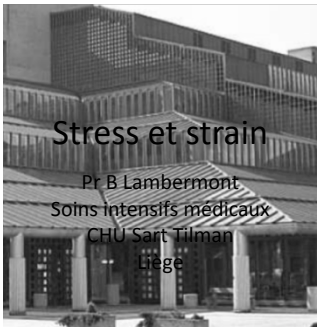
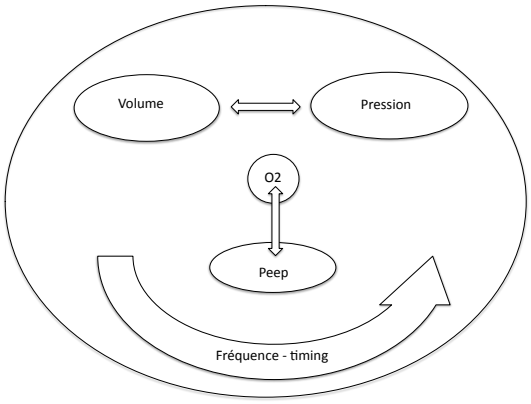


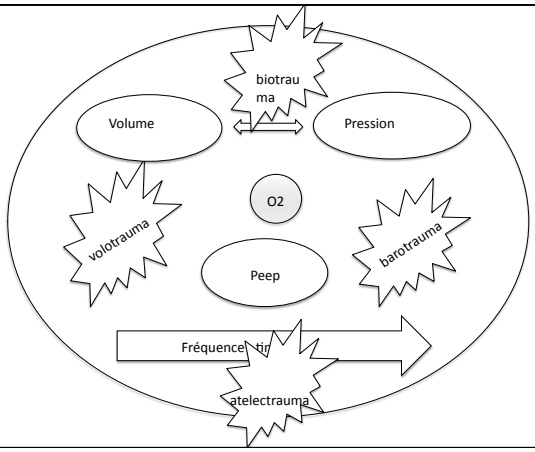
Stress et strain

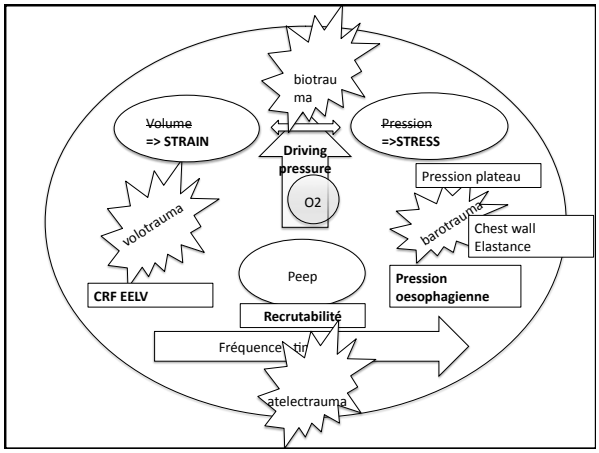
Pr B Lambermont
Soins intensifs médicaux
CHU Sart Tilman
Liège

Plan de l'exposé

- Définition
- Stress strain et VILI
- Aspects expérimentaux
- Aspects cliniques
- Aspects pratiques







La ventilation protectrice : pas si simple…

- Quels réglages appliquer?
  - Quel volume: 6ml/kg? Pour quel poumon?
  - Quelle pression?: plateau 30 cmH2O? Cela correspond à quelle pression transpulmonaire?
  - Quelle peep? Recrutement ou surdistension alvéolaire? Niveau optimal

=> Nécessité de tenir compte d'autres paramètres car la CRF et l'élastance thoracique sont variables:

Le strain, statique, dynamique, strain rate

Le stress pulmonaire

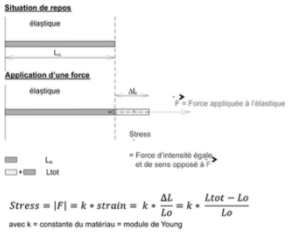
La recrutabilité

La driving pressure

Stress et strain

- Modèle linéaire : l'élastic
- Modèle à trois dimensions: le poumon

Modèle linéaire

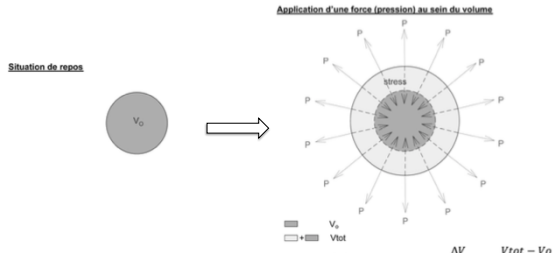


$$Stress = |F| = k * strain = k * \frac{\Delta L}{Lo} = k * \frac{Ltot - Lo}{Lo}$$

avec k = constante du matériau = module de Young

Fig. 1 Concept de *stress et strain* dans un modèle linéaire. F : force appliquée ; L_0 : longueur initiale ; L_{tot} : longueur totale ; ΔL : variation de longueur ; k : constante du matériau = module de Young

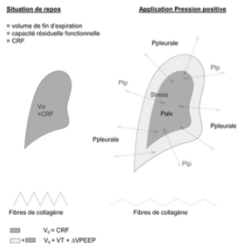
Modèle volumétrique



$$Stress = |P| = k * strain = k * \frac{\Delta V}{Vo} = k * \frac{Vtot - Vo}{Vo}$$

Fig. 2 Concept de *stress et strain* dans un modèle volumétrique. F : force appliquée ; V_0 : volume initial ; V_{tot} : volume total ; ΔV : variation de volume ; k : constante du matériau = module de Young

Stress et strain appliqués au poumon



stress = élastance spécifique x (VT + ΔVPEP)/CRF

Fig. 3 Concept de *stress et strain* appliqué au poumon. Palv : pression alvéolaire ; Ptp : pression transpulmonaire ; VT : volume courant ; ΔVPEP : augmentation de volume expiratoire induite par la PEP ; CRF : capacité résiduelle fonctionnelle

La mesure du stress pulmonaire

- Stress = Ptranspulmonaire = Palvéolaire – Ppleurale
- Pplateau = Ptranspulmonaire téléinspiratoire + Ppleurale téléinspiratoire
- Stress max = Ptranspulmonaire téléinspiratoire = **Pplateau – Ppleurale téléinspiratoire**
- Ptranspulmonaire téléinspiratoire = Pplateau × EL/ERS

Le strain

- Strain = ΔV/CRF
- Strain = Vt/CRF si Peep = 0
- Strain = (VT + ΔVPEP)/CRF
- Strain = 1 => volume pulmonaire aéré de fin d'inspiration = CRF x2
- Strain = 2 => volume pulmonaire aéré de fin d'inspiration = CRF x 3 = CPT

La mesure du strain

- Scanner thoracique
- Technique de dilution à l'helium
- Washin-washout azote (Engström Care Station-GE)

Données expérimentales

Intensive Care Med (2011) 37:1913–1920
DOI 10.1007/s00134-011-2388-9

ORIGINAL

Time to generate ventilator-induced lung injury among mammals with healthy lungs: a unifying hypothesis

Pietro Caironi
Thomas Langer
Eleonora Carlesso
Alessandro Protti
Luciano Gattinoni

Received: 8 November 2010
Accepted: 5 August 2011
Published online: 4 November 2011

This article is discussed in the editorial available at:
doi:10.1007/s00134-011-2394-y.

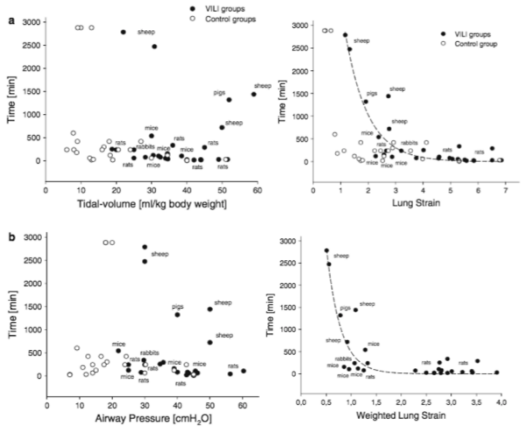
Electronic supplementary material
The online version of this article (doi:10.1007/s00134-011-2388-9) contains supplementary material, which is available to authorized users.

P. Caironi · T. Langer · E. Carlesso · A. Protti · L. Gattinoni
Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan, Italy

L. Gattinoni (✉)
Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, Fondazione IRCCS—Ospedale Maggiore Policlinico, Mangiagalli, Regina Elena di Milano, Università degli Studi di Milano, Via F. Sforza 35, 20122 Milan, Italy
e-mail: gattinon@policlinico.mi.it
Tel.: +39-2-55033232
Fax: +39-2-55033230

Abstract *Purpose:* To investigate ventilator-induced lung injury (VILI), several experimental models were designed including different mammalian species and ventilator settings, leading to a large variability in the observed time-course and injury severity. We hypothesized that the time-course of VILI may be fully explained from a single perspective when considering the insult actually applied, i.e. lung stress and strain. *Methods:* Studies in which healthy animals were aggressively ventilated until pretermINal VILI were selected via a Medline search. Data on morphometry, ventilator settings, respiratory function and duration of ventilation were derived. For each animal group, lung stress (transpulmonary pressure) and strain (end-inspiratory lung inflation/lung resting volume ratio) were estimated. *Results:* From the Medline search 20 studies including five mammalian species (sheep, pigs, rabbits, rats, mice) were selected. Time to achieve preterminal VILI varied widely (18–2,784 min), did not correlate with either tidal volume (expressed in relation to body weight) or airway pressure applied, but was weakly associated with lung stress ($r^2 = 0.25$, $p = 0.008$). In contrast, the duration of mechanical ventilation was closely correlated with both lung strain ($r^2 = 0.85$, $p < 0.0001$) and lung strain weighted for the actual time of application during each breath ($r^2 = 0.83$, $p < 0.0001$), according to exponential decay functions. When it was normalized for the lung strain applied, larger species showed a greater resistance to VILI than smaller species (medians, 25th–75th percentiles: 690, 460–2,001 min vs. 16, 4–59 min, respectively; $p < 0.001$). *Conclusion:* Lung strain may play a critical role as a unifying rule describing the development of VILI among mammals with healthy lungs.

Keywords Ventilator-induced lung injury · Mechanical ventilation · Lung stress · Lung strain · Comparative physiology



Lung Stress and Strain during Mechanical Ventilation
Any Safe Threshold?

Alessandro Protti[1], Massimo Cressoni[1], Alessandro Santini[1], Thomas Langer[1], Cristina Mietto[1], Daniela Febres[1], Monica Chierichetti[1], Silvia Coppola[1], Grazia Conte[2], Stefano Gatti[2], Orazio Leopardi[1], Serge Masson[3], Luciano Lombardi[4], Marco Lazzerini[4], Erica Rampoldi[5], Paolo Cadringher[1], and Luciano Gattinoni[1,6]

[1]Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, and [2]Centro di Ricerche Chirurgiche Precliniche, Università degli Studi di Milano, Milan, Italy; [3]Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; and [4]Dipartimento di Radiologia, [5]Unità Operativa Laboratorio Centrale, and [6]Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

Lung Stress and Strain during Mechanical Ventilation
Any Safe Threshold?

Alessandro Protti[1], Massimo Cressoni[1], Alessandro Santini[1], Thomas Langer[1], Cristina Mietto[1], Daniela Febres[1], Monica Chierichetti[1], Silvia Coppola[1], Grazia Conte[2], Stefano Gatti[2], Orazio Leopardi[1], Serge Masson[3], Luciano Lombardi[4], Marco Lazzerini[4], Erica Rampoldi[5], Paolo Cadringher[1], and Luciano Gattinoni[1,6]

[1]Dipartimento di Anestesiologia, Terapia Intensiva e Scienze Dermatologiche, and [2]Centro di Ricerche Chirurgiche Precliniche, Università degli Studi di Milano, Milan, Italy; [3]Department of Cardiovascular Research, Istituto Mario Negri, Milan, Italy; and [4]Dipartimento di Radiologia, [5]Unità Operativa Laboratorio Centrale, and [6]Dipartimento di Anestesia, Rianimazione (Intensiva e Subintensiva) e Terapia del Dolore, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milan, Italy

Rationale: Unphysiologic strain (the ratio between tidal volume and functional residual capacity) and stress (the transpulmonary pressure) can cause ventilator-induced lung damage.
Objectives: To identify a strain–stress threshold (if any) above which ventilator-induced lung damage can occur.
Methods: Twenty-nine healthy pigs were mechanically ventilated for 54 hours with a tidal volume producing a strain between 0.45 and 3.30. Ventilator-induced lung damage was defined as net increase in lung weight.
Measurements and Main Results: Initial lung weight and functional residual capacity were measured with computed tomography. Final lung weight was measured using a balance. After setting tidal volume, data collection included respiratory system mechanics, gas exchange and hemodynamics (every 6 h); cytokine levels in serum (every 12 h) and bronchoalveolar lavage fluid (end of the experiment); and blood laboratory examination (start and end of the experiment). Two clusters of animals could be clearly identified: animals that increased their lung weight ($n = 14$) and those that did not ($n = 15$). Tidal volume was 38 ± 9 ml/kg in the former and 22 ± 8 ml/kg in the latter group, corresponding to a strain of 2.16 ± 0.58 and 1.29 ± 0.57 and a stress of 13 ± 5 and 8 ± 3 cm H_2O, respectively. Lung weight gain was associated with deterioration in respiratory system mechanics, gas exchange, and hemodynamics, pulmonary and systemic inflammation and multiple organ dysfunction.
Conclusions: In healthy pigs, ventilator-induced lung damage develops only when a strain greater than 1.5–2 is reached or overcome. Because of differences in intrinsic lung properties, caution is warranted in translating these findings to humans.

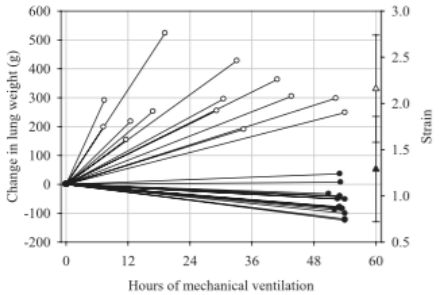
AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Mechanical ventilation can cause lung damage, perhaps proportionally to the applied strain and stress. Accordingly, use of small tidal volume (rough surrogate of strain) has been recommended not only in diseased but even in healthy lungs.

What This Study Adds to the Field

Ventilator-induced lung damage does not develop proportionally to the applied strain and stress, but only when a critical threshold is reached or overcome. On average, in healthy pigs, mechanical ventilation does not induce gross lung damage unless the applied strain is greater than 1.5–2 (corresponding to tidal volumes far greater than 20 ml/kg), that is, when the strain–stress relationship ceases to be linear. Mechanical ventilation seems to be reasonably safe in healthy lungs, unless very large tidal volumes are used.



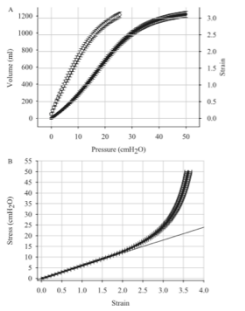


Figure 3. Mechanical properties of pig respiratory system and lung. (*A*) Average pressure–volume curve computed from the fittings of individual recordings, available in 22 pigs. Data are presented as mean ± SE. (*B*) Average stress–strain relationship computed from the fitting of individual recordings, available in 22 pigs. Stress was defined as the transpulmonary pressure, here presented at intervals of 0.5 cm H_2O. Strain was calculated as the volume corresponding to each level of stress (according to individual fitting equations) divided by individual functional residual capacity. The *straight line* represents the linear part of the stress–strain relationship. Data are presented as mean ± SE.

TABLE 5. BLOOD LABORATORY EXAMINATION (NON-PULMONARY ORGANS FUNCTION)

		No Ventilator-induced Lung Edema ($n = 13$)	Ventilator-induced Lung Edema ($n = 14$)	*P* Value
Urea, mg/dl	Baseline	21 ± 5 (n = 14)	23 ± 8 (n = 12)	
	End of experiment	43 ± 27 (n = 14)	67 ± 18 (n = 12)	
	Δ (End − Baseline)	22 ± 30 (n = 14)	44 ± 21 (n = 12)	<0.01
Creatinine, mg/dl	Baseline	0.9 ± 0.2 (n = 14)	0.9 ± 0.2 (n = 12)	
	End of experiment	1.3 ± 0.6 (n = 14)	2 ± 0.7 (n = 12)	
	Δ (End − Baseline)	0.2 ± 0.6 (n = 14)	1.1 ± 0.7 (n = 12)	<0.01
Albumin, g/dl	Baseline	2.3 ± 0.3 (n = 12)	2.9 ± 0.4 (n = 12)	
	End of experiment	1.8 ± 0.2 (n = 12)	1.9 ± 0.3 (n = 12)	
	Δ (End − Baseline)	−0.7 ± 0.3 (n = 12)	−1 ± 0.3 (n = 12)	0.04
Total bilirubin, mg/dl	Baseline	0.1 ± 0.1 (n = 14)	0.1 ± 0.0 (n = 12)	
	End of experiment	0.1 ± 0.1 (n = 14)	0.2 ± 0.1 (n = 12)	
	Δ (End − Baseline)	0 ± 0.1 (n = 14)	0.1 ± 0.1 (n = 12)	0.01
AST, IU/L	Baseline	45 ± 11 (n = 14)	44 ± 9 (n = 12)	
	End of experiment	101 ± 148 (n = 14)	445 ± 445 (n = 12)	
	Δ (End − Baseline)	55 ± 146 (n = 14)	400 ± 443 (n = 12)	<0.001
ALT, IU/L	Baseline	51 ± 8 (n = 14)	56 ± 14 (n = 12)	
	End of experiment	42 ± 12 (n = 14)	54 ± 19 (n = 12)	
	Δ (End − Baseline)	−9 ± 13 (n = 14)	−2 ± 15 (n = 12)	0.05
Potassium, mEq/L	Baseline	4.1 ± 0.4 (n = 14)	3.8 ± 0.5 (n = 12)	
	End of experiment	3.6 ± 0.5 (n = 14)	5.7 ± 1.3 (n = 12)	
	Δ (End − Baseline)	−0.6 ± 0.8 (n = 14)	1.9 ± 1.4 (n = 12)	<0.001
Sodium, mEq/L	Baseline	139 ± 3 (n = 14)	140 ± 3 (n = 12)	
	End of experiment	142 ± 3 (n = 14)	142 ± 3 (n = 12)	
	Δ (End − Baseline)	3 ± 4 (n = 14)	1 ± 4 (n = 12)	0.42
Chloride, mEq/L	Baseline	104 ± 3 (n = 14)	104 ± 2 (n = 12)	
	End of experiment	115 ± 3 (n = 14)	112 ± 3 (n = 12)	
	Δ (End − Baseline)	12 ± 4 (n = 14)	8 ± 5 (n = 12)	0.1
Total calcium, mEq/L	Baseline	9.6 ± 0.4 (n = 12)	10.1 ± 0.5 (n = 11)	
	End of experiment	8.4 ± 0.4 (n = 12)	8.4 ± 0.6 (n = 11)	
	Δ (End − Baseline)	−1.2 ± 0.7 (n = 12)	−1.7 ± 0.8 (n = 11)	0.28
Phosphate, mEq/L	Baseline	8.7 ± 0.9 (n = 12)	8.9 ± 1.7 (n = 11)	
	End of experiment	6.3 ± 0.7 (n = 12)	11.2 ± 3.4 (n = 11)	
	Δ (End − Baseline)	−2.4 ± 1.2 (n = 12)	2.3 ± 3.3 (n = 11)	<0.001
Magnesium, mEq/L	Baseline	1.8 ± 0.2 (n = 12)	1.8 ± 0.2 (n = 11)	
	End of experiment	1.6 ± 0.2 (n = 12)	2 ± 0.4 (n = 11)	
	Δ (End − Baseline)	−0.2 ± 0.2 (n = 12)	0.2 ± 0.4 (n = 11)	0.01
Troponin T, ng/ml	Baseline	0.02 ± 0.01 (n = 12)	0.01 ± 0.00 (n = 12)	
	End of experiment	0.01 ± 0.01 (n = 12)	0.14 ± 0.14 (n = 12)	
	Δ (End − Baseline)	0.00 ± 0.01 (n = 12)	0.13 ± 0.14 (n = 12)	<0.01
Hemoglobin, g/dl	Baseline	9.2 ± 0.5 (n = 13)	10 ± 1.9 (n = 13)	
	End of experiment	8.7 ± 1.4 (n = 13)	11.6 ± 2.4 (n = 13)	
	Δ (End − Baseline)	−0.5 ± 1.2 (n = 13)	1.6 ± 2.8 (n = 13)	0.02
Platelets, 10^3/ml	Baseline	530 ± 147 (n = 13)	532 ± 132 (n = 13)	
	End of experiment	257 ± 137 (n = 13)	160 ± 105 (n = 13)	
	Δ (End − Baseline)	−273 ± 97 (n = 13)	−371 ± 150 (n = 13)	0.07

Definition of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Baseline refers to time before the experimental ventilatory set was applied. End refers to the last set of data collected (after the scheduled time or immediately before death). Changes occurred across the experimental period were compared between groups with the Wilcoxon test.

TABLE 6. SIGNS OF PULMONARY AND SYSTEMIC INFLAMMATION

		No Ventilator-induced Lung Edema ($n = 13$)	Ventilator-induced Lung Edema ($n = 14$)	*P* Value
Serum TNF-α, pg/ml	Baseline	113 ± 47 (n = 12)	88 ± 43 (n = 13)	
	End of experiment	77 ± 31 (n = 12)	83 ± 59 (n = 13)	
	Δ (End − Baseline)	−36 ± 45 (n = 12)	−5 ± 41 (n = 13)	0.08
Serum IL-6, pg/ml	Baseline	49 ± 91 (n = 12)	88 ± 183	
	End of experiment	18 ± 36 (n = 12)	680 ± 711	
	Δ (End − Baseline)	−30 ± 73 (n = 12)	592 ± 720	<0.001
Serum IL-8, pg/ml	Baseline	169 ± 96 (n = 6)	71 ± 34 (n = 4)	
	End of experiment	47 ± 48 (n = 6)	149 ± 240 (n = 4)	
	Δ (End − Baseline)	−122 ± 123 (n = 6)	78 ± 196 (n = 4)	0.07
Serum IL-10, pg/ml	Baseline	<4	<4	
	End of experiment	<4	<4	
	Δ (End − Baseline)			
BALF TNF-α, pg/ml		202 ± 252 (n = 13)	46 ± 71	0.07
BALF IL-6, pg/ml		211 ± 364 (n = 13)	2,198 ± 1,685	<0.0001
BALF IL-8, pg/ml		1,569 ± 1,475 (n = 13)	725 ± 1,092	0.1
BALF IL-10, pg/ml		<4	<4	
Prothrombin time International Normalized Ratio	Baseline	1 ± 0 (n = 7)	1 ± 0 (n = 8)	
	End of experiment	0.9 ± 0.1 (n = 7)	1.4 ± 0.7 (n = 8)	
	Δ (End − Baseline)	0 ± 0.1 (n = 7)	0.4 ± 0.7 (n = 8)	0.13
Activated partial thromboplastin time ratio	Baseline	0.6 ± 0.1 (n = 11)	0.6 ± 0.1 (n = 11)	
	End of experiment	0.6 ± 0.1 (n = 11)	0.8 ± 0.3 (n = 11)	
	Δ (End − Baseline)	0 ± 0.1 (n = 11)	0.2 ± 0.2 (n = 11)	0.15
Fibrinogen, mg/dl	Baseline	182 ± 31 (n = 8)	188 ± 24 (n = 10)	
	End of experiment	317 ± 63 (n = 8)	337 ± 95 (n = 10)	
	Δ (End − Baseline)	135 ± 66 (n = 8)	150 ± 85 (n = 10)	0.9
D-dimer, μg/L	Baseline	148 ± 73 (n = 8)	215 ± 123 (n = 10)	
	End of experiment	136 ± 86 (n = 8)	9,963 ± 10,843 (n = 10)	
	Δ (End − Baseline)	−12 ± 84 (n = 8)	9,748 ± 10,898 (n = 10)	<0.0001
White blood cells, ml^{-1}	Baseline	13,727 ± 3,902 (n = 13)	13,820 ± 4,781 (n = 13)	
	End of experiment	12,787 ± 5,439 (n = 13)	20,327 ± 11,277 (n = 13)	
	Δ (End − Baseline)	−940 ± 5,500 (n = 13)	6,507 ± 12,239 (n = 13)	0.14
Body core temperature, °C	Baseline	39.7 ± 2.4	39.7 ± 1.8	
	End of experiment	38.5 ± 1.1	39.5 ± 1.3	
	Δ (End − Baseline)	−1.2 ± 2.8	−0.3 ± 1.8	0.23

Definition of abbreviations: BALF = bronchoalveolar lavage fluid; TNF-α = tumor necrosis factor-α.
IL-8: only few data are available because of technical problems in handling the samples collected during the first experiments. IL-10: always below the limit of detection.
Baseline refers to time before the experimental ventilatory set was applied. End refers to the last set of data collected (after the scheduled time or immediately before death). Changes occurred across the experimental period were compared between groups with the Wilcoxon test.

Conclusion

- Si strain < 1,5 : survie sans lésion pulmonaire après 54h de ventilation
- Si strain > 2,5: décès avec lésions pulmonaires
- Cela correspond au moment où la relation linéaire entre stress et strain disparait
- VILI s'accompagne d'une réaction inflammatoire systémique et d'une défaillance multiorganique

La notion de strain statique et de strain dynamique

Lung Stress and Strain During Mechanical Ventilation: Any Difference Between Statics and Dynamics?*

Alessandro Protti, MD[1]; Davide T. Andreis, MD[1]; Massimo Monti, MD[1]; Alessandro Santini, MD[1]; Cristina C. Sparacino, MD[1]; Thomas Langer, MD[1]; Emiliano Votta, PhD[2]; Stefano Gatti, MD[3]; Luciano Lombardi, RT[4]; Orazio Leopardi, MD[1]; Serge Masson, PhD[1]; Massimo Cressoni, MD[1]; Luciano Gattinoni, MD FRCP[1,5]

Objective: Tidal volume (V_t) and volume of gas caused by positive end-expiratory pressure (V_{PEEP}) generate dynamic and static lung strains, respectively. Our aim was to clarify whether different combinations of dynamic and static strains, resulting in the same large global strain, constantly produce lung edema.
Design: Laboratory investigation.
Setting: Animal unit.
Subjects: Twenty-eight healthy pigs.
Interventions: After lung computed tomography, 20 animals were ventilated for 54 hours at a global strain of 2.5, either entirely dynamic (V_t 100% and V_{PEEP} 0%), partly dynamic and partly static (V_t 75–50% and V_{PEEP} 25–50%), or mainly static (V_t 25% and V_{PEEP} 75%) and then killed. In eight other pigs (V_t 25% and V_{PEEP} 75%), V_{PEEP} was abruptly zeroed after 36–54 hours and ventilation continued for 3 hours.
Measurements and Main Results: Edema was diagnosed when final lung weight (balance) exceeded the initial weight (computed tomography). Mortality, lung mechanics, gas exchange, pulmonary histology, and inflammation were evaluated. All animals ventilated with entirely dynamic strain (V_t 825±424 mL) developed pulmonary edema (lung weight from 334±38 to 658±99 g, $p < 0.01$), whereas none of those ventilated with mainly static strain (V_t 237±21 mL and V_{PEEP} 906±114 mL, corresponding to 19±1 cm H_2O of positive end-expiratory pressure) did (from 314±55 to 277±46 g, $p = 0.65$). Animals ventilated with intermediate combinations finally had normal or largely increased lung weight. Smaller dynamic and larger static strains lowered mortality ($p < 0.01$), derangement of lung mechanics ($p < 0.01$), and arterial oxygenation ($p < 0.01$), histological injury score ($p = 0.03$), and bronchoalveolar interleukin-6 concentration ($p < 0.01$). Removal of positive end-expiratory pressure did not result in abrupt increase in lung weight (from 336±36 to 351±77 g, $p = 0.51$).
Conclusions: Lung edema forms (possibly as an all-or-none response) depending not only on global strain but also on its components. Large static are less harmful than large dynamic strains, but not because the former merely counteracts fluid extravasation. (*Crit Care Med* 2013; 41:1046–1055)
Key Words: healthy lung; lung strain; lung stress; mechanical ventilation; positive end-expiratory pressure; transpulmonary pressure; ventilator-induced lung injury

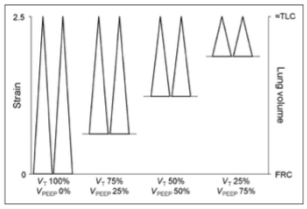


Figure 1. Study protocol. Four different combinations of dynamic and static strains, always resulting in a global lung strain of 2.5 (and an end-inspiratory lung volume close to total capacity [TLC]) were studied. Dynamic strain (tidal volume [V_t]) could contribute 100% down to 25% of total lung strain. Static strain (volume of gas corresponding to positive end-expiratory pressure [V_{PEEP}]) could accordingly account for 0–75% of global strain. FRC = functional residual capacity.

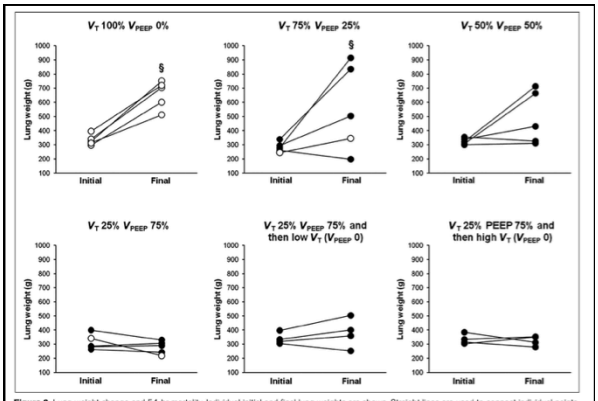


Figure 2. Lung weight change and 54-hr mortality. Individual initial and final lung weights are shown. Straight lines are used to connect individual points to help visualize how lung weight changed in every single animal (and not to suggest that these changes occurred linearly over time). White circles indicate animals that died within 54 hr, whereas black circles indicate those that survived. §$p < 0.01$ vs. initial lung weight. V_t = tidal volume; V_{PEEP} = volume corresponding to positive end-expiratory pressure.

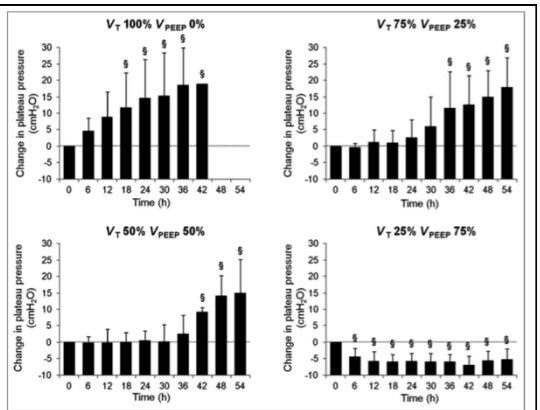


Figure 3. Temporal changes in plateau airway pressure. Changes in plateau airway pressure were computed as the difference between actual (measured every 6 hours) and initial values. Individual data were averaged within groups of ventilation. §$p < 0.05$ vs. time 0 within the same group. V_t = tidal volume; V_{PEEP} = volume corresponding to positive end-expiratory pressure.

TABLE 3. Lung Histology

	V_T 100%; V_{PEEP} 0%	V_T 75%; V_{PEEP} 25%	V_T 50%; V_{PEEP} 50%	V_T 25%; V_{PEEP} 75%	*p*
Emphysematous change	2 (1–2)	2 (2–3)	1 (0–2)	3[ac] (3–4)	<0.01
Interstitial congestion	2 (2–2)	3 (2–3)	2 (2–4)	1[b] (1–2)	0.02
Alveolar hemorrhage	2 (1–2)	1 (1–2)	1 (1–3)	1 (0–1)	0.11
Alveolar neutrophil infiltration	3 (2–4)	3 (1–3)	4 (4–4)	0[c] (0–1)	<0.01
Alveolar macrophage proliferation	3 (2–3)	3 (2–3)	3 (2–3)	1 (1–2)	0.14
Alveolar type II pneumocyte proliferation	2 (1–3)	2 (2–2)	2 (1–2)	1 (1–2)	0.32
Interstitial lymphocyte proliferation	2 (1–2)	1 (1–2)	2 (1–2)	1 (1–2)	0.95
Interstitial thickening	3 (2–4)	3 (3–3)	2 (2–3)	1 (1–2)	0.05
Hyaline membrane formation	3 (2–4)	2 (1–2)	0 (0–2)	0[c] (0–0)	<0.01
Interstitial fibrosis	2 (1–3)	2 (2–2)	1 (1–2)	1 (1–2)	0.51
Organization of alveolar exudate	2 (1–3)	2 (1–2)	1 (1–2)	1 (0–1)	0.18
Total injury score	23 (19–26)	23 (18–26)	20 (17–23)	10[a] (9–17)	0.03

V_T = tidal volume; V_{PEEP} = volume corresponding to positive end-expiratory pressure.
[a]$p < 0.05$ vs. V_T 100% and V_{PEEP} 0%.
[b]$p < 0.05$ vs. V_T 75% and V_{PEEP} 25%.
[c]$p < 0.05$ vs. V_T 50% and V_{PEEP} 50%.
Histological alterations were graded from 0 to 4 based on visual inspection (under the microscope), with higher scores indicating more severe and diffused abnormalities (43). Total injury score was the sum of all individual scores. The *p* values reported in the last column refer to overall comparisons between groups.

TABLE 4. Final Lung and Systemic Inflammation

	V_T 100%; V_{PEEP} 0%	V_T 75%; V_{PEEP} 25%	V_T 50%; V_{PEEP} 50%	V_T 25%; V_{PEEP} 75%	*p*
Bronchoalveolar lavage fluid IL-6 (pg/mL)	1019±251	1037±363	534±612	120±144[ab]	<0.01
Serum IL-6 (pg/mL)	602 (215–1200)	204 (52–470)	14 (8–225)	2[a] (2–10)	0.01

V_T = tidal volume; V_{PEEP} = volume corresponding to positive end-expiratory pressure; IL-6 = interleukin-6.
[a]$p < 0.05$ vs. V_T 100% and V_{PEEP} 0%.
[b]$p < 0.05$ vs. V_T 75% and V_{PEEP} 25%.
The *p* values reported in the last column refer to overall comparisons between groups.

conclusion

- L'apparition de VILI dépend du strain global mais plus de sa composante dynamique (le volume courant) que statique (la peep)

Le strain rate

Role of Strain Rate in the Pathogenesis of Ventilator-Induced Lung Edema*

Alessandro Protti, MD[1]; Tommaso Maraffi, MD[2]; Marta Milesi, MD[2]; Emiliano Votta, PhD[3]; Alessandro Santini, MD[2]; Paola Pugni, MD[2]; Davide T. Andreis, MD[2]; Francesco Nicosia, MD[2]; Emanuela Zannin, PhD[3]; Stefano Gatti, MD[4]; Valentina Vaira, MD, PhD[2,5,6]; Stefano Ferrero, MD[6,7]; Luciano Gattinoni, MD, FRCP[1,2]

Objective: Lungs behave as viscoelastic polymers. Harms of mechanical ventilation could then depend on not only amplitude (strain) but also velocity (strain rate) of lung deformation. Herein, we tested this hypothesis.
Design: Laboratory investigation.
Setting: Animal unit.
Subjects: Thirty healthy piglets.
Interventions: Two groups of animals were ventilated for 54 hours with matched lung strains (ratio between tidal volume and functional residual capacity) but different lung strain rates (ratio between strain and inspiratory time). Individual strains ranged between 0.6 and 3.5 in both groups. Piglets ventilated with low strain rates had an inspiratory-to-expiratory time ratio of 1:2–1:3. Those ventilated with high strain rates had much lower inspiratory-to-expiratory time ratios (down to 1:9). Respiratory rate was always 15 breaths/min. Lung viscoelastic behavior, with ventilator setting required per protocol, was "quantified" as dynamic respiratory system hysteresis (pressure-volume loop [in Joules]) and stress relaxation (airway pressure drop during an end-inspiratory pause [in cm H_2O]). Primary outcome was the occurrence of pulmonary edema within 54 hours.
Measurements and Main Results: On average, the two study groups were ventilated with well-matched strains (2.1±0.9 vs 2.1±0.9; $p = 0.864$) but different strain rates (1.8±0.8 vs 4.6±1.5 s^{-1}; $p < 0.001$), dynamic respiratory system hysteresis (0.6±0.3 vs 1.4±0.8 J; $p = 0.001$), and stress relaxation (3.1±0.9 vs 5.0±2.3 cm H_2O; $p = 0.008$). The prevalence of pulmonary edema was 20% among piglets ventilated with low strain rates and 73% among those ventilated with high strain rates ($p = 0.010$).
Conclusions: High strain rate is a risk factor for ventilator-induced pulmonary edema, possibly because it amplifies lung viscoelastic behavior. (*Crit Care Med* 2016; 44:e838–e845)
Key Words: inspiratory flow; lung hysteresis; lung viscoelasticity; mechanical ventilation; pulmonary edema; ventilator-induced lung injury

*See also p. 1800.

[1]Dipartimento di Anestesia, Rianimazione ed Emergenza Urgenza, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.
[2]Dipartimento di Fisiopatologia Medico-Chirurgica e dei Trapianti, Università degli Studi, Milan, Italy.
[3]Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano, Milan, Italy.
[4]Centro di Ricerche Chirurgiche Precliniche, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Università degli Studi, Milan, Italy.
[5]U.O.C. Anatomia Patologica, Fondazione IRCCS Ca' Granda–Ospedale Maggiore Policlinico, Milan, Italy.
[6]Istituto Nazionale Genetica Molecolare "Romeo ed Enrica Invernizzi", Milan, Italy.
[7]Dipartimento di Scienze Biomediche, Chirurgiche e Odontoiatriche, Università degli Studi, Milan, Italy.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).
Supported, in part, by an Italian grant provided by Fondazione Fiera di Milano for Translational and Competitive Research (2007, Luciano Gattinoni) and by GE Healthcare.

TABLE 1. Ventilator Settings Used in the Two Study Groups

Variable of Interest	Low Strain Rate	High Strain Rate	*p*
n	15	15	
Strain	2.1 ± 0.9 (0.6–3.5)	2.1 ± 0.9 (0.8–3.5)	0.864
Tidal volume (mL)	562 ± 162 (299–766)	588 ± 163 (325–787)	0.648[a]
Functional residual capacity (mL)	293 ± 84 (174–488)	309 ± 85 (187–488)	0.597
Strain rate (s^{-1})	1.8 ± 0.8 (0.5–2.9)	4.6 ± 1.5 (2.1–6.4)	< 0.001[a]
Inspiratory flow (mL/s)	469 ± 156 (250–833)	1322 ± 245 (800–1600)	< 0.001
Respiratory rate	15	15	
Inspiratory-to-expiratory time ratio	1:2–1:3	1:5–1:9	
Inspiratory time (s)	1.3 ± 0.1 (1.0–1.3)	0.5 ± 0.1 (0.4–0.7)	< 0.001[a]

Animals assigned to the two study groups were ventilated with the same strain (ratio between tidal volume and functional residual capacity) and respiratory rate but diverse inspiratory-to-expiratory rate and therefore strain rate (ratio between strain and inspiratory time). Data are reported as means ± SD (range); they were compared between animals ventilated with "low" or "high" strain rates with Student *t* or Mann-Whitney rank sum (†) tests.

TABLE 2. Respiratory System Mechanics, Lung Mechanics, Gas Exchange Across the Study Period, and Major Outcomes

	Low Strain Rate	High Strain Rate	*p*
Respiratory system compliance (mL/cm H_2O)			
Start of experiment	27 ± 5	25 ± 5	0.001
End of experiment	23 ± 6[b]	15 ± 6[ab]	
Lung compliance (mL/cm H_2O)			
Start of experiment	63 ± 14	59 ± 21	0.025
End of experiment	48 ± 18[b]	29 ± 18[ab]	
Arterial pH†			
Start of experiment	7.49 ± 0.03	7.48 ± 0.03	0.060
End of experiment	7.43 ± 0.13	7.31 ± 0.15	
Arterial Co_2 tension (mm Hg)			
Start of experiment	39 ± 2	39 ± 3	0.008
End of experiment	34 ± 5	46 ± 14[ab]	
Arterial O_2 tension (mm Hg)			
Start of experiment	243 ± 41	241 ± 36	0.031
End of experiment	200 ± 68	131 ± 69[ab]	
Body weight (kg)			
Start of experiment	23 ± 2	22 ± 3	0.925
End of experiment	24 ± 3	23 ± 3	
Lung weight (g)			
Start of experiment	357 ± 41	362 ± 43	<0.001
End of experiment	283 ± 67[b]	460 ± 165[ab]	
Prevalence of pulmonary edema			
By end of experiment	3/15 (20%)	11/15 (73%)	0.010
Early mortality			
By end of experiment	2/15 (13%)	7/15 (47%)	0.100
Interleukin-6 in bronchoalveolar lavage fluid (pg/mL)			
End of experiment	433 ± 501	968 ± 475	0.006
Total lung injury score			
End of experiment	6 (3–10)	10 (5–11)	0.050[a]

[a]$p < 0.05$ within group at post-hoc multiple comparisons.
[b]$p < 0.05$ between groups at post-hoc multiple comparisons (Holm-Sidak test).
Data (means ± SD, medians [interquartile range] or proportions) were compared between animals ventilated with "low" or "high" strain rates with Student *t* or Mann-Whitney rank sum tests (†), two-way repeated measures analysis of variance or Fisher exact test.
Physiological variables were recorded at the beginning and end of the study. Compliance was the ratio between tidal volume and plateau (0-s end-inspiratory occlusion) airway (respiratory system) or transpulmonary (lung) pressure. Pulmonary edema was diagnosed if final lung weight (measured with a balance) exceeded initial one (measured with CT). Total lung injury score refers to the presence and severity of 11 histopathologic pulmonary changes (as reported in Table E4, Supplemental Digital Content 1, http://links.lww.com/CCM/B608).

conclusion

- Strain rate est un facteur de risque important pour le VILI, indépendamment du strain:
  - Élongation tissulaire moins uniforme et phénomène d'hysteresis => microfracture
  - Distribution des gaz moins uniforme et donc risque de surdistension des alveoles les plus saines
  - Augmente le shear stress alveolaire

Role de la distribution du strain

Laboratory Investigations

Prone position delays the progression of ventilator-induced lung injury in rats: Does lung strain distribution play a role?*

Franco Valenza, MD; Massimiliano Guglielmi, MD; Micol Maffioletti, MD; Cecilia Tedesco, MD; Patrizia Maccagni, MD; Tommaso Fossali; Gabriele Aletti; Giuliana Anna Porro, MD; Manuela Irace; Eleonora Carlesso, MSc; Nadia Carboni, MD; Marco Lazzerini, MD; Luciano Gattinoni, MD, FRCP

Objective: **To investigate if prone position delays the progression of experimental ventilator-induced lung injury, possibly due to a more homogeneous distribution of strain within lung parenchyma.**

Design: **Prospective, randomized, controlled trial.**

Setting: **Animal laboratory of a university hospital.**

Subjects: **Thirty-five Sprague Dawley male rats (weight 257 ± 45 g).**

Interventions: **Mechanical ventilation in either supine or prone position and computed tomography scan analysis.**

Measurements: **Animals were ventilated in supine (n = 15) or prone (n = 15) position until a similar ventilator-induced lung injury was reached. To do so, experiments were interrupted when respiratory system elastance was 150% of baseline. Ventilator-induced lung injury was assessed as lung wet-to-dry ratio and histology. Time to reach lung injury was considered as a main outcome measure. In five additional animals, computed tomography scans (GE Light Speed QX/I, thickness 1.25 mm, interval 0.6 mm, 100 MA, 100 Kv) were randomly taken at end-expiration and end-inspiration in both positions, and quantitative analysis was performed. Data are shown as mean ± SD.**

Measurements and Main Results: **Similar ventilator-induced lung injury was reached (respiratory system elastance, wet-to-dry ratio, and histology). The time taken to achieve the target ventilator-induced lung injury was longer with prone position (73 ± 37 mins vs. 112 ± 42, supine vs. prone, $p = .011$). Computed tomography scan analysis performed before lung injury revealed that at end-expiration, the lung was wider in prone position ($p = .004$) and somewhat shorter ($p = .09$), despite similar lung volumes ($p = .455$). Lung density along the vertical axis increased significantly only in supine position ($p = .002$). Lung strain was greater in supine as opposed to prone position (width strain, 7.8 ± 1.8% vs. 5.6 ± 0.9, supine vs. prone, $p = .029$).**

Conclusions: **Prone position delays the progression of ventilator-induced lung injury. Computed tomography scan analysis suggests that a more homogeneous distribution of strain may be implicated in the protective role of prone position against ventilator-induced lung injury. (Crit Care Med 2005; 33:361–367)**

Key Words: **prone position; ventilation; lung injury; acute; animal experimentation; tomography, spiral computed**

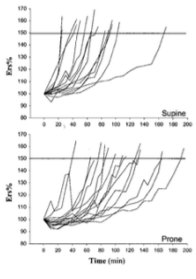


Figure 2. Time course of the increase of respiratory system elastance (*Ers*) over time. We measured Ers at time intervals and stopped once Ers was 150%, which corresponded to a similar lung injury (see Results). The upper panel represents animals ventilated in supine position, whereas the lower panel animals in prone position. Each line is representative of a single animal. As one can see, prone position delayed the progression of ventilator-induced lung injury.

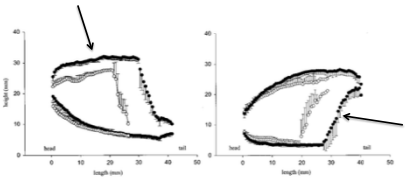


Figure 4. Average shape of the lungs at end-expiration (*open circles*) and end-inspiration (*filled circles*) of animals in supine (*left panel*) and prone (*right panel*) position. The figure suggests that the distribution of tidal volume was different between supine and prone position.

In this study we have confirmed that prone position delays the progression of VILI in an experimental model. We have also shown that lungs are more homoge- neously inflated in prone position and tidal volume distribution is different be- tween supine and prone position. In fact, tidal volume preferentially strains the nondependent lung regions in supine po- sition, whereas in the prone position the downward displacement of the dia- phragm is more relevant.

conclusion

- La prone position
  - Retarde l'apparition du VILI
  - induit une distribution plus homogène du strain qui peut etre impliquée dans ce délai d'apparition du VILI

J Appl Physiol 110: 1374–1383, 2011.
First published March 10, 2011; doi:10.1152/japplphysiol.00439.2010.

Lung regional stress and strain as a function of posture and ventilatory mode

Gaetano Perchiazzi,[1,4] Christian Rylander,[2] Antonio Vena,[3] Savino Derosa,[1] Debora Polieri,[1] Tommaso Fiore,[1] Rocco Giuliani,[1] and Göran Hedenstierna[4]

[1]*Emergency and Organ Transplant, Bari University, Bari, Italy;* [2]*Anaesthesia and Intensive Care Medicine, Sahlgrenska University Hospital, Göteborg, Sweden;* [3]*Intensive Care Unit, SS Annunziata Hospital, Taranto, Italy; and* [4]*Medical Sciences–Clinical Physiology, Uppsala University, Uppsala, Sweden*

Submitted 23 April 2010; accepted in final form 7 March 2011

Perchiazzi G, Rylander C, Vena A, Derosa S, Polieri D, Fiore T, Giuliani R, Hedenstierna G. Lung regional stress and strain as a function of posture and ventilatory mode. *J Appl Physiol* 110: 1374–1383, 2011. First published March 10, 2011; doi:10.1152/japplphysiol.00439.2010.—During positive-pressure ventilation parenchymal deformation can be assessed as strain (volume increase above functional residual capacity) in response to stress (transpulmonary pressure). The aim of this study was to explore the relationship between stress and strain on the regional level using computed tomography in anesthetized healthy pigs in two postures and two patterns of breathing. Airway opening and esophageal pressures were used to calculate stress; change of gas content as assessed from computed tomography was used to calculate strain. Static stress-strain curves and dynamic strain-time curves were constructed, the latter during the inspiratory phase of volume and pressure-controlled ventilation, both in supine and prone position. The lung was divided into nondependent, intermediate, dependent, and central regions: their curves were modeled by exponential regression and examined for statistically significant differences. In all the examined regions, there were strong but different exponential relations between stress and strain. During mechanical ventilation, the end-inspiratory strain was higher in the dependent than in the nondependent regions. No differences between volume- and pressure-controlled ventilation were found. However, during volume control ventilation, prone positioning decreased the end-inspiratory strain of dependent regions and increased it in nondependent regions, resulting in reduced strain gradient. Strain is inhomogeneously distributed within the healthy lung. Prone positioning attenuates differences between dependent and nondependent regions. The regional effects of ventilatory mode and body positioning should be further explored in patients with acute lung injury.

Fig. 4. Difference in strain between dependent and nondependent lung regions reached at different levels of delta transpulmonary pressure (ΔPtp). Data were obtained by calculating the difference between strains on the regression curves belonging to dependent and nondependent lung regions at specific ΔPtp. Plot represents the mean of the differences found in the 5 animals.

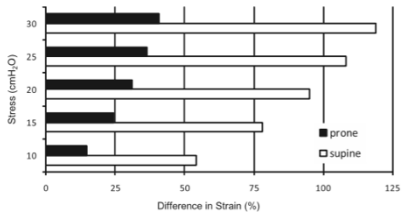
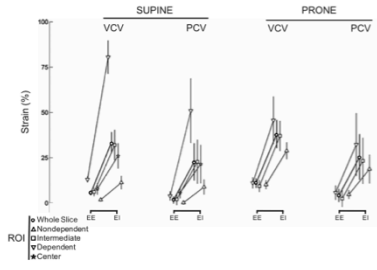


Fig. 5. Dynamic strain in 2 postures and 2 ventilatory modes. EE, end expiration; EI, end inspiration. Whole slice is represented in bold. Vertical lines represent SE.



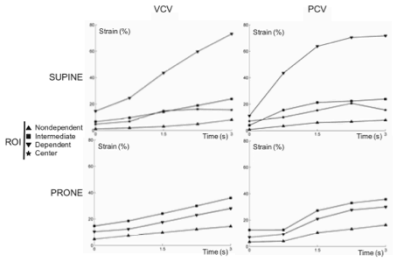


Fig. 6. Strain over time of a representative animal. VCV, volume control ventilation; PCV: pressure control ventilation.

Conclusion

- La prone position induit une distribution plus homogène du strain
- Le mode ventilatoire n'a pas d'influence sur le strain

Données cliniques

Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome

Davide Chiumello[1], Eleonora Carlesso[2], Paolo Cadringher[2], Pietro Caironi[1,2], Franco Valenza[1,2], Federico Polli[2], Federica Tallarini[2], Paola Cozzi[2], Massimo Cressoni[2], Angelo Colombo[1], John J. Marini[3], and Luciano Gattinoni[1,2]

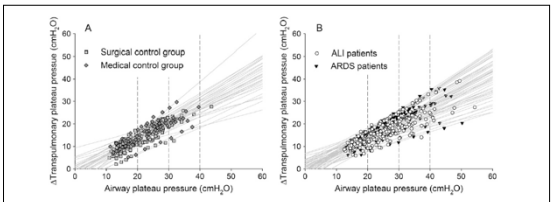


Figure 4. ΔTranspulmonary and airway pressure relationship in surgical control subjects, medical control subjects, patients with acute lung injury (ALI) and patients with acute respiratory distress syndrome (ARDS). (*A*) The ΔtranspulmonaryPL to airway pressure relationship in 30 control subjects, and (*B*) the ΔtranspulmonaryPL to airway pressure relationship in 50 patients with ALI/ARDS. In both panels, *gray solid lines* represent the relationship observed in each individual subjects in the eight experimental conditions (i.e., four different V_T [6, 8, 10, 12 ml/kg idea body weight]), at two different positive end-expiratory pressure (PEEP) levels (5 and 15 cm H_2O). A linear function ($y = \alpha x + y_0$) was used. *Vertical dashed lines* at 20, 30, and 40 cm H_2O airway pressure were drawn to underline the large variability of the corresponding ΔtranspulmonaryPL pressure both in control subjects and patients.

Am J Respir Crit Care Med Vol 178. pp 346–355, 2008

Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome

Davide Chiumello[1], Eleonora Carlesso[2], Paolo Cadringher[2], Pietro Caironi[1,2], Franco Valenza[1,2], Federico Polli[2], Federica Tallarini[2], Paola Cozzi[2], Massimo Cressoni[2], Angelo Colombo[1], John J. Marini[3], and Luciano Gattinoni[1,2]

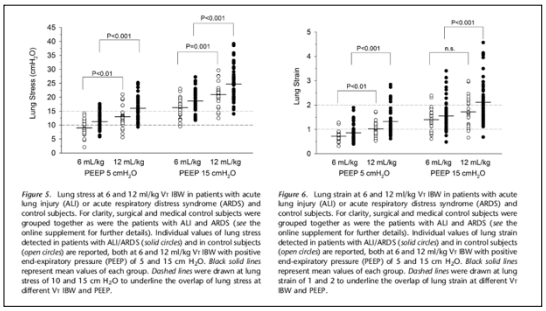


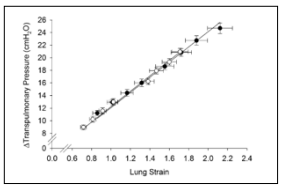
Figure 5. Lung stress at 6 and 12 ml/kg Vt IBW in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) and control subjects. For clarity, surgical and medical control subjects were grouped together as were the patients with ALI and ARDS (see the online supplement for further details). Individual values of lung stress detected in patients with ALI/ARDS (*solid circles*) and in control subjects (*open circles*) are reported, both at 6 and 12 ml/kg Vt IBW with positive end-expiratory pressure (PEEP) of 5 and 15 cm H_2O. *Black solid lines* represent mean values of each group. *Dashed lines* were drawn at lung stress of 10 and 15 cm H_2O to underline the overlap of lung stress at different Vt IBW and PEEP.

Figure 6. Lung strain at 6 and 12 ml/kg Vt IBW in patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) and control subjects. For clarity, surgical and medical control subjects were grouped together as were the patients with ALI and ARDS (see the online supplement for further details). Individual values of lung strain detected in patients with ALI/ARDS (*solid circles*) and in control subjects (*open circles*) are reported, both at 6 and 12 ml/kg Vt IBW with positive end-expiratory pressure (PEEP) of 5 and 15 cm H_2O. *Black solid lines* represent mean values of each group. *Dashed lines* were drawn at lung strain of 1 and 2 to underline the overlap of lung strain at different Vt IBW and PEEP.

Am J Respir Crit Care Med Vol 178. pp 346–355, 2008

Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome

Davide Chiumello[1], Eleonora Carlesso[2], Paolo Cadringher[2], Pietro Caironi[1,2], Franco Valenza[1,2], Federico Polli[2], Federica Tallarini[2], Paola Cozzi[2], Massimo Cressoni[2], Angelo Colombo[1], John J. Marini[3], and Luciano Gattinoni[1,2]



- Stress = E_{Lspec} x Strain

⇒ Ptranspulm = E_{Lspec} x ΔV /CRF

⇒ E_{lspec} = Ptranspulm /(ΔV /CRF)

= 13.5 cm H_2O

La relation Stress/strain est linéaire et identique chez tous les patients; cela signifie que toute augmentation de P de 13,5 cmH2O double la CRF
Ce qui supporte le concept de Baby Lung dans l'ARDS

Am J Respir Crit Care Med Vol 178. pp 346–355, 2008

Lung Stress and Strain during Mechanical Ventilation for Acute Respiratory Distress Syndrome

Davide Chiumello[1], Eleonora Carlesso[2], Paolo Cadringher[2], Pietro Caironi[1,2], Franco Valenza[1,2], Federico Polli[2], Federica Tallarini[2], Paola Cozzi[2], Massimo Cressoni[2], Angelo Colombo[1], John J. Marini[3], and Luciano Gattinoni[1,2]

- Ni la pression plateau ni le volume courant ne sont des bons prédicteurs du stress et du strain pulmonaire -> principaux déterminants des lésions pulmonaires induites par la ventilation

⇒ Stress = **Esp** (specific lung elastance) x Strain

Objectifs de la ventilation protectrice:
=> Strain max: < 2
- Stress = 13.5 x strain

=> Stress max: ± 27 cmH2O

- Vu la relation qui unit stress et strain, en pratique clinique mesurer l'un ou l'autre est équivalent:

Strain = ΔV (Vol tidal+Vol PEEP)/CRF

⇒ **Stress et strain nouveaux garde-fou de la ventilation protectrice?**

Am J Respir Crit Care Med Vol 178. pp 346–355, 2008

Applications et bénéfices cliniques

- Le stress => mesure de la pression pleurale
- Le strain => mesure de la CRF
- Alternatives?
- Et la peep?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 13, 2008 VOL. 359 NO. 20

Mechanical Ventilation Guided by Esophageal Pressure in Acute Lung Injury

Daniel Talmor, M.D., M.P.H., Todd Sarge, M.D., Atul Malhotra, M.D., Carl R. O'Donnell, Sc.D., M.P.H., Ray Ritz, R.R.T., Alan Lisbon, M.D., Victor Novack, M.D., Ph.D., and Stephen H. Loring, M.D.

La mesure de la pression transpulmonaire

- Pour titrer la peep: éviter une P transpulm négative en fin d'expiration
- Pour évaluer le stress pulmonaire: régler la pression transpulmonaire de fin d'inspiration à 25 cmH2O

Esophageal-Pressure–Guided Group

F_IO_2	0.4	0.5	0.5	0.6	0.6	0.7	0.7	0.8	0.8	0.9	0.9	1.0
P_{EEO}	0	0	2	2	4	4	6	6	8	8	10	10

Control Group

F_IO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	20–24

Figure 1. Ventilator Settings According to the Protocol.

For the intervention group, keep the partial pressure of arterial oxygen (PaO_2) between 55 and 120 mm Hg or keep the oxygen saturation, as measured by pulse oximeter, between 88 and 98% by using the ventilator settings in one column at a time. Set the positive end-expiratory pressure (PEEP) at such a level that transpulmonary pressure during end-expiratory occlusion (P_{EEO}) stays between 0 and 10 cm of water, and keep transpulmonary pressure during end-inspiratory occlusion at less than 25 cm of water. For the control group, keep PaO_2 between 55 and 120 mm Hg (or keep oxygen saturation according to pulse oximeter between 88 and 98%) by using the ventilator settings in one column at a time. Set the PEEP and tidal volume at such levels that the airway pressure during end-inspiratory occlusion stays at less than 30 cm of water. In both groups, apply ventilation with either pressure-control ventilation or volume-control ventilation with a ratio of inspiratory time to expiratory time between 1:1 and 1:3 to minimize dyssynchrony between the patient and the ventilator while achieving a tidal volume of 6±2 ml per kilogram of predicted body weight and a respiratory rate of 35 breaths per minute or less. Lung-recruitment maneuvers are permitted to reverse episodic hypoxemia after suctioning or inadvertent airway disconnection, but not on a routine basis.

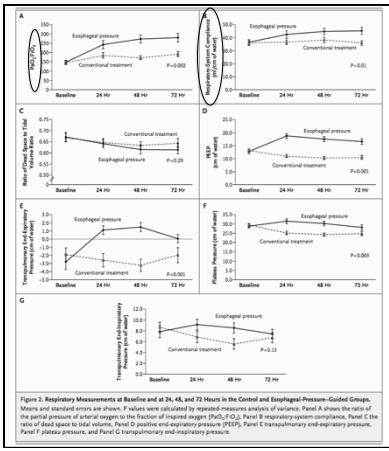


Figure 2. **Respiratory Measurements at Baseline and at 24, 48, and 72 Hours in the Control and Esophageal-Pressure–Guided Groups.**
Means and standard errors are shown. P values were calculated by repeated-measures analysis of variance. Panel A shows the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2/F_IO_2), Panel B respiratory-system compliance, Panel C the ratio of dead space to tidal volume, Panel D positive end-expiratory pressure (PEEP), Panel E transpulmonary end-expiratory pressure, Panel F plateau pressure, and Panel G transpulmonary end-inspiratory pressure.

As compared with the current standard of care, a ventilator strategy using oesophageal pressures to estimate the transpulmonary pressure significantly improves oxygenation and compliance

Table 4. Clinical Outcomes.*

Outcome	Esophageal-Pressure–Guided (N=30)	Conventional Treatment (N=31)	P Value
28-Day mortality — no. (%)	5 (17)	12 (39)	0.055
180-Day mortality — no. (%)	8 (27)	14 (45)	0.13
Length of ICU stay — days			0.16
Median	15.5	13.0	
Interquartile range	10.8–28.5	7.0–22.0	
No. of ICU-free days at 28 days			0.96
Median	5.0	4.0	
Interquartile range	0.0–14.0	0.0–16.0	
No. of ventilator-free days at 28 days			0.50
Median	11.5	7.0	
Interquartile range	0.0–20.3	0.0–17.0	
No. of days of ventilation among survivors			0.71
Median	12.0	16.0	
Interquartile range	7.0–27.5	7.0-20.0	

Conclusion

- Une stratégie ventilatoire utilisant la Poeso pour estimer la Ptranspulm ameliore l'oxygenation et la compliance
- Nécessité d'études multicentriques pour voir le bénéfice réel de cette stratégie

Intensive Care Med (2012) 38:395–403
DOI 10.1007/s00134-012-2490-7

ORIGINAL

Salvatore Grasso
Pierpaolo Terragni
Alberto Birocco
Rosario Urbino
Lorenzo Del Sorbo
Claudia Filippini
Luciana Mascia
Antonio Pesenti
Alberto Zangrillo
Luciano Gattinoni
V. Marco Ranieri

ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure

ECMO criteria for influenza A (H1N1)-associated ARDS: role of transpulmonary pressure

- 14 pts adressés pour potentielle ECMO (H1N1)
- ECMO si PaO2/FiO2<70 malgré peep >15 +/- DV+/-Noi ou pH < 7,25
- Mesure Poesoph (Stress pulmonaire)
- Ptranspulm = Pplat x (E_L/E_{RS})
- Si Ptranspulm < 25 cmH2O => Peep ↗ pour Ptranspulm = 25cmH2O

Table 1 Individual values of $PPLAT_{RS}$ and $PPLAT_L$ (cmH_2O)

Patient no.	ECMO		Patient no.	No ECMO			
	Conventional ventilation			Conventional ventilation		Conventional ventilation and higher PEEP	
	$PPLAT_{RS}$	$PPLAT_L$		$PPLAT_{RS}$	$PPLAT_L$	$PPLAT_{RS}$	$PPLAT_L$
1	32.1	28.5	8	31.7	18.8	37.2	26.1
2	29.7	25.8	9	31.9	15.1	38.5	25.2
3	31.3	25.6	10	31.8	12.3	40.6	27.1
4	30.4	27.6	11	31.8	15.9	38.6	27.3
5	30.8	26.9	12	31	15.8	38	23.5
6	31.2	28.8	13	30.5	16.9	37.5	22.8
7	31.4	27.2	14	31.7	21.7	38.7	25
Mean ± SD	31 ± 1	27.2 ± 1.2	Mean ± SD	31 ± 0.5	16.6 ± 2.9	38.4 ± 1	25.3 ± 1.7

$PPLAT_{RS}$ end-inspiratory plateau pressure of the respiratory system, *$PPLAT_L$* end-inspiratory plateau pressure of the lung, *ECMO* extracorporeal membrane oxygenation, *SD* standard deviation

Titrating Peep to target a Pplat value of 25 cmH2O instead of a PplatRS of 30 cmH2O may optimize oxygenation and prevent inappropriate use of ECMO

conclusion

- Distinguer la mécanique pulmonaire de la mécanique thoracique révèle un groupe de patients dont l'hypoxémie réfractaire au réglage conventionnel du respirateur est due non pas à une altération du parenchyme pulmonaire mais à une cage thoracique trop rigide qui empêche d'appliquer une pression suffisante au poumon
- Chez ces patients, atteindre une P transpulm de 25 cmH2O au lieu de la pression plat classique de 30 cmH2O permet de corriger l'oxygenation

CURRENT OPINION

Measurement of esophageal pressure at bedside: pros and cons

Laurent Brochard

Lack of clinical use
The main problem of the esophageal catheter technique is that it is not used clinically. The technique is underused in clinical settings for technical reasons but often by lack of knowledge about current application of physiology. Outcome data are scarce, technical difficulties exist, and a solid physiological background is needed for a good interpretation. All these aspects probably explain the relatively limited use of this technique.

Curr Opin Crit Care 2014, 20:39–46

Intensive Care Med (2016) 42:1360–1373
DOI 10.1007/s00134-016-4400-x

REVIEW

Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives

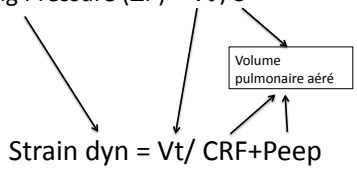
Tommaso Mauri[1], Takeshi Yoshida[2,3,4], Giacomo Bellani[5], Ewan C. Goligher[6,7,12], Guillaume Carteaux[8,9], Nuttapol Rittayamai[10,11,12], Francesco Mojoli[13], Davide Chiumello[1,14], Lise Piquilloud[15,16], Salvatore Grasso[17], Amal Jubran[18], Franco Laghi[18], Sheldon Magder[19], Antonio Pesenti[1,14], Stephen Loring[20], Luciano Gattinoni[1,14], Daniel Talmor[20], Lluis Blanch[21], Marcelo Amato[22], Lu Chen[11,12], Laurent Brochard[11,12*], Jordi Mancebo[23] and the PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine)

Le strain

- Nécessite la mesure de la CRF ou de EELV
  - Scanner
  - Dilution de gaz
  - Washin washout méthode (GE)
- Stress= k x Strain

La pression motrice (driving pressure)

- Compliance (C) = Vt/(Pplat-Peep)
- Pplat-Peep= Vt/C
- Driving Pressure (ΔP) = Vt /C



Manœuvres visant à diminuer la driving pressure

- Réglage de la Peep
- Prone position en condition isocapnique réduit DP
- Sedation et curarisation precoces
- Reduction de l'espace mort
- Augmenter la pause inspiratoire améliorerait la clearance du CO2
- Ecco2r?

La notion de driving pressure

- DP = Vt/Crs,

=> bedside tool to estimate dynamic Strain

- DP est la variable ventilatoire la mieux corrélée à la survie, >14 cmH2O => mortalité plus élevée
- Prone position en condition isocapnique reduit DP
- ECCO2-R to reduce DP is under investigation

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D., Laurent Brochard, M.D., Eduardo L.V. Costa, M.D., David A. Schoenfeld, Ph.D., Thomas E. Stewart, M.D., Matthias Briel, M.D., Daniel Talmor, M.D., M.P.H., Alain Mercat, M.D., Jean-Christophe M. Richard, M.D., Carlos R.R. Carvalho, M.D., and Roy G. Brower, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

Marcelo B.P. Amato, M.D., Maureen O. Meade, M.D., Arthur S. Slutsky, M.D., Laurent Brochard, M.D., Eduardo L.V. Costa, M.D., David A. Schoenfeld, Ph.D., Thomas E. Stewart, M.D., Matthias Briel, M.D., Daniel Talmor, M.D., M.P.H., Alain Mercat, M.D., Jean-Christophe M. Richard, M.D., Carlos R.R. Carvalho, M.D., and Roy G. Brower, M.D.

ABSTRACT

BACKGROUND

Mechanical-ventilation strategies that use lower end-inspiratory (plateau) airway pressures, lower tidal volumes (V_T), and higher positive end-expiratory pressures (PEEPs) can improve survival in patients with the acute respiratory distress syndrome (ARDS), but the relative importance of each of these components is uncertain. Because respiratory-system compliance (C_{rs}) is strongly related to the volume of aerated remaining functional lung during disease (termed functional lung size), we hypothesized that driving pressure ($\Delta P = V_T/C_{rs}$), in which V_T is intrinsically normalized to functional lung size (instead of predicted lung size in healthy persons), would be an index more strongly associated with survival than V_T or PEEP in patients who are not actively breathing.

METHODS

Using a statistical tool known as multilevel mediation analysis to analyze individual data from 3562 patients with ARDS enrolled in nine previously reported randomized trials, we examined ΔP as an independent variable associated with survival. In the mediation analysis, we estimated the isolated effects of changes in ΔP resulting from randomized ventilator settings while minimizing confounding due to the baseline severity of lung disease.

RESULTS

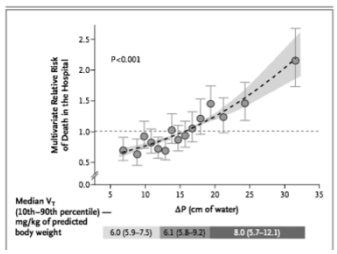
Among ventilation variables, ΔP was most strongly associated with survival. A 1-SD increment in ΔP (approximately 7 cm of water) was associated with increased mortality (relative risk, 1.41; 95% confidence interval [CI], 1.31 to 1.51; P<0.001), even in patients receiving "protective" plateau pressures and V_T (relative risk, 1.36; 95% CI, 1.17 to 1.58; P<0.001). Individual changes in V_T or PEEP after randomization were not independently associated with survival; they were associated only if they were among the changes that led to reductions in ΔP (mediation effects of ΔP, P=0.004 and P=0.001, respectively).

CONCLUSIONS

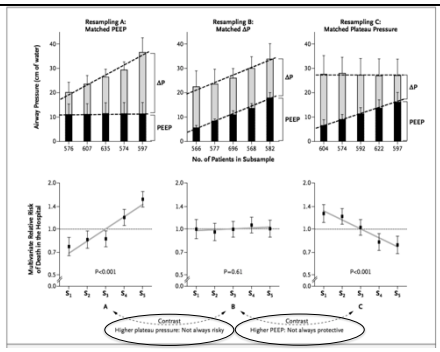
We found that ΔP was the ventilation variable that best stratified risk. Decreases in ΔP owing to changes in ventilator settings were strongly associated with increased survival. (Funded by Fundação de Amparo e Pesquisa do Estado de São Paulo and others.)

From the Cardio-Pulmonary Department, Pulmonary Division, Heart Institute (InCor), University of São Paulo (M.B.P.A., E.L.V.C., C.R.R.C.), and the Research and Education Institute, Hospital Sírio-Libanês (E.L.V.C.) — both in São Paulo; the Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, ON (M.O.M., T.E.S., M.B.), and the Keenan Research Centre for Biomedical Science, St. Michael's Hospital (A.S.S., L.B.), and the Interdepartmental Division of Critical Care Medicine (A.S.S., L.B., D.T.), University of Toronto (A.S.S., L.B.), Toronto — all in Canada; the Massachusetts General Hospital Biostatistics Center, Harvard Medical School (D.A.S.), and Department of Anesthesia, Critical Care, and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School (D.T.) — both in Boston; the Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland (M.B.); the Department of Intensive Care and Hyperbaric Medicine, Angers University Hospital (CHU), Angers (J.-C.M.R.), the Department, General Hospital of Annecy, Annecy (J.-C.M.R.), and INSERM UMR 955, Créteil (J.-C.M.R.) — all in France; and the Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore (J.G.H.). Address reprint requests to Dr. Amato at Faculdade de Medicina, Universidade de São Paulo, Av. Dr. Arnaldo 455, sala 2144 (2nd Fl.), 01246-903, São Paulo, Brazil, or at amato.marcelo.bp@gmail.com.

N Engl J Med 2015;372:747-55.
DOI: 10.1056/NEJMsa1410639



The results showed that a lower DP was the ventilator variable the most strongly associated to improved clinical outcome; any change in VT, VT/PBW, Pplat, and PEEP affected clinical outcome only when modifying DP, which appeared to be the strongest mediator of the effects of all ventilator settings on survival.



Impressively, changes in Pplat led to improved survival when associated to a lower DP, did not modify clinical outcome in case of unchanged DP and worsened mortality if resulting in any DP increase.

- Une augmentation de la Peep n'est bénéfique que quand elle s'accompagne d'une diminution de DP.
- Une augmentation de pression plateau n'est pas dangereuse si DP reste constant (strain dyn vs strain statique)
- DP est une evaluation du strain dynamique
- Rapporter le Vt au parenchyme aéré (càd la compliance) semble plus logique que de le rapporter au PBW

Research

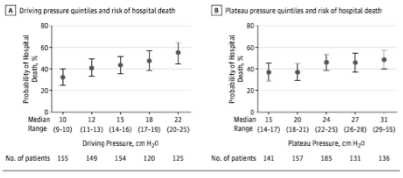
JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

JAMA. 2016;315(8):788-800.

Figure 5. Driving Pressure and Plateau Pressure and Outcome From ARDS



A, Mortality increased with increasing quintiles of driving pressure on first day of ARDS. B, The relationship between mortality and quintiles of plateau pressure is provided for comparison. Error bars indicate 95% confidence interval.

Higher survival was detected in patients with DP 14 cmH2O. In addition, a linear relationship between quintiles of DP and ICU mortality was documented, thus hypothesizing that, although DP>14cmH2O can predict a worse outcome, a well tolerated threshold for such parameter is yet to be identified. It must be noted that the design of the study, aiming at describing ARDS management in a wide variety of institutions and outside the procedures of rigorously designed clinical trials, corroborates the relevance, the external validity, and the reproducibility of the 'driving pressure approach' in the clinical setting.

JAMA. 2016;315(8):788-800.

Table 4. Use of Adjunctive and Other Optimization Measures in Invasively Ventilated Patients With Acute Respiratory Distress Syndrome[a]

	Patients of No. (%) [95% CI]				
	All (n = 2377)	Mild[a] (n = 498)	Moderate[a] (n = 1150)	Severe[a] (n = 729)	*P* Value[b]
Neuromuscular blockade	516 (21.7) [20.1-23.4]	34 (6.8) [4.8-9.4]	208 (18.1) [15.9-20.4]	274 (37.8) [34.1-41.2]	<.001
Recruitment maneuvers	496 (20.9) [19.2-22.6]	58 (11.7) [9.0-14.8]	200 (17.4) [15.2-19.7]	238 (32.7) [29.3-36.2]	<.001
Prone positioning	187 (7.9) [6.8-9.0]	5 (1.0) [0.3-2.3]	63 (5.5) [4.2-7.0]	119 (16.3) [13.7-19.2]	<.001
ECMO	76 (3.2) [2.5-4.0]	1 (0.2) [0.05-1.2]	27 (2.4) [1.6-3.4]	48 (6.6) [4.9-8.6]	<.001
Inhaled vasodilators	182 (7.7) [6.6-8.8]	17 (3.4) [02.0-5.4]	70 (6.1) [4.8-7.6]	95 (13.0) [10.7-15.7]	<.001
HFOV	28 (1.2) [0.8-1.7]	3 (0.6) [0.1-1.7]	14 (1.2) [0.7-2.0]	11 (1.5) [0.8-2.7]	.347
None of the above	1431 (60.2) [58.2-62.2]	397 (79.7) [75.9-83.2]	750 (65.2) [62.4-68.0]	284 (39.0) [35.4-42.6]	<.001
Esophageal pressure catheter	19 (0.8) [0.04-1.4]	2 (0.4) [0.04-1.4]	8 (0.7) [0.3-1.3]	9 (1.2) [0.6-2.3]	.233
Tracheostomy	309 (13.0) [11.6-14.4]	48 (9.6) [7.1-12.6]	155 (13.5) [11.6-15.6]	106 (14.5) [12.1-17.3]	.034
High-dose corticosteroids[c]	425 (17.9) [16.4-19.5]	61 (12.3) [9.5-15.5]	194 (16.9) [14.7-19.2]	170 (23.3) [20.3-26.6]	<.001
Pulmonary artery catheter	107 (4.5) [3.7-5.4]	9 (1.8) [0.8-3.4]	53 (4.6) [3.4-6.0]	45 (6.2) [4.5-8.2]	.001

Abbreviations: ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HFOV, high-frequency oscillatory ventilation; PEEP, positive end-expiratory pressure.

[a] For this analysis, ARDS severity was defined based on the patients' worst severity category over the course of their ICU stay in patients who developed ARDS on day 1 or 2.

[b] *P* value represents comparisons across the ARDS severity categories for each variable.

[c] High-dose corticosteroids was defined as doses that were equal to or greater than the equivalent of 1 mg/kg of methylprednisolone.

Recognition of ARDS

ARDS was underdiagnosed, with 60.2% of all patients with ARDS being clinician-recognized. Clinician recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) for mild ARDS to 78.5% (95% CI, 74.8%-81.8%) for severe ARDS (eTable 4 in the Supplement). Clinician recognition of ARDS at the time of fulfillment of ARDS criteria was 34.0% (95% CI, 32.0-36.0), suggesting that diagnosis of ARDS was frequently delayed.

JAMA. 2016;315(8):788-800.

Conclusions
Among ICUs in 50 countries, the period prevalence of ARDS was 10.4% of ICU admissions. This syndrome appeared to be underrecognized, undertreated, and associated with a high mortality rate. These findings indicate the potential for improvement in management of patients with ARDS.

JAMA. 2016;315(8):788-800.

En conclusion

- Stress et strain sont des déterminants majeurs des VILI
- Strain et stress ne peuvent être prédits à partir de Vt et Pplat
- Stress et strain sont difficiles à mesurer en pratique clinique courante
- Une pression plateau limitée à 30 cmH2O sur évalue parfois le stress pulmonaire alors que un Vt de 6ml/kg sous évalue parfois le strain (baby lung)
- Une meilleure reconnaissance de l'ARDS, une meilleure application des recommandations internationales seraient déjà un premier pas vers une amélioration de la prise en charge
- La mesure de la pression motrice (driving pressure) pourrait être une alternative à la mesure du strain dynamique