min. Neither 11 nor 22 ml/kg TV induced lethal VILI when delivered at a respiratory rate of 15 breaths/min for 54 h.[17]

Measurements. At baseline and every 6 h or less, if changes occurred (*e.g.*, increase in peak/plateau pressure despite tracheal suctioning, decrease in peripheral saturation, and unexpected arterial hypotension or hypertension), we took two CT scans (end-expiration and end-inspiration pause), acquired dynamic and static pressure–volume curves of the respiratory system, and collected a complete set of physiological variables. A static pressure–volume curve was plotted in 100-ml steps (inflation and deflation) with a supersyringe, and a dynamic curve was acquired during tidal ventilation.

The study ended after 54 h of mechanical ventilation or if whole-lung edema developed, defined as densities occupying all CT scan lung fields. Piglets were euthanized with a KCl bolus and autopsied, and samples for lung pathology were collected.

Measured/computed variables were as follows: respiratory variables (peak, plateau, end-expiratory airway, and esophageal pressures; TV; and chest wall and lung elastances), gas-exchange variables (arterial and central venous P_{O_2}, P_{CO_2}, and pH), lactates, hemoglobin concentration and saturation, and hemodynamics (arterial and central venous pressure, urinary output, fluid intake, vasoactive drugs, and fluid balance) (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259, for details).

Stress Relaxation. We measured the following during the end-inspiratory pause (5-s duration):

- Peak pressure: highest pressure recorded
- P1: pressure recorded when inspiratory flow reached zero
- P2: pressure recorded at the end of the inspiratory pause

Stress relaxation is the observed decrease in stress in response to the same amount of strain generated in the structure and was defined as the difference between P1 and P2 (cm H_2O).

CT Scan Variables. CT scan variables were as follows: lung weight; lung gas volume; overinflated, normally inflated, poorly inflated, and noninflated lung tissue; and lung recruitment (percentage of lung tissue that regains inflation between end-expiration and end-inspiration pause).[22–24] Lung inhomogeneities were computed as previously described.[25] The lung was divided into six fields (apex–hilum–base and dependent/nondependent), and we visually classified the CT scan damage as follows[19]: grade 0, the baseline scan; grade 1, regions of density clearly distinguishable from the remaining parenchyma; grade 2, density occupying at least one lung field; and grade 3, density occupying all six fields (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259, for details).

Mechanical Power

The data were analyzed in terms of power delivered to the respiratory system, that is, the amount of energy delivered to the respiratory system by the ventilator in the time unit (J/min). The delivered energy per breath (airways + lung)

was defined as the area between the inspiratory limb of the Δ-transpulmonary pressure (x)–volume curve and the volume axis (y) and was measured in joule (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259, for computation of Δ-transpulmonary pressure–volume curve).

Statistical Methods. Sample size was determined on the basis of previous experience. We estimated a power threshold using the data from a previously published study.[17] We estimated a lethal TV threshold of 750 ml (approximately 34 ml/kg) when delivered at a respiratory rate of 15 breaths/min. As we set a TV of approximately 38 ml/kg, similar to the one used in a previous study,[19] we expected that piglets ventilated at respiratory rates of 12 and 15 breaths/min would develop VILI but that those ventilated at respiratory rates of 3 and 6 breaths/min would not. We were unable to make any prediction about the piglets ventilated at 9 breaths/min, but we estimated that—if the study hypothesis was confirmed—with at least six piglets treated below the threshold and six treated above the threshold, it would be sufficient to demonstrate changes in most of the CT scan and physiological variables.[17]

The relationship between mechanical power and severity of CT scan damage was assessed with the Spearman correlation. The effect of respiratory rate on physiological and CT scan variables at baseline was assessed with linear regression. In both cases, mechanical power was used as a continuous variable, CT scan damage was assessed as a categorical variable, and changes in oxygenation, lung elastance, and total lung weight were assessed as continuous variables. Changes in physiological variables between the start and the end of the confirmatory experiments in piglets ventilated with mechanical power above and below the threshold were compared using an unpaired *t* test. A *P* value of less than 0.05 was considered to indicate statistical significance. All tests were two tailed. Statistical analysis was done using R software.[26]

Results

The baseline physiological and CT scan variables at 3, 6, 9, 12, and 15 breaths/min are summarized in table 1. Owing to the different total ventilation, there were differences only in $Paco_2$ and pH, whereas oxygenation, mechanics, and CT scan-related variables were similar at all respiratory rates. pH was acidotic at the respiratory rate 3 breaths/min and alkalotic at 6, 9, 12, and 15 breaths/min. The transpulmonary mechanical power increased with the respiratory rate (mechanical power = delivered energy per breath × respiratory rate). Whereas the respiratory rate rose five-fold from 3 to 15 breaths/min, the mechanical power increased approximately 11 times from 2 ± 0.2 to 22 ± 2 J/min due to the effect of flow (table 2).

Table 1. Baseline Physiological Variables, Lung Mechanics, and CT Scan Parameters in Piglets

	RR 3	RR 6	RR 9	RR 12	RR 15		
	n = 3	n = 3	n = 3	n = 3	n = 3	*P* Value	r^2
Weight (kg)	21 ± 2	22 ± 2	21 ± 2	21 ± 2	20 ± 2	0.44	0.05
TV							
ml	775 ± 90	813 ± 71	825 ± 125	767 ± 29	800 ± 87	1	0
ml/kg	37 ± 4	38 ± 2	39 ± 2	37 ± 3	40 ± 0	0.27	0.09
Strain (TV/FRC)	3.0 ± 0.2	2.9 ± 0.4	2.5 ± 0.3	3.4 ± 0.6	2.1 ± 0.8	0.64	0.02
TV/tissue (ml/g)	2.0 ± 0.3	1.8 ± 0.1	2.2 ± 0.4	2.1 ± 0.1	2.1 ± 0.5	0.48	0.05
Peak pressure (cm H_2O)	31 ± 1	37 ± 5	40 ± 3	40 ± 4	46 ± 6	< 0.0001	0.74
Plateau pressure (cm H_2O)	27 ± 1	26 ± 1	26 ± 1	27 ± 2	27 ± 2	0.09	0.21
Transpulmonary pressure (cm H_2O)	18 ± 1	17 ± 4	15 ± 2	20 ± 2	19 ± 3	0.39	0.06
Pao_2/Fio_2	501 ± 81	526 ± 55	484 ± 35	531 ± 27	506 ± 88	0.9	0
pH	7.35 ± 0.13	7.56 ± 0.12	7.66 ± 0.06	7.65 ± 0.04	7.74 ± 0.08	< 0.001	0.64
$Paco_2$ (mmHg)	55 ± 16	29 ± 10	23 ± 7	21 ± 3	15 ± 5	< 0.001	0.61
Respiratory system elastance (cm H_2O/l)	33.2 ± 5.0	29.8 ± 5.3	29.0 ± 6.7	35.4 ± 2.4	34.1 ± 6.4	0.95	0
Lung elastance (cm H_2O/l)	24 ± 3	22 ± 6	19 ± 6	28 ± 1	26 ± 5	0.67	0.01
Chest wall elastance (cm H_2O/l)	9 ± 5	8 ± 4	10 ± 2	8 ± 3	8 ± 4	0.60	0.02
Mean arterial pressure (mmHg)	100 ± 24	96 ± 27	99 ± 8	95 ± 19	87 ± 28	0.47	0.04
Heart rate (beats/min)	98 ± 46	100 ± 13	128 ± 40	135 ± 15	113 ± 25	0.25	0.1
Total lung volume (ml)	670 ± 69	629 ± 53	716 ± 95	547 ± 37	814 ± 197	0.43	0.06
Total lung tissue (g)	403 ± 12	421 ± 36	386 ± 7	370 ± 15	389 ± 67	0.31	0.09
Well-inflated tissue (%)	21 ± 10	3 ± 2	38 ± 21	8 ± 7	52 ± 27	0.17	0.16
Poorly inflated tissue (%)	71 ± 9	87 ± 3	55 ± 17	78 ± 2	42 ± 26	0.11	0.21
Noninflated tissue (%)	8 ± 1	10 ± 1	7 ± 4	15 ± 9	6 ± 4	0.96	0
Inhomogeneity (%)	7.6 ± 1.7	8.6 ± 1.9	7.2 ± 3.6	9.8 ± 1.3	7.2 ± 3.7	0.94	0

Piglets are divided according to the respiratory rate (RR) (breaths/min). Data are mean ± SD. We tested the effect of increasing RR with linear regression to avoid type 2 error due to the small number of piglets in each group. Computed tomography (CT) scan was not available for two piglets (with RR 3 and RR 6 breaths/min). We reported the lung strain, defined as tidal volume (TV) divided by functional residual capacity (FRC), and the ratio of TV to lung tissue at the beginning of the study as it is the lung tissue that is deformed by TV.

Table 2. Energy per Breath and Mechanical Power at Different Respiratory Rates in Piglets

	RR 3	RR 6	RR 9	RR 12	RR 15		
	n = 3	n = 3	n = 3	n = 3	n = 3	*P* Value	r^2
Delivered dynamic transpulmonary energy per breath (J)	0.72 ± 0.081	1.2 ± 0.57	1.1 ± 0.29	1.1 ± 0.16	1.4 ± 0.1	0.02	0.35
Average inspiratory flow (l/s)	0.11 ± 0.02	0.24 ± 0.02	0.37 ± 0.07	0.43 ± 0.01	0.57 ± 0.08	< 0.0001	0.93
Mechanical power (transpulmonary) (J/min)	2 ± 0.2	7 ± 3	10 ± 3	14 ± 2	22 ± 2	< 0.0001	0.90

Piglets are divided according to the respiratory rate (RR). Data are mean ± SD. We tested the effect of increasing RR with linear regression to avoid type 2 error due to the small number of piglets in each group.

Development of VILI

The effects of the mechanical power on VILI are presented in figure 1A, which shows the severity of lung damage in relation to the mechanical power. Up to a mechanical power of approximately 12 J/min, CT scans showed mostly isolated densities, whereas above approximately 12 J/min, all piglets developed whole-lung edema. Figure 1B illustrates the nine confirmatory experiments performed below and above the VILI threshold. Piglets with normocapnia developed VILI when ventilated above the threshold. Table 3 summarizes the differences in the main physiological and CT scan features at the beginning and at the end of the study. Piglets ventilated with a mechanical power above the threshold had a larger increase in lung weight at the end of the study (412 ± 55 *vs.* 20 ± 47 g, $P < 0.0001$), greater lung elastance (59 ± 7 *vs.* 16 ± 9 cm H_2O/l, $P < 0.001$), and larger drop in oxygenation (−332 ± 59 *vs.* −20 ± 81 mmHg, $P < 0.001$).

Higher power at the beginning of mechanical ventilation was associated with increases in lung weight ($r^2 = 0.41$, $P = 0.001$) and elastance ($r^2 = 0.33$, $P = 0.003$) and a

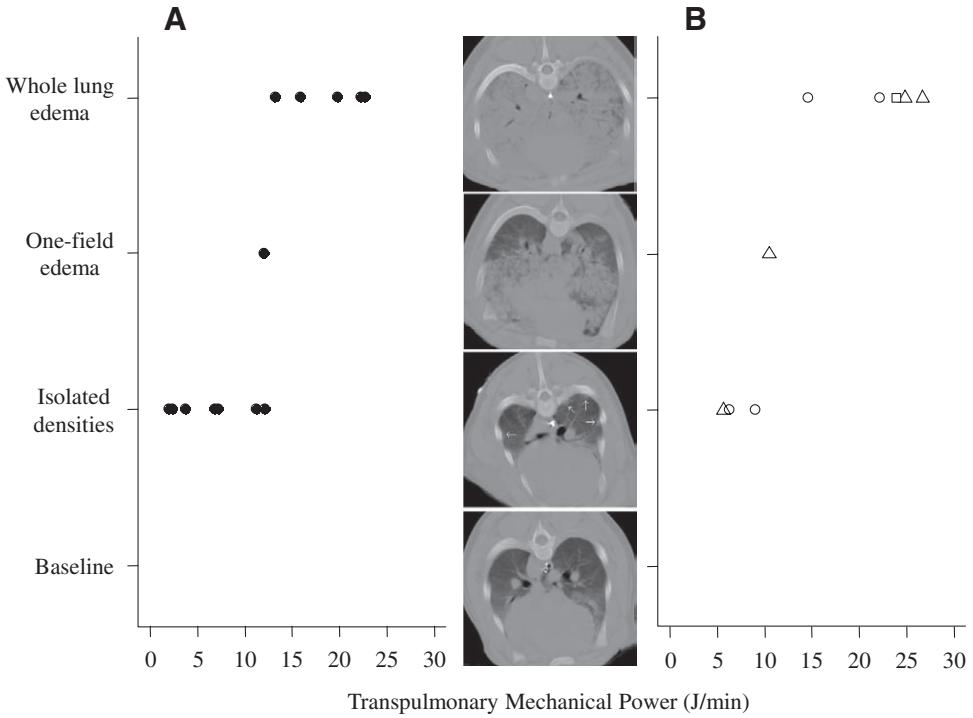

Fig. 1. Computed tomography (CT) scan showing lung damage in relation to transpulmonary mechanical power. The last expiratory CT scan acquired before the end of the study was qualitatively analyzed. Lung damage was rated as follows: grade 0 = baseline (no new lesions appeared during the study); grade 1 = isolated densities (new densities distinguishable from the surrounding parenchyma); grade 2 = one-field edema (edema occupying at least one of the six lung fields) (apex–hilum–base and dependent/nondependent); and grade 3 = whole-lung edema (edema in all lung fields). Lung-damage severity is plotted in relation to the transpulmonary mechanical power. (*A*) *Black dots* indicate 13 of the 15 piglets ventilated with high tidal volume and different respiratory rates (CT scan not available for two piglets). Spearman rank correlation was applied, giving a correlation coefficient (ρ) of 0.86 ($P < 0.001$). (*B*) Illustrates the nine confirmatory experiments (lower tidal volume and higher respiratory rate). *Circles* represent piglets ventilated without arterial carbon dioxide control, *triangles* represent piglets ventilated with arterial carbon dioxide control by variable supplementation, and the *square* represents the piglet that developed pneumothorax after the formation of a giant bulla. Spearman rank correlation was applied, giving a correlation coefficient (ρ) of 0.89 ($P = 0.001$).

Table 3. Physiological Variables, Energy Load, Lung Mechanics, and CT Scan Parameters in Piglets Ventilated with Mechanical Power below and above Threshold

	Low Mechanical Power < 12 J/Min; Tidal Volume 11 ± 0.22 ml/kg; Respiratory Rate 35 Breaths/Min (n = 4)	High Mechanical Power > 12 J/Min; Tidal Volume 22 ± 3.9 ml/kg; Respiratory Rate 35 Breaths/Min (n = 5)	*P* Value
Piglet weight (kg)	22 ± 5	24 ± 5	0.46
Transpulmonary energy per breath (J)	0.23 ± 0.065	0.64 ± 0.13	< 0.001
Mechanical power (J/min)	7.9 ± 2.3	22 ± 4.7	< 0.001
Average inspiratory flow (l/s)	0.42 ± 0.09	0.93 ± 0.21	< 0.01
Plateau pressure (cm H_2O)			
Start	14 ± 1	18 ± 2	
End	17 ± 2	50 ± 6	
Delta	3 ± 2	32 ± 6	< 0.001
Transpulmonary pressure (cm H_2O)			
Start	8 ± 1	10 ± 5	
End	12 ± 2	37 ± 5	
Delta	3 ± 3	27 ± 3	< 0.0001
Pa_{O_2}/F_{IO_2}			
Start	463 ± 46	510 ± 55	
End	444 ± 47	178 ± 88	
Delta	–20 ± 81	–332 ± 59	< 0.001
pH*			
Start	7.51 ± 0.108 / 7.43 ± 0.0339	7.75 ± 0.0198 / 7.45 ± 0.0387	
End	7.6 ± 0.0714 / 7.43 ± 0.00141	7.35 ± 0.0297 / 7.4 ± 0.0326	
Delta	0.04 ± 0.0638	–0.189 ± 0.2	0.06
Pa_{CO_2} (mmHg)*			
Start	39 ± 5 / 41 ± 2	16 ± 1 / 40 ± 5	
End	19 ± 2 / 43 ± 0	28 ± 1 / 45 ± 2	
Delta	–9 ± 12	8 ± 5	0.07
Respiratory system elastance (cm H_2O/l)			
Start	57 ± 9	40 ± 11	
End	72 ± 19	95 ± 17	
Delta	14 ± 11	55 ± 8	< 0.01
Lung elastance (cm H_2O/l)			
Start	38 ± 11	26 ± 15	
End	54 ± 15	85 ± 21	
Delta	16 ± 9	59 ± 7	< 0.001
Chest wall elastance (cm H_2O/l)			
Start	19 ± 2	14 ± 6	
End	18 ± 6	10 ± 5	
Delta	–1 ± 7	–4 ± 1	0.48
Total tissue (g)			
Start	337 ± 33	393 ± 71	
End	357 ± 31	781 ± 78	
Delta	20 ± 47	412 ± 55	< 0.0001
Inhomogeneity (% of lung volume)			
Start	7 ± 2	7 ± 2	
End	12 ± 2	26 ± 9	
Delta	5 ± 4	18 ± 11	0.09

P values are for unpaired *t* tests. Data are mean ± SD. One piglet (high mechanical power) was excluded from the mechanical and computed tomography (CT) scan data because it developed pneumothorax after the formation of a gigantic bulla.*pH and Pa_{CO_2} columns report separately the data for piglets in which arterial Pa_{CO_2} was not controlled (right column) and for those in which it was kept constant by variable supplementation (left column).

Delta = difference between the last recorded value (End) and the first recorded value (Start); End = last data collection; Start = first data collection after setting study tidal volume.

decrease in Pa_{O_2}/F_{IO_2} ($r^2 = 0.40$, $P < 0.001$) at the end of the experiment (fig. 2). All piglets ventilated with higher power developed full-blown (all-field lung) edema. The experiment ended after 34 ± 13 h.

In piglets treated with mechanical power below the threshold, the energy delivered by a single breath remained constant up to the end of the study. In contrast, in piglets where the mechanical power at baseline was greater than the threshold, the

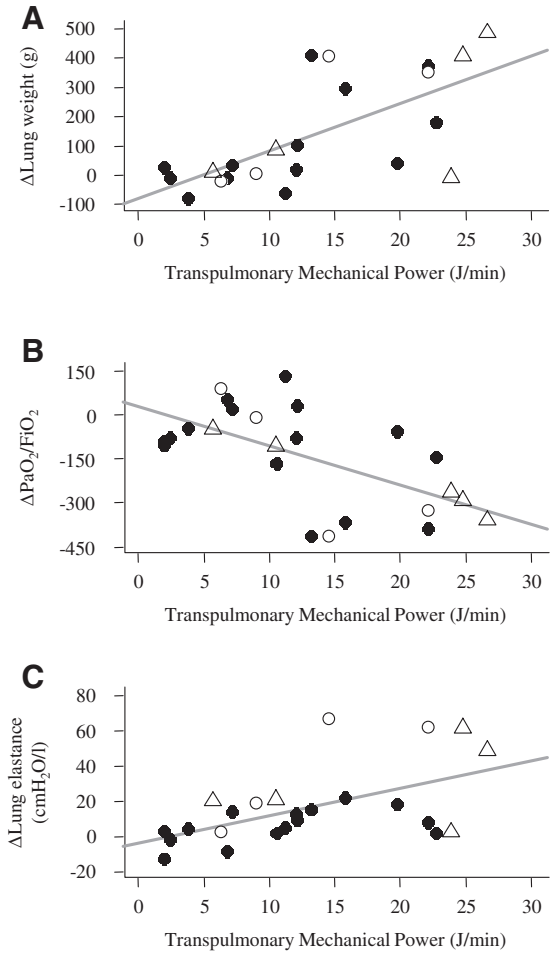

Fig. 2. Effects of transpulmonary mechanical power on lung weight, oxygenation, and lung mechanics in piglets. *Black circles* represent the 15 piglets ventilated with high tidal volume (approximately 38 ml/kg). Computed tomography (CT) scans of lung weights were available for 13 piglets. *Open symbols* indicate the nine confirmative experiments (lower tidal volume and higher respiratory rate). *Open circles* represent piglets ventilated without arterial carbon dioxide control, *triangles* represent piglets ventilated with arterial carbon dioxide control by variable supplementation. In confirmatory experiments, piglets were intubated with an endotracheal tube with internal diameter of 8 mm, so transpulmonary mechanical power is underestimated in confirmatory experiments in comparison with the main experiments. (*A*) Lung weights at the start (baseline expiratory CT scan) and at the end of the study (last expiratory CT scan). Δ Lung weight (g) = 69.5 + 14.8 × transpulmonary mechanical power (r^2 = 0.41, P = 0.001). (*B*) Pao_2/Fio_2 from the start to the end of the study. Δ Pao_2/Fio_2 = 28.7 − 13.1 × transpulmonary mechanical power (r^2 = 0.40, P < 0.001). (*C*) Lung elastance from the start to the end of the study. Δ Lung elastance (cm H_2O/l) = −4.11 + 1.41 × transpulmonary mechanical power (r^2 = 0.33, P < 0.01).

energy delivered by a single breath rose during the study (fig. 3). The increases in transpulmonary energy per breath were positively correlated with the worsening of lung strain (r^2 = 0.14, P < 0.0001), collapse and decollapse (r^2 = 0.23, P < 0.0001), and lung inhomogeneity (r^2 = 0.37, P < 0.0001) (fig. 4).

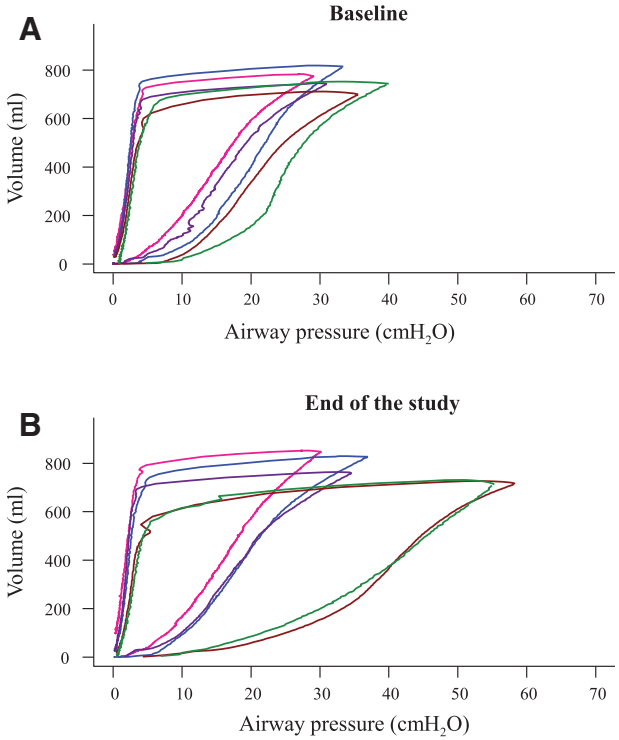

Fig. 3. Dynamic airways pressure–volume curves at different respiratory rates (RRs) in piglets. Each curve was obtained averaging airway pressure and volume for a single respiratory cycle in each group (RRs were 3 [magenta], 6 [violet], 9 [blue], 12 [dark red], and 15 [green] breaths/min). As each group comprised three piglets, each curve is the average of these, so we have five curves, one for each RR. At the higher RRs, by the end of the study, the inspiratory limb of the curve is shifted to higher pressures, indicating that the total delivered energy to the respiratory system is increased. This figure is purely representative as the expiratory limb of the curve is dependent only on expiratory flows and resistances. (*A*) Average airway pressure–volume curves at different RRs at baseline. The changes in total delivered energy to the respiratory system at different rates were analyzed with linear regression: total delivered energy to the respiratory system (J) = 1.109 + 0.043 × RR (r^2 = 0.28, P = 0.04). (*B*) Average airway pressure–volume curves at different RRs at the end of the study. The total delivered energy to the respiratory system at different rates was analyzed with linear regression: total delivered energy to the respiratory system (J) = 0.806 + 0.140 × RR (r^2 = 0.72, P < 0.0001).

Stress Relaxation

The transpulmonary energy per breath was associated with "stress relaxation," that is, the drop in airway pressure during an end-inspiratory pause (see fig. 11; Supplemental Digital Content 1, http://links.lww.com/ALN/B259).

Histology

Lungs of animals that did not develop ventilator-induced lung edema appeared macroscopically pink and normally inflated, with only small areas of atelectasis. In contrast,

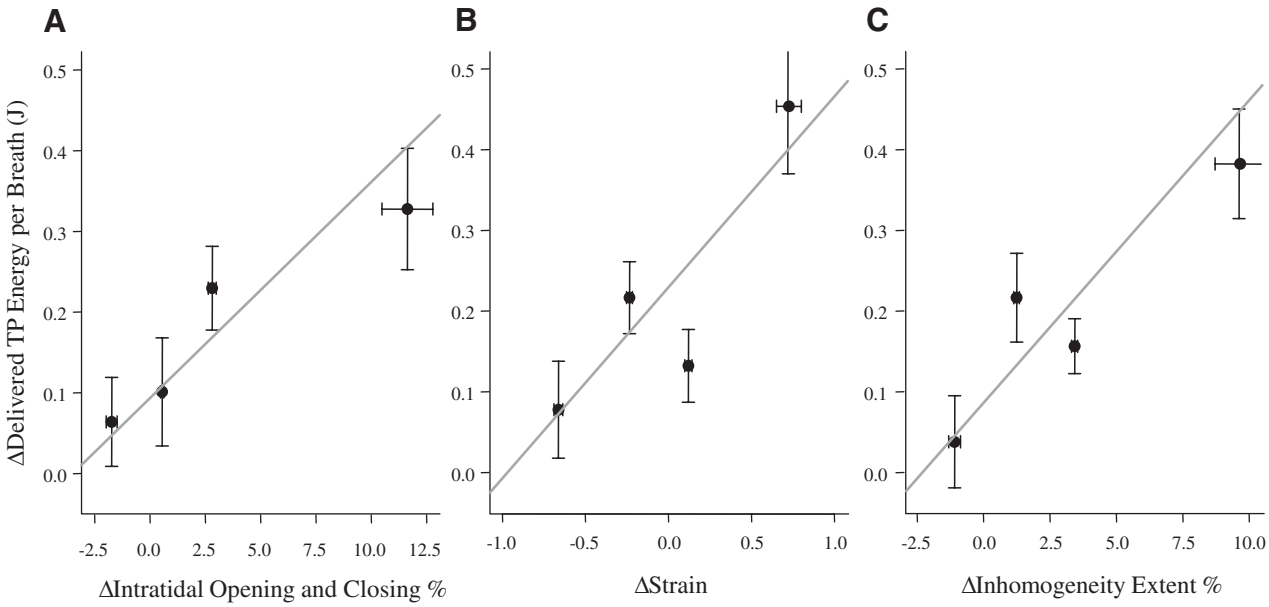

Fig. 4. Determinants of transpulmonary (TP) mechanical power. Transpulmonary mechanical power was computed from dynamic transpulmonary pressure–volume curves (collected throughout the study) and is presented in relation to three possible determinants of ventilator-induced lung injury. Changes from baseline in intratidal opening and closing, strain, and extent of lung inhomogeneities are divided into quartiles, and the changes in delivered dynamic transpulmonary energy are presented as mean ± standard error. Regression lines were not computed on means but on individual data points (see Supplemental Digital Content 1, http://links.lww.com/ALN/B259). (*A*) Δ Delivered dynamic transpulmonary energy (J) = 0.09 + 0.03 × Δ intratidal opening and closing (%), $r^2 = 0.23$, $P < 0.0001$. (*B*) Δ Delivered dynamic transpulmonary energy (J) = 0.23 + 0.24 × Δ strain, $r^2 = 0.14$, $P < 0.0001$. (*C*) Δ Delivered dynamic transpulmonary energy (J) = 0.08 + 0.04 × Δ lung inhomogeneity (%), $r^2 = 0.37$, $P < 0.0001$.

lungs of piglets that developed VILI were purple and congested. Blinded qualitative assessment indicated that histological changes (hyaline membranes, ruptured alveoli, and interstitial and intraalveolar infiltrate) tended to be more severe in piglets that developed ventilator-induced lung edema. However, the piglets that did not develop edema also presented relevant histological alterations (see table 7 and fig. 22 in the Supplemental Digital Content 1, http://links.lww.com/ALN/B259).

Discussion

In this study, we hypothesized that, for VILI to occur, what matters is the amount of energy delivered to the respiratory system in the unit of time (joule/min), that is, the mechanical power. In these healthy piglets, widespread edema developed only when the delivered transpulmonary mechanical power exceeded 12.1 J/min.

Mechanical ventilation, depending on the ventilator setting and the lung mechanics, is based on different combinations of TV, airway pressures, flows, and respiratory rates. We quantified these variables, together, as mechanical power. TV 2.5 times the functional residual capacity (38 ml/kg) resulted in lethal widespread edema within 54 h if delivered at a respiratory rate of 15 breaths/min,[17–19] with lesions starting at the interfaces between structures with different elasticity (stress raiser).[19] We postulated that VILI was not due to the TV *per se* but due to the mechanical power, that is, the product of TV, plateau pressure, and respiratory rate. To prove this theory, in the first 15 experiments, we lowered the respiratory rate: the TV that was lethal at 15 breaths/min was not lethal at 3, 6, and 9 breaths/min. This established the mechanical power threshold at approximately 12 J/min. The idea that lowering the respiratory rate might be beneficial, permitting lung rest and protection, has already been used clinically[27] and experimentally,[28,29] together with extracorporeal carbon dioxide removal. Those studies, however, did not focus directly on VILI as an endpoint. There are only a few reports of studies on the effect of respiratory rate on VILI, most of them finding that the higher the rate, the worse the damage.[5–7]

If the power is "excessive," then the chemical bonds of the polymers composing the extracellular matrix may be disrupted. This can be considered a kind of "extracellular matrix fatigue" in analogy with material fatigue, where microfractures result from cyclic application of mechanical power above a given threshold.[10] Furthermore, the microfractures of the polymers of the extracellular matrix produce low-molecular-weight hyaluronans, which may act as a trigger for both an inflammatory reaction[30] and repair processes.[30,31]

Our nine confirmatory experiments corroborated the mechanical power hypothesis. TVs of 11 and 22 ml/kg at a respiratory rate of 35 breaths/min produced mechanical power below and above the threshold, respectively. The piglets above the threshold developed VILI, whereas those below the threshold did not. These findings suggest that

neither the TV alone (38, 22, and 11 ml/kg) nor the respiratory rate (15 or 35 breaths/min) is the cause of VILI, which instead is induced by their combination when the mechanical power produced is higher than a certain threshold. In this experimental setting, quite likely because of the wide mechanical power variations induced, we could not find any difference with or without control of the P_{CO_2}. Increases in mechanical power were associated with a deterioration of the main CT scan variables, such as intratidal opening and closing,[32,33] lung strain,[3] and extent of lung inhomogeneity.[25] The damaged lung needed increased mechanical power to be ventilated at constant TV: the reduction of inflated lung, the decrease in open airways, and the increased collapse all lead to a rise in pressures and flows. This will result, for a given TV, in an increase in the delivered mechanical power, accelerating the vicious cycle that might partly explain the exponential increase of lung damage previously observed when we studied the time course of VILI.[19]

We may wonder to what extent the results of this study can be translated to a clinical scenario. The TV that we used largely exceeded that adopted in clinical practice (38 ml/kg as opposed to 6 ml/kg)[1]; however, in acute respiratory distress syndrome, the tissue open to ventilation becomes progressively less in proportion to severity. Consequently, with lower TV, levels of strain may be similar.[3] Moreover, stress raisers may worsen the whole situation.[25,34] The basic concept of the lung-protective strategy, in our opinion, is to provide the lowest possible mechanical power while maintaining the lung as homogenous as possible by prone positioning[35] and "adequate" positive end-expiratory pressure.[36] Although the TV concept is well accepted in the lung-protective framework,[37] less attention has been paid to the respiratory rate. Too high a respiratory rate may well cause damage, even if the TV is at least partly reduced. High-frequency oscillations,[38] as an example, may at first glance seem a safe form of support, as the delta-volume is low. However, the energy required to oscillate the system may be so high as to exceed the energy threshold for VILI. Therefore, in our opinion, paying attention to mechanical power might help extending our focus on VILI, taking into account not only the TV and driving pressure, as recently suggested,[39] but also the flows and the respiratory rate and—maybe more important—their combination. Thus, any reduction in any component of the cyclic mechanical power should lower the risk of VILI.

Acknowledgments

The authors thank Patrizia Minunno (Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Milan, Italy) for valuable logistic support; Fabio Ambrosetti (Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy) for technical assistance; Greta Rossignoli, M.D., and Cristina Rovati, M.D. (Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Università degli Studi di Milano), for assistance in the experiment; and Massimo Monti, M.D., and Manuela Chiodi, M.D. (Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Fondazione IRCCS Ca' Granda-Ospedale Maggiore Policlinico, Università degli Studi di Milano), for technical assistance with computed tomography scan analysis.

Supported by European Society of Intensive Care Medicine 2014 Clinical Research Award (Bruxelles, Belgium; to Dr. Cressoni) and by institutional funds.

Competing Interests

Dr. Cressoni, Mr. Cadringher, and Dr. Gattinoni hold an Italian patent for determination of lung inhomogeneities (0001409041) and have applied for European and U.S. patents. The other authors declare no competing interests.

Correspondence

Address correspondence to Dr. Gattinoni: Department of Anesthesiology and Intensive Care Medicine, Georg-August-University Goettingen, Robert-Koch-Street 40, 37075 Göttingen, Goettingen, Germany. gattinoniluciano@gmail.com.

References

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000; 342:1301–8
2. Dreyfuss D, Saumon G: Ventilator-induced lung injury: Lessons from experimental studies. Am J Respir Crit Care Med 1998; 157:294–323
3. Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 2008; 178:346–55
4. Suzuki S, Hotchkiss JR, Takahashi T, Olson D, Adams AB, Marini JJ: Effect of core body temperature on ventilator-induced lung injury. Crit Care Med 2004; 32:144–9
5. 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
6. Rich PB, Reickert CA, Sawada S, Awad SS, Lynch WR, Johnson KJ, Hirschl RB: Effect of rate and inspiratory flow on ventilator-induced lung injury. J Trauma 2000; 49:903–11
7. Rich PB, Douillet CD, Hurd H, Boucher RC: Effect of ventilatory rate on airway cytokine levels and lung injury. J Surg Res 2003; 113:139–45
8. Simonson DA, Adams AB, Wright LA, Dries DJ, Hotchkiss JR, Marini JJ: Effects of ventilatory pattern on experimental lung injury caused by high airway pressure. Crit Care Med 2004; 32:781–6
9. Fujita Y, Fujino Y, Uchiyama A, Mashimo T, Nishimura M: High peak inspiratory flow can aggravate ventilator-induced lung injury in rabbits. Med Sci Monit 2007; 13:BR95–100
10. Gattinoni L, Carlesso E, Cadringher P, Valenza F, Vagginelli F, Chiumello D: Physical and biological triggers of ventilator-induced lung injury and its prevention. Eur Respir J Suppl 2003; 47:15–25s
11. Hotchkiss JR, Simonson DA, Marek DJ, Marini JJ, Dries DJ: Pulmonary microvascular fracture in a patient with

acute respiratory distress syndrome. Crit Care Med 2002; 30:2368–70

12. Gammon RB, Shin MS, Buchalter SE: Pulmonary barotrauma in mechanical ventilation: Patterns and risk factors. Chest 1992; 102:568–72
13. Frank JA, Wray CM, McAuley DF, Schwendener R, Matthay MA: Alveolar macrophages contribute to alveolar barrier dysfunction in ventilator-induced lung injury. Am J Physiol Lung Cell Mol Physiol 2006; 291:L1191–8
14. Belperio JA, Keane MP, Burdick MD, Londhe V, Xue YY, Li K, Phillips RJ, Strieter RM: Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. J Clin Invest 2002; 110:1703–16
15. Vlahakis NE, Hubmayr RD: Invited review: Plasma membrane stress failure in alveolar epithelial cells. J Appl Physiol (1985) 2000; 89:2490–6; discussion 2497
16. Vlahakis NE, Hubmayr RD: Response of alveolar cells to mechanical stress. Curr Opin Crit Care 2003; 9:2–8
17. 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
18. Protti A, Andreis DT, Monti M, Santini A, Sparacino CC, Langer T, Votta E, Gatti S, Lombardi L, Leopardi O, Masson S, Cressoni M, Gattinoni L: Lung stress and strain during mechanical ventilation: Any difference between statics and dynamics? Crit Care Med 2013; 41:1046–55
19. 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
20. National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals: Guide for the Care and Use of Laboratory Animals, 8th edition. Washington, D.C., National Academies Press (US), 2011
21. Zanella A, Cressoni M, Epp M, Hoffmann V, Stylianou M, Kolobow T: Effects of tracheal orientation on development of ventilator-associated pneumonia: An experimental study. Intensive Care Med 2012; 38:677–85
22. Gattinoni L, Pesenti A, Avalli L, Rossi F, Bombino M: Pressure-volume curve of total respiratory system in acute respiratory failure: Computed tomographic scan study. Am Rev Respir Dis 1987; 136:730–6
23. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, Russo S, Patroniti N, Cornejo R, Bugedo G: Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med 2006; 354:1775–86
24. Gattinoni L, Chiumello D, Cressoni M, Valenza F: Pulmonary computed tomography and adult respiratory distress syndrome. Swiss Med Wkly 2005; 135:169–74
25. 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
26. R Development Core Team: R: A Language and Environment for Statistical Computing. Vienna, Austria, 2010. Available at: http://www.R-project.org/. Accessed January 21, 2016
27. Gattinoni L, Pesenti A, Mascheroni D, Marcolin R, Fumagalli R, Rossi F, Iapichino G, Romagnoli G, Uziel L, Agostoni A: Low-frequency positive-pressure ventilation with extracorporeal CO_2 removal in severe acute respiratory failure. JAMA 1986; 256:881–6
28. Cressoni M, Zanella A, Epp M, Corti I, Patroniti N, Kolobow T, Pesenti A: Decreasing pulmonary ventilation through bicarbonate ultrafiltration: An experimental study. Crit Care Med 2009; 37:2612–8
29. Zanella A, Castagna L, Salerno D, Scaravilli V, Abd El Aziz El Sayed Deab S, Magni F, Giani M, Mazzola S, Albertini M, Patroniti N, Mantegazza F, Pesenti A: Respiratory electrodialysis: A novel, highly efficient extracorporeal CO_2 removal technique. Am J Respir Crit Care Med 2015; 192:719–26
30. Jiang D, Liang J, Fan J, Yu S, Chen S, Luo Y, Prestwich GD, Mascarenhas MM, Garg HG, Quinn DA, Homer RJ, Goldstein DR, Bucala R, Lee PJ, Medzhitov R, Noble PW: Regulation of lung injury and repair by Toll-like receptors and hyaluronan. Nat Med 2005; 11:1173–9
31. Pelosi P, Rocco PR: Effects of mechanical ventilation on the extracellular matrix. Intensive Care Med 2008; 34:631–9
32. Muscedere JG, Mullen JB, Gan K, Slutsky AS: Tidal ventilation at low airway pressures can augment lung injury. Am J Respir Crit Care Med 1994; 149:1327–34
33. Caironi P, Cressoni M, Chiumello D, Ranieri M, Quintel M, Russo SG, Cornejo R, Bugedo G, Carlesso E, Russo R, Caspani L, Gattinoni L: Lung opening and closing during ventilation of acute respiratory distress syndrome. Am J Respir Crit Care Med 2010; 181:578–86
34. Mead J, Takishima T, Leith D: Stress distribution in lungs: A model of pulmonary elasticity. J Appl Physiol 1970; 28:596–608
35. Gattinoni L, Taccone P, Carlesso E, Marini JJ: Prone position in acute respiratory distress syndrome: Rationale, indications, and limits. Am J Respir Crit Care Med 2013; 188:1286–93
36. Cressoni M, Chiumello D, Carlesso E, Chiurazzi C, Amini M, Brioni M, Cadringher P, Quintel M, Gattinoni L: Compressive forces and computed tomography-derived positive end-expiratory pressure in acute respiratory distress syndrome. Anesthesiology 2014; 121:572–81
37. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS; ARDS Definition Task Force: Acute respiratory distress syndrome: The Berlin Definition. JAMA 2012; 307:2526–33
38. Slutsky AS, Drazen JM: Ventilation with small tidal volumes. N Engl J Med 2002; 347:630–1
39. 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