ARDS

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INTENSIVE CARE MEDICINE
CHUM

Treatment

- Treat the precipitating cause

- Support
  - NIPPV and high-flow nasal cannula
  - Invasive mechanical-ventilation needed in most cases

- *MV can harm patients*

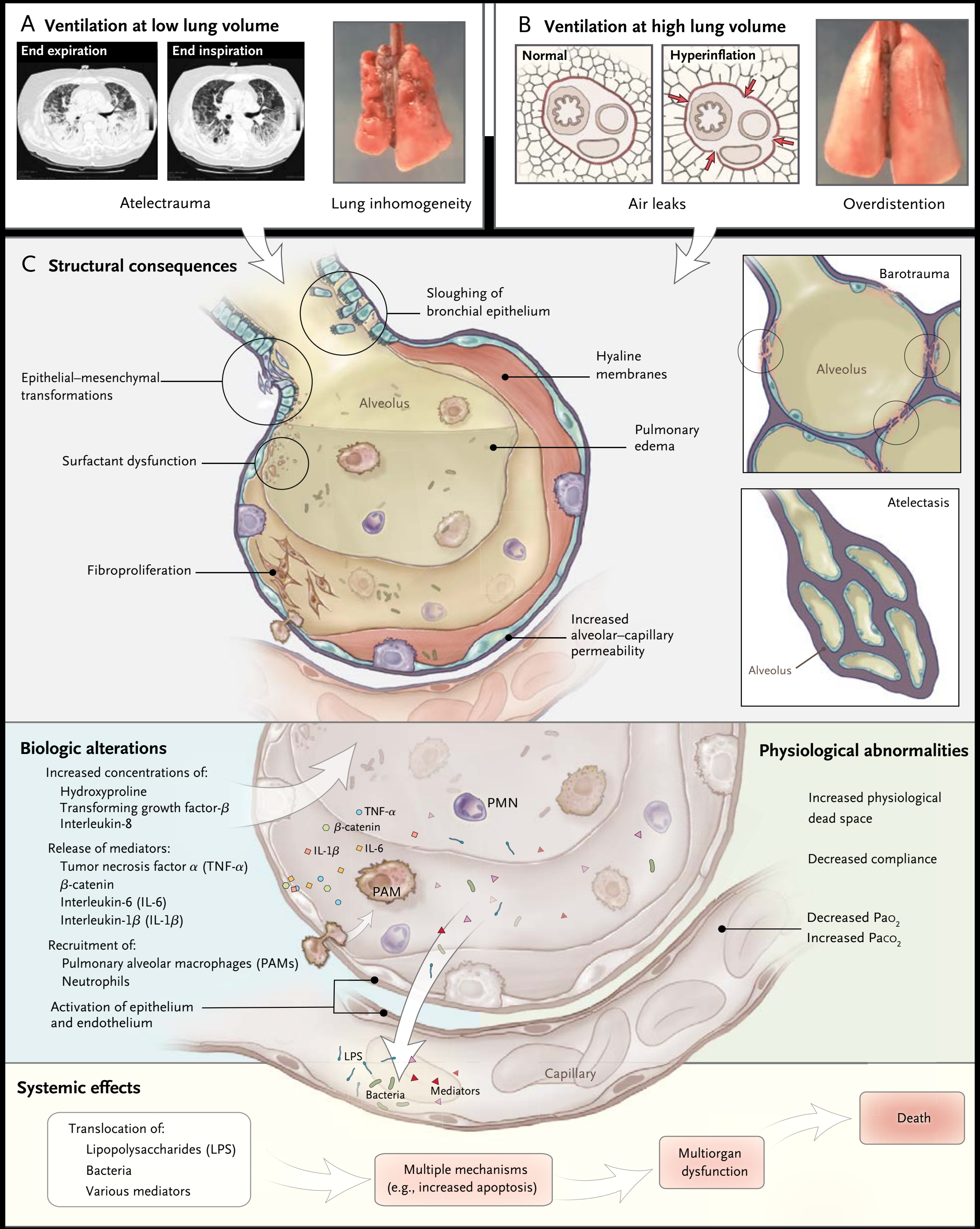
HFNO / CPAP / NIV

- No specific ARDS trials
- Definition of treatment failure
- Delay in intubation = increased mortality?
- High transpulmonary pressures from respiratory drive = increased P-SILI?

Ventilator-induced lung Injury

- ‘Respirator lung’ coined in 1967
- Term VILI coined by Webb and Tierney (AJRCCM 1974, 110 (5), p. 556)
- Indistinguishable from ARDS itself

- **Key concepts**
  - Baby lung
  - Volutrauma and overdistension
  - Atelectrauma
  - Biotrauma (Stress + strain + mechanical power)



A Ventilation at low lung volume
End expiration
End inspiration
Atelectrauma
Lung inhomogeneity
B Ventilation at high lung volume
Normal
Hyperinflation
Air leaks
Overdistention
C Structural consequences
Sloughing of bronchial epithelium
Epithelial–mesenchymal transformations
Hyaline membranes
Alveolus
Pulmonary edema
Surfactant dysfunction
Fibroproliferation
Increased alveolar–capillary permeability
Barotrauma
Alveolus
Atelectasis
Alveolus
Biologic alterations
Increased concentrations of:
Hydroxyproline
Transforming growth factor-β
Interleukin-8
Release of mediators:
Tumor necrosis factor α (TNF-α)
β-catenin
Interleukin-6 (IL-6)
Interleukin-1β (IL-1β)
Recruitment of:
Pulmonary alveolar macrophages (PAMs)
Neutrophils
Activation of epithelium and endothelium
TNF-α
β-catenin
IL-1β
IL-6
PMN
PAM
Physiological abnormalities
Increased physiological dead space
Decreased compliance
Decreased Pa_{O_2}
Increased Pa_{CO_2}
LPS
Bacteria
Mediators
Capillary
Systemic effects
Translocation of:
Lipopolysaccharides (LPS)
Bacteria
Various mediators
Multiple mechanisms (e.g., increased apoptosis)
Multiorgan dysfunction
Death

Baby Lung

- Lungs not stiff but small
  - Ratio respiratory system compliance : residual healthy lung = 1:1 (compliance 20 cc/cmH2O = 20% open lung)

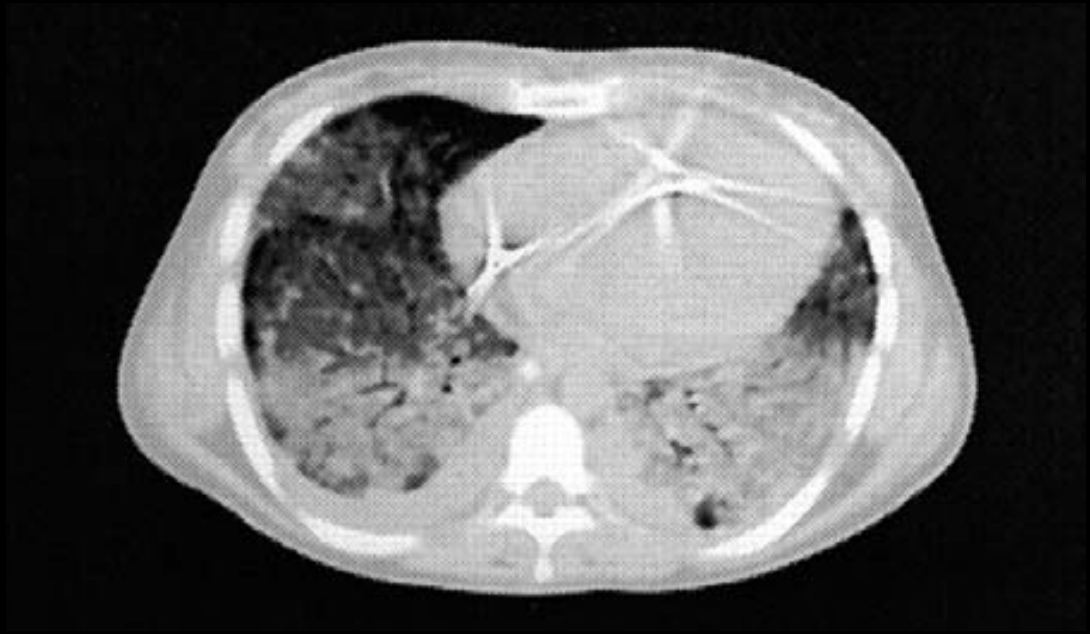
- Heterogeneity
  - Boundary zones = stress junctions
  - Overdistension of normal and opened lung areas
  - Stress and strain = inflammation / biotrauma

Baby Lung

- **Two distinct anatomical structures**

- **Posterior/dorsal** = collapsed/consolidated
  - Intrapulmonary shunt
  - Atelectrauma

- **Anterior/Ventral** = aerated (baby lung)
  - Dead space
  - Volutrauma (overdistension)



Ventilator-induced lung Injury

- **Barotrauma**
  - Misleading
  - Cause of air leaks remains overdistension, not high airway pressure
  - Pneumothorax
  - Pneumomediastinum
  - Pneumopericardium
  - Subcutaneous emphysema

Ventilator-induced lung Injury

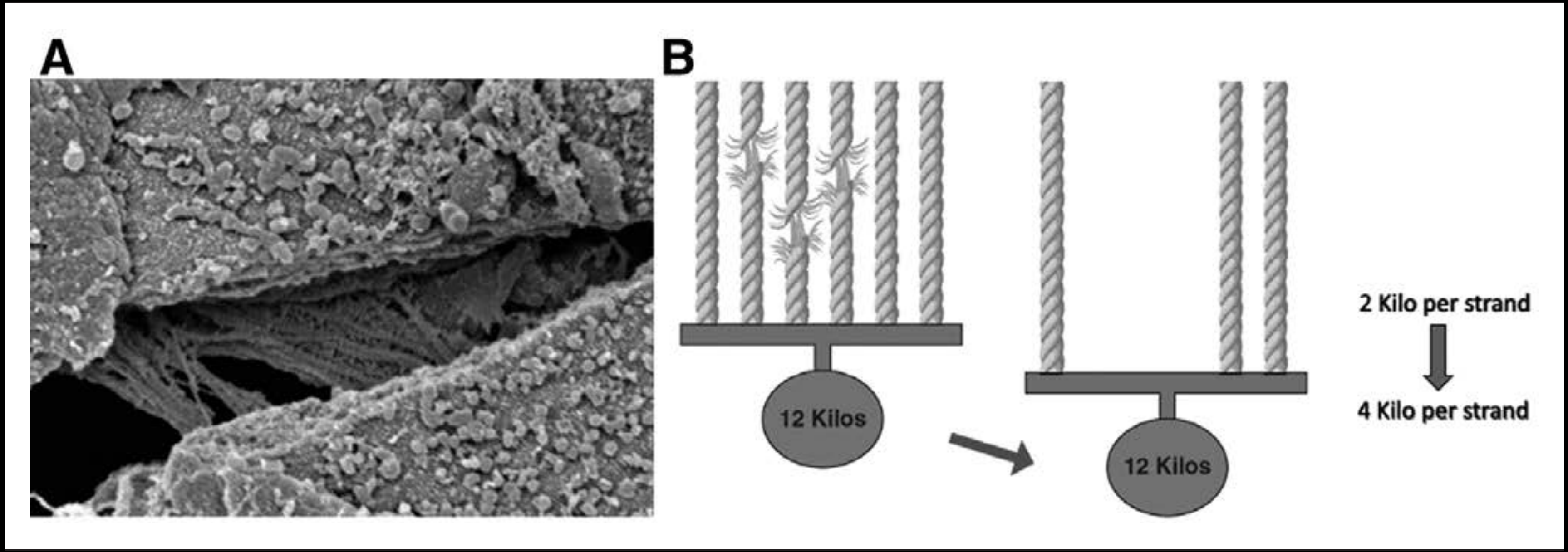
- **Volutrauma / Overdistension**
  - Dreyfuss et al., Am Rev Respir Dis 1988, 137, p. 1159
  - Animal study
  - Baby lung
  - **High tidal volumes** and high airway pressures = pulmonary oedema
  - Same high airway pressure but **limited tidal volumes** (chest and abdominal straps) = no pulmonary oedema

Ventilator-induced lung Injury

- **Atelectrauma**
  - Lung heterogeneity
  - Collapsed and non-aerated zones
  - Repetitive opening and closing of the airways
  - Regional hypoxemia and surfactant dysfunction
  - Boundary zones = opened and closed lung units = stress raisers

Ventilator-induced lung Injury

- **Biotrauma**
  - ‘Common final pathway’
  - Stress and strain
  - Activation of mechano-transduction-related inflammation (**cellular**)
  - Breaking of molecular bonds in the extracellular matrix (**tissular**)
  - Vascular barrier compromise = alveolar flooding = surfactant dysfunction = increased alveolar surface tension = more stress and strain = vicious cycle (**vascular**)



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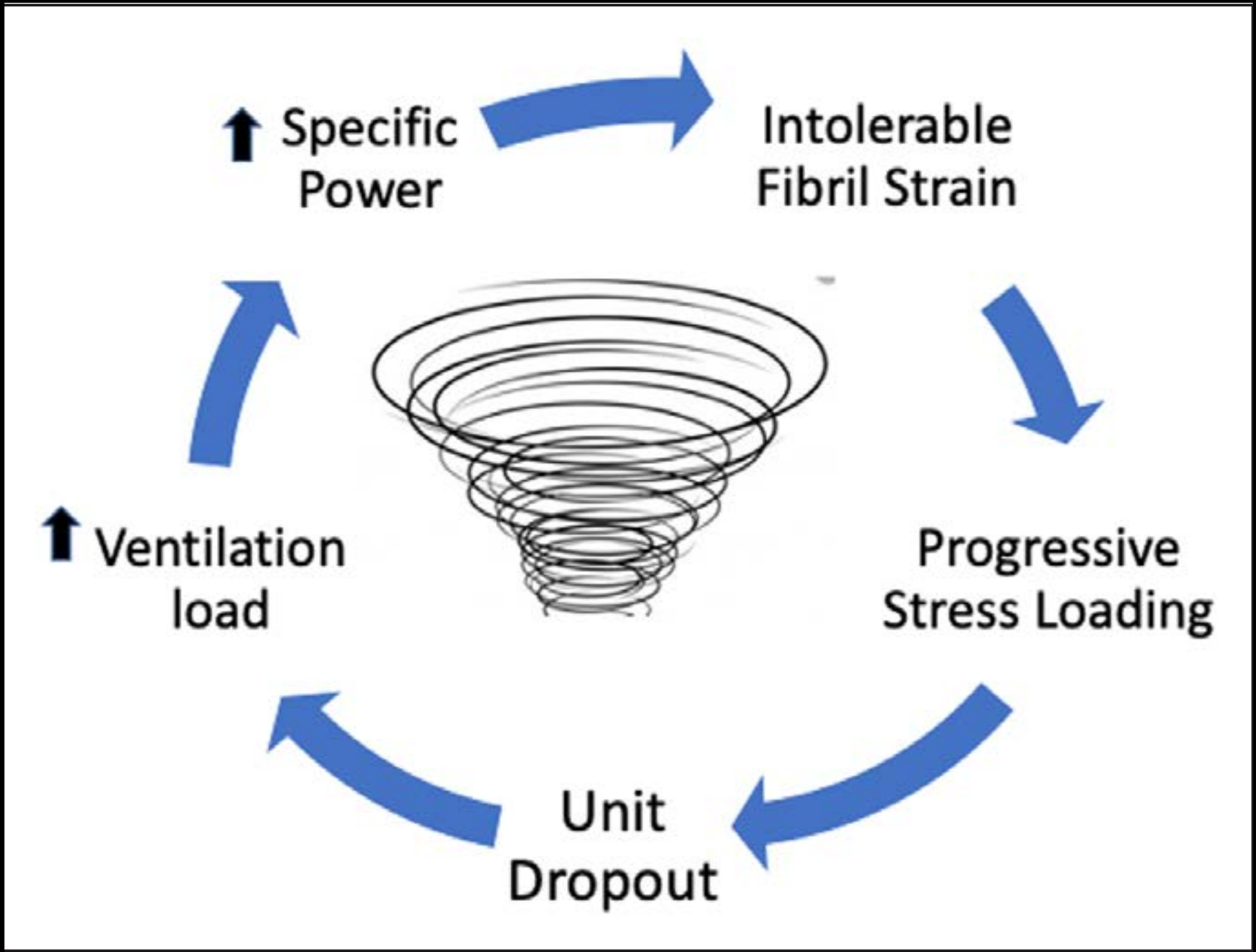

Specific
Power
Intolerable
Fibril Strain
Progressive
Stress Loading
Unit
Dropout
Ventilation
load

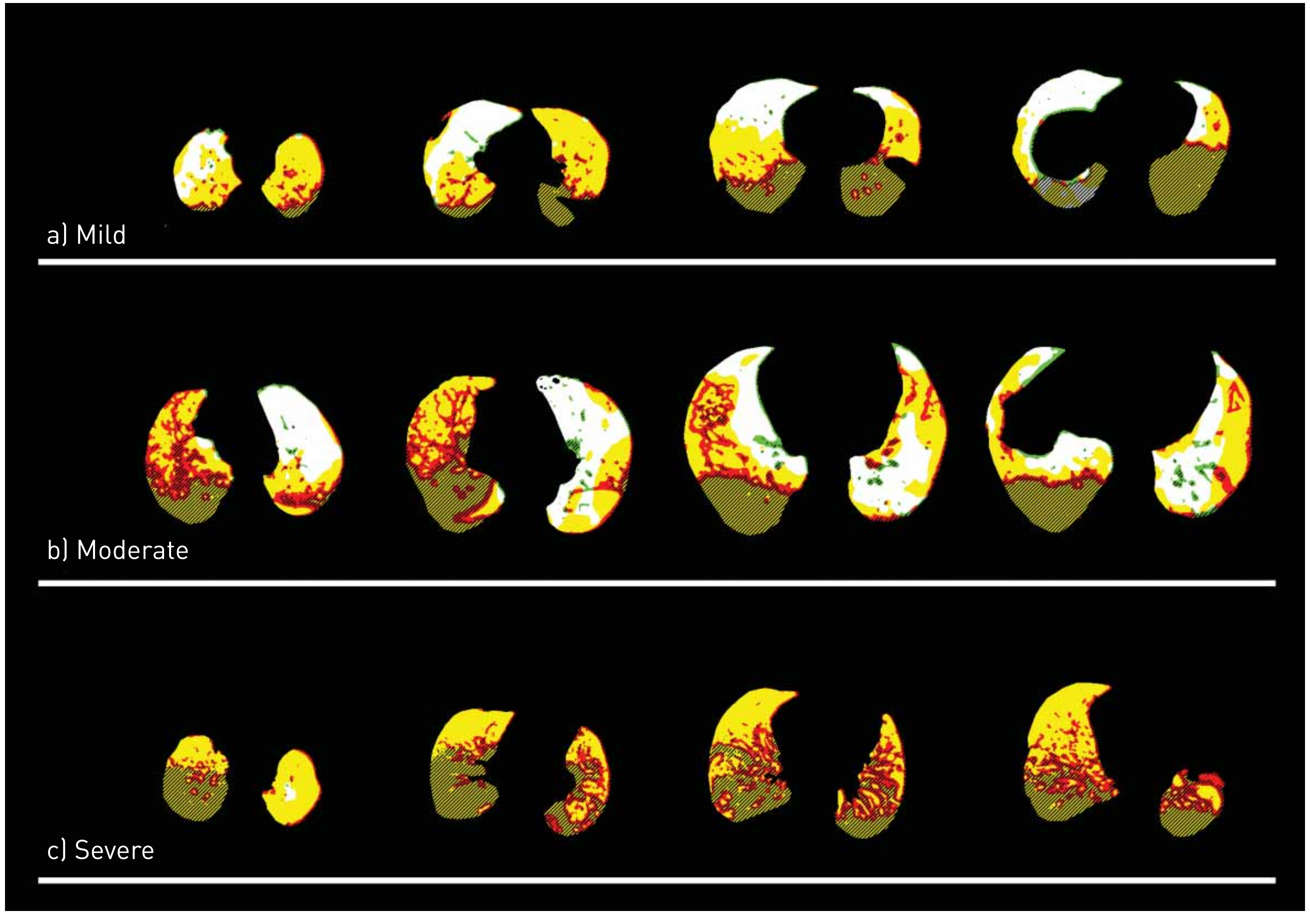

FIGURE 1 Interaction between [^{18}F]FDG uptake rate and lung inhomogeneity in mild, moderate and severe ARDS. Lung compartments at different lung levels from the apex to the base. Lung compartment colour code: white, homogeneous with normal [^{18}F]FDG uptake rate; green, inhomogeneous with normal [^{18}F]FDG uptake rate; yellow, homogeneous with high [^{18}F]FDG uptake rate; red, inhomogeneous with high [^{18}F]FDG uptake rate; shadowed areas represent not inflated tissue. Patient a) mild ARDS (polytrauma with bilateral pulmonary contusion), P_{aO_2}/F_{iO_2} 257, ICU outcome: alive. Patient b) moderate ARDS (bacterial pneumonia: *Streptococcus pneumoniae*), P_{aO_2}/F_{iO_2} 172, ICU outcome: alive. Patient c) severe ARDS (bacterial pneumonia: *Staphylococcus aureus*) P_{aO_2}/F_{iO_2} 87, ICU outcome: dead. See online supplementary material for images of all the patients. [^{18}F]FDG: [^{18}F]2-fluoro-2-deoxy-D-glucose; ARDS: acute respiratory distress syndrome; P_{aO_2}: arterial oxygen tension; F_{iO_2}: inspiratory oxygen fraction; ICU: intensive care unit.

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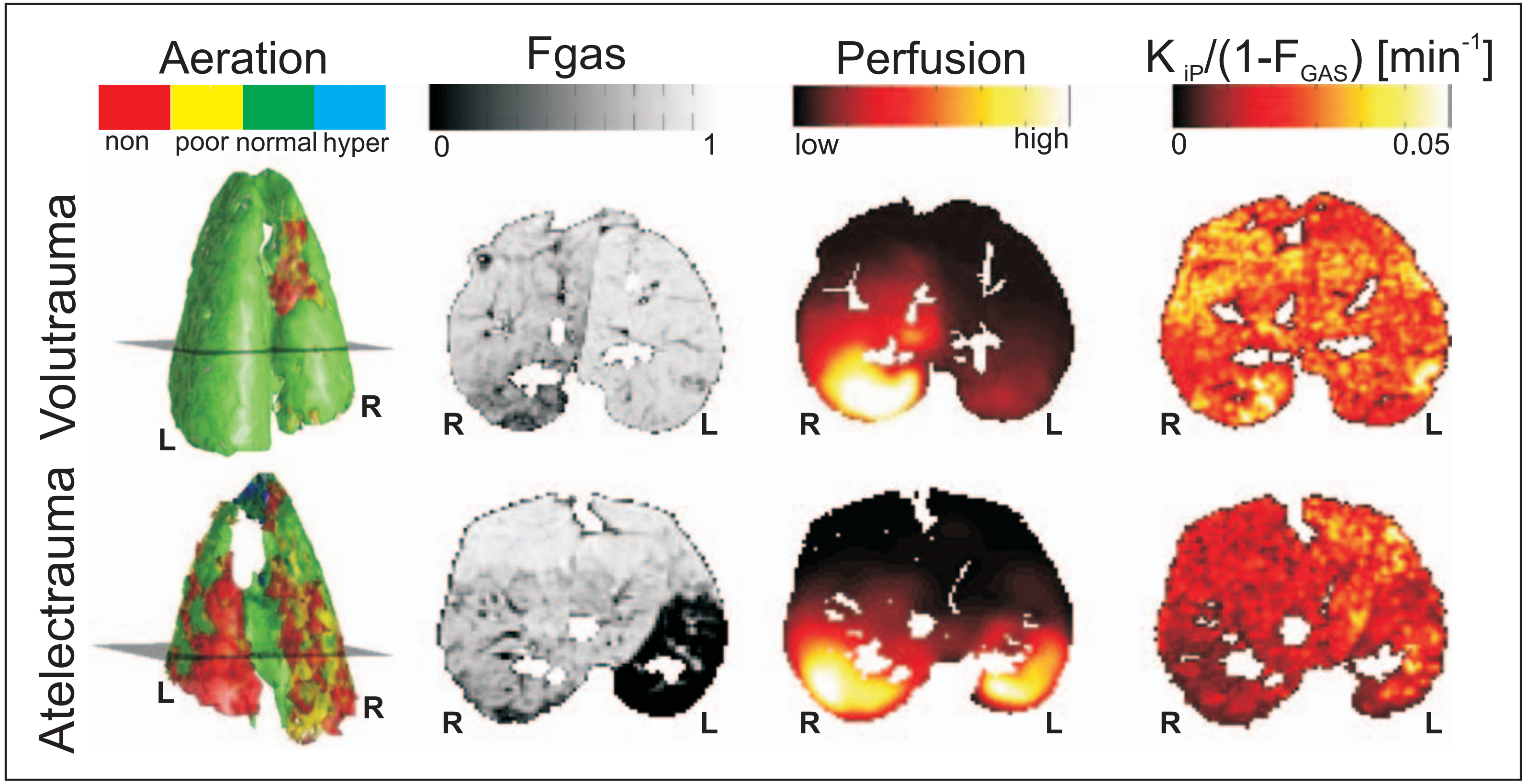

Figure 2. Three-dimensional illustration of the distributions of aeration and single-slice images of gas fraction, perfusion, and [18F]-fluorodeoxyglucose uptake rate (K_i) of representative animals. Three-dimensional illustration of the distribution of aeration, as well as 2D slice images of the gas fraction (F_{GAS}), perfusion, and [18F]-fluorodeoxyglucose uptake rate (K_{iP}, computed voxel by voxel using Patlak method, and normalized to [$1 - F_{GAS}$]) in representative animals of the volutrauma (*upper*) and atelectrauma groups (*lower*), respectively. Two-dimensional slice images represent the maximal cross-sectional areas of the respective slice in the whole lung images. *Horizontal color bars* denote the respective scales. Hyper = hyperaerated compartment, L = left VILI (ventilated) lung, non = nonaerated compartment, normal = normally aerated compartment, poor = poorly aerated compartment, R = right control (nonventilated) lung.

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Ventilator-induced lung Injury

- **Stress**
  - Net force acting on a material structure
  - Net distending pressures applied on the lung parenchyma, opposed by the elastic recoil pressures generated by the tensioned alveolar walls and lung scaffold
  - PL (Paw – Ppl) under zero flow conditions
  - Surrogate = Plateau pressure

Ventilator-induced lung Injury

- **Strain**
  - Deformation experienced by a structure, defined by a change in length or volume compared to the initial length and volume of the structure
  - Vt / FRC
  - Surrogate = Vt

Ventilator-induced lung Injury

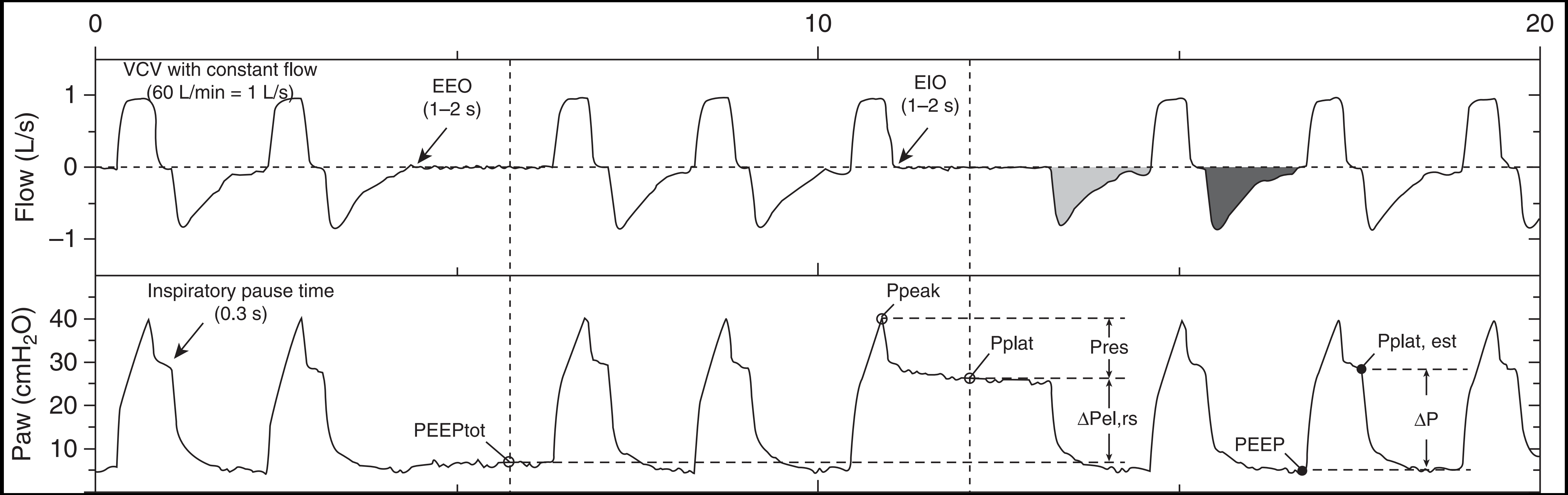
- Stress and strain = delivery of mechanical energy to the lung
- Two possibilities
  - Mechanical energy so great = stress-at-rupture (barotrauma)
  - Mechanical energy below stress-at-rupture threshold and sufficient time = lung damage
- *Energy X time = mechanical power = VILI*

Motion Equation

- ***Paw = Pvent + Pmus = Pel + Pres + PEEPtot + Pin***

- During passive ventilation, Pmus is nil
- Aside from HFOV and coughing, inertance is negligible

- ***Paw = (El X Vt) + (R X Q) + PEEPtot***



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Mechanical Power

- **Mechanical power**
  - Amount of **energy transferred** from the mechanical ventilator to the **respiratory system** within a given **timeframe**
  - Parameters set by **clinician** = Vt + RR + inspiratory flow + PEEP
  - **Patient-dependent** variables = Peak + plateau + driving pressures

- **Mechanical energy**
  - Sum of potential and kinetic energy
  - **Potential energy** = baseline tension of respiratory system (**PEEP**)
  - **Kinetic energy** = required to overcome elastic and resistive forces of the respiratory system to generate movement (**elastance** and **resistance**)

- **Intensity**
  - Mechanical power **normalized** to the amount of **ventilated pulmonary surface**
  - Reference to baby lung theory

$$\text{Power}_{rs} = 0.098 \cdot RR \cdot \left\{ \Delta V^2 \cdot \left[\frac{1}{2} \cdot E_{rs} + RR \cdot \frac{(1 + I:E)}{60 \cdot I:E} \cdot R_{aw} \right] + \Delta V \cdot PEEP \right\}$$

Mechanical Power

$$E_{RS}\,\frac{1}{2}\Delta V^2$$

Dynamic Power

$$\Delta V^2 \cdot RR \cdot \frac{(1 + I:E)}{60 \cdot I:E} \cdot R_{aw}$$

Resistive Power

$$\Delta V \cdot PEEP$$

Static Power

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			MECHANICAL POWER (J/MIN)					
			Power of inspiration ($cmH_2O \cdot L/min$)					X Conversion factor
			Work of inspiration ($cmH_2O \cdot L$)				X Rate (bpm)	
			Volume (L) X	Pressure (cmH2O)				
				Elastic static component +	Elastic dynamic component +	Resistive component		
VCV	Extended equation	Gattinoni et al	ΔV	$PEEP$	$\Delta V \cdot \frac{1}{2} EL_{rs}$	$RR \cdot \frac{(1 + I:E)}{(60 \cdot I:E)} \cdot R_{aw}$	RR	0,098
	Simplified equation	Gattinoni et al	ΔV	$Peak\ Pressure - \frac{(Plateau\ Pressure - PEEP)}{2}$			RR	0,098
	Surrogate	Giosa et al	ΔV	$\frac{Peak\ Pressure + PEEP + F/6}{2}$			RR	0,1
PCV	Extended equation	Van der Meijden et al	ΔV	$PEEP$	$P_{insp} \cdot \left(1 - e^{\frac{-T_{insp}}{\tau}}\right)$		RR	0,098
		Becher et al	$(PEEP + P_{insp}) \cdot \Delta V - P^2_{insp} \cdot C \cdot \left(0.5 - \left(\frac{R \cdot C}{T_{slope}}\right) + \left(\frac{R \cdot C}{T_{slope}}\right)^2 \cdot \left(1 - e^{\frac{-T_{slope}}{R \cdot C}}\right)\right)$				RR	0,098
	Surrogate	Becher et al	ΔV	$PEEP$	P_{insp}		RR	0,098

Fig. 1 Mechanical power equations for volume-controlled and pressure-controlled ventilation. Six equations for the calculation of mechanical power are available to date. For volume-controlled ventilation, the extended equation proposed by Gattinoni et al. still represents the reference equation and the simplified equation proposed by the same group is a mathematical rearrangement of it, which means that the two formulas can be considered identical. The surrogate equation that we propose in this paper carries a small bias (underestimation), but also the advantage of being simple and easily available just by looking at the ventilator. For pressure-controlled ventilation, the two extended equations proposed by Van der Meijden et al. and by Becher et al. are both very accurate, but complex. As for our surrogate, the one proposed by Becher et al. carries a small bias (overestimation), but also the advantage of being simple and easily available just by looking at the ventilator

Mechanical Power

- Mechanical power differs according to **mode of ventilation**
  - Higher in VCV where peak pressure is higher than plateau pressure
  - PCV => peak pressure is equivalent to plateau pressure
- **Assisted ventilation**
  - Dissociation of mechanical power imparted by the machine vs. respiratory muscles

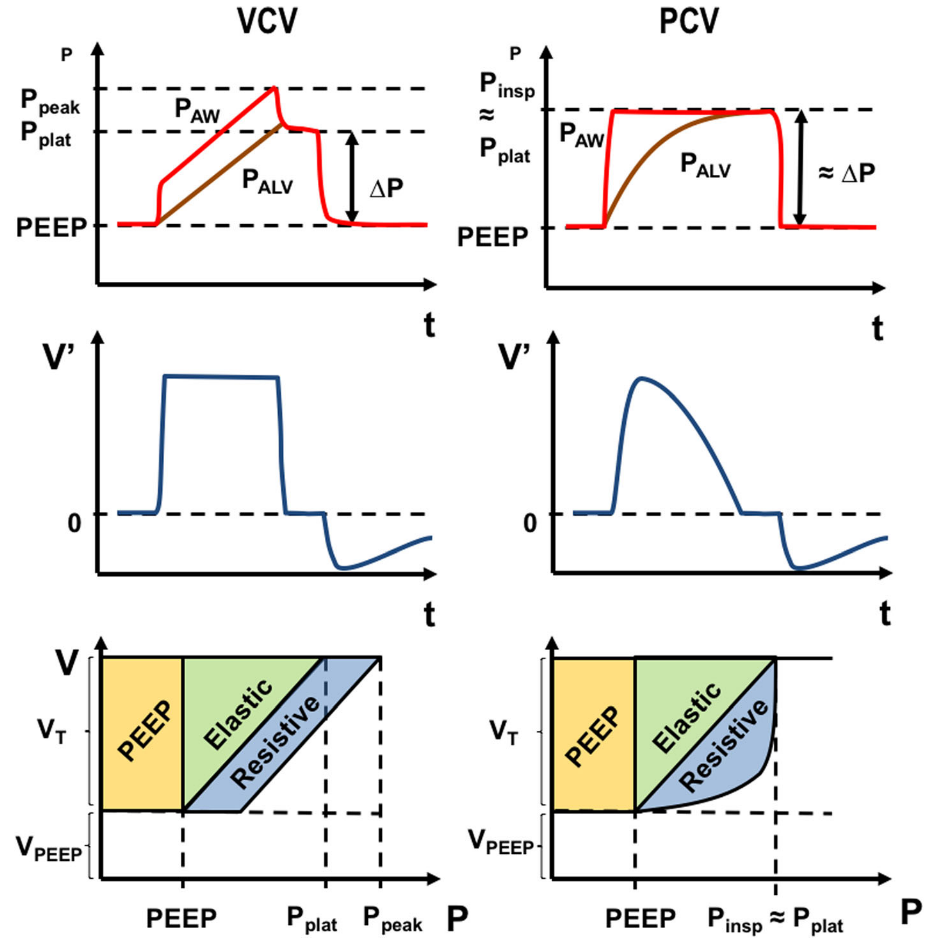


Fig. 5 Mechanical power during volume- and pressure-controlled ventilation. Top panels represent the typical pressure-time curve of these two controlled ventilation modes; middle panels, the flow-time curves; and bottom panels, the weight of different power components in the two ventilation modes. VCV, volume-controlled ventilation; PCV, pressure-controlled ventilation

Mechanical Power

- **Temporal factor**
  - Distribution of energy throughout the respiratory cycle
    - Potential energy accumulated during inspiration
    - Energy dissipation with lung tissue recoil during expiration
  - Consideration for RR (# of insults per minute)
  - Consideration for I:E ratio
    - Directly proportional with mechanical power
    - Higher I:E = shorter expiratory time = less energy dissipation = higher mechanical power

Mechanical Power

- No account for **intensity (spatial factor)**
  - Heterogeneity (regional + alveolar stress and strain)
  - Regional intensity
    - Energy applied to **opened units** (baby lung - volutrauma)
  - Alveolar intensity
    - Energy applied to **boundary zones** (atelectrauma)
  - Normalize to open and available lung?
    - FRC measurements?
    - SCAN-derived aerated lung?
    - Ideal body weight?
  - *Measured mechanical power* ***underestimation***

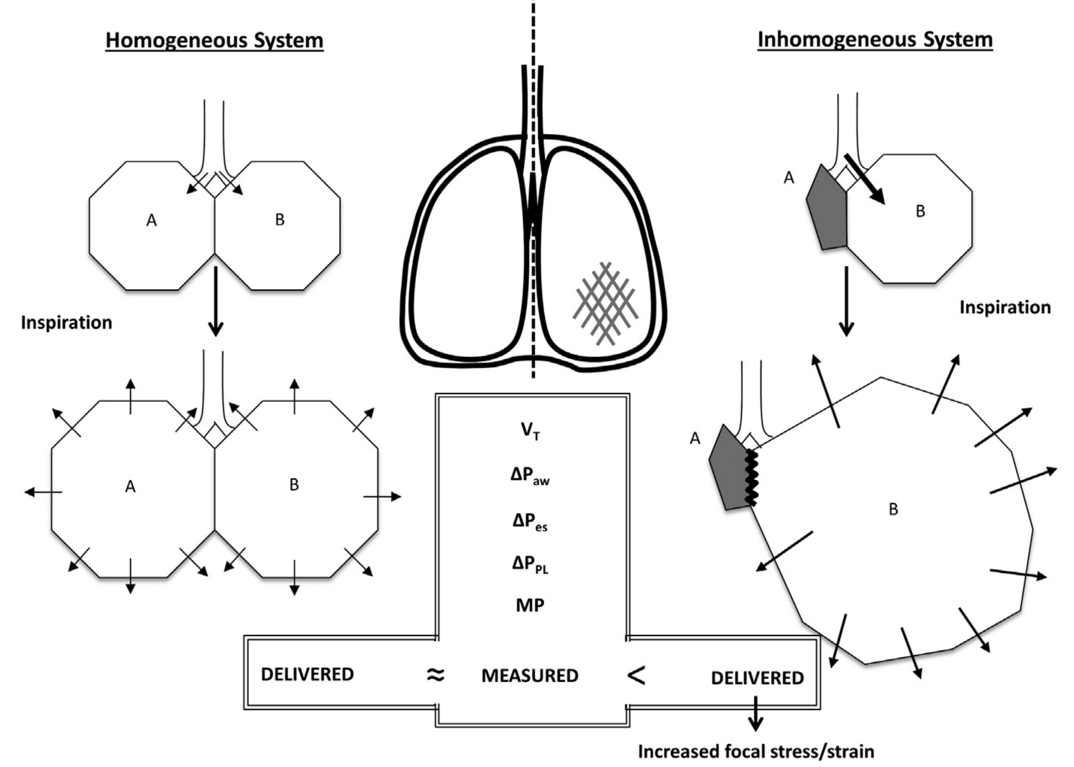


Fig. 1. (*Left*) Theoretic model of a homogeneous system, represented as 2 normal and identical pulmonary units. (*Right*) Theoretic model of an inhomogeneous system, represented as one atelectatic unit (*gray*) and a normal, contiguous unit (*white*). ΔP_{aw}, airway driving pressure; ΔP_{es}, driving esophageal pressure; ΔP_{pl}, driving transpulmonary pressure; MP, mechanical power; V_t, tidal volume.

Mechanical Power

- Stronger association with outcome than any of the components
- Prognostic threshold?
  - 12-18 J/min according to different studies (mainly animal)
  - Yet to be defined in humans
  - Normalization to the size of the lungs (body weight? CRF? Compliance?)
  - Not all the elements of MP have equal weight = iso-power packages

- Recruitability, best-PEEP determination and protective ventilation?
  - Achieving the lowest mechanical power and intensity

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*

- ARMA trial (NEJM 2000, 342 (18), p. 1301)
- Maintain low Vt and airway pressures
- Maintain lung open and avoid cyclic lung collapse at end-expiration (role of PEEP)

ARDSnet Protocol

- Decreased mortality (40% vs. 31%)
- Should be standard of care
- Increased mortality in control group?

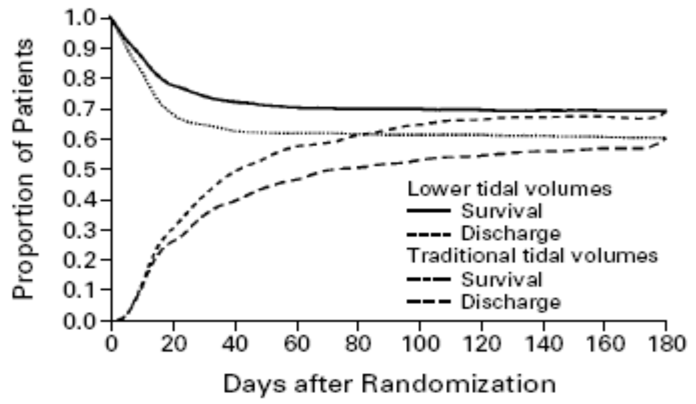


Figure 1. Probability of Survival and of Being Discharged Home and Breathing without Assistance during the First 180 Days after Randomization in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.

The status at 180 days or at the end of the study was known for all but nine patients. Data on these 9 patients and on 22 additional patients who were hospitalized at the time of the fourth interim analysis were censored.

TABLE 4. MAIN OUTCOME VARIABLES.*

VARIABLE	GROUP RECEIVING LOWER TIDAL VOLUMES	GROUP RECEIVING TRADITIONAL TIDAL VOLUMES	P VALUE
Death before discharge home and breathing without assistance (%)	31.0	39.8	0.007
Breathing without assistance by day 28 (%)	65.7	55.0	<0.001
No. of ventilator-free days, days 1 to 28	12±11	10±11	0.007
Barotrauma, days 1 to 28 (%)	10	11	0.43
No. of days without failure of nonpulmonary organs or systems, days 1 to 28	15±11	12±11	0.006

*Plus–minus values are means ±SD. The number of ventilator-free days is the mean number of days from day 1 to day 28 on which the patient had been breathing without assistance for at least 48 consecutive hours. Barotrauma was defined as any new pneumothorax, pneumomediastinum, or subcutaneous emphysema, or a pneumatocele that was more than 2 cm in diameter. Organ and system failures were defined as described in the Methods section.

ARDSnet Protocol

- **Aim for**
  - Vt 4-6 cc/Kg PBW
  - Plateau pressures (Pplat) < 30 cmH2O
  - SatO2 ≥ 88%, PaO2 > 55 mmHg (FiO2 ≤ 60%)
  - Adjust PEEP according to FiO2 scale
  - No recruitment in protocol
  - RR ≤ 35
  - Permissive hypercapnia with pH ≥ 7.30

ARDSnet Protocol

- Maintain **FiO2 < 60%**, aim for SaO2 > 88%
  - Prevention of *oxygen toxicity*
  - Controversial… Largely based on animal studies

- Security of *permissive hypoxemia* not documented
  - More cognitive impairment and psychiatric disorders?
  - Differences from patient to patient, organs to organs
  - Biomarkers?

Permissive Hypoxemia

- Two trials demonstrating potential benefits from conservative oxygen therapy

- **IOTA**, Lancet 2018, 391, p. 1693 (systematic review and meta-analysis)
  - Lower rate of death
  - Trials included were considerably more liberal for oxygen therapy in the usual-care groups
  - Few patients were critically ill

- **Oxygen-ICU** trial, JAMA 2016, 316, p. 1583 (single-center trial)
  - More ventilator free-days and decreased mortality
  - Heterogenous population (not specific to ARDS)
  - Time-weighted PaO2 = higher mortality for lower PaO2

Permissive Hypoxemia

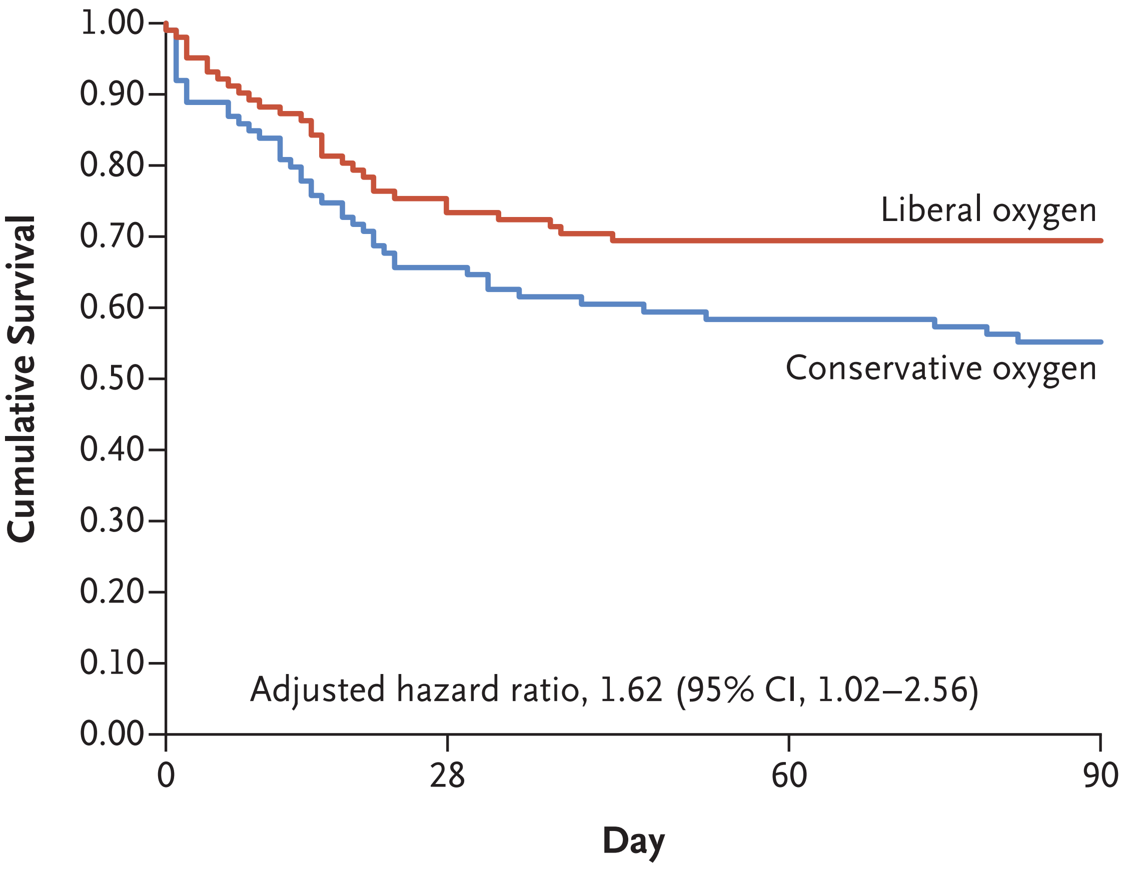
ICU-ROX	HOT-ICU	PILOT
NEJM 2020	NEJM 2021	NEJM 2022
1000 patients	2928 patients	2541 patients
ICU - Multicenter	ICU - Multicenter	ED + ICU – Single Center
Mechanical ventilation	< 60% mechanical ventilation	Mechanical ventilation
Not specific to ARDS	Not specific to ARDS (12-13%)	Not specific to ARDS (190 patients)
Post-hoc = increased mortality in sepsis? (ICM 2020)	Post-Hoc = increased survival in shock patients with liberal approach? (Br J Anesth 2022)	N/A
No differences in primary outcome	No differences in primary outcome	No differences in primary outcome

ORIGINAL ARTICLE

Liberal or Conservative Oxygen Therapy for Acute Respiratory Distress Syndrome

- $LOCO_2$ Trial, NEJM 2020, 382 (11), p. 999
- Multicenter randomized trial of 205 ARDS patients according to Berlin definition

- ***Trial stopped early for futility and safety concerns***



No. at Risk

	0	28	60	90
Liberal oxygen	102	74	69	63
Conservative oxygen	99	64	55	45

Figure 3. Kaplan–Meier Survival Curves over the First 90 Days.

Data regarding survival were censored at 90 days. Mortality was adjusted for age, ratio of Pa_{O_2} to F_{IO_2}, and Simplified Acute Physiology Score III.

28 day mortality = 34% vs. 26%

90 day mortality = 44% vs. 30%

5 cases of mesenteric ischemia

Trend toward more cardiac events (arrhythmias, tachycardia)

Permissive Hypoxemia

- Numerous challenges to its safety
  - Time-weighted PaO2 in OXYGEN-ICU (higher mortality for lower PaO2)
  - Higher mortality in septic subgroup in ICU-ROX (post-hoc analysis)
  - Signals of harm in $LOCO_2$
  - Retrospective review (CC 2008, 12:R156) = higher mortality for PaO2 < 67 mmHg
  - Systemic oxygenation target could help some tissue beds and harm others
  - Post-hoc analysis HOT-ICU = higher oxygen targets might be better in patients with shock (Br J Anaesth 2022, 128, p. 55)

- *Challenge to lower range of SpO2 tolerated in ARDS patients*

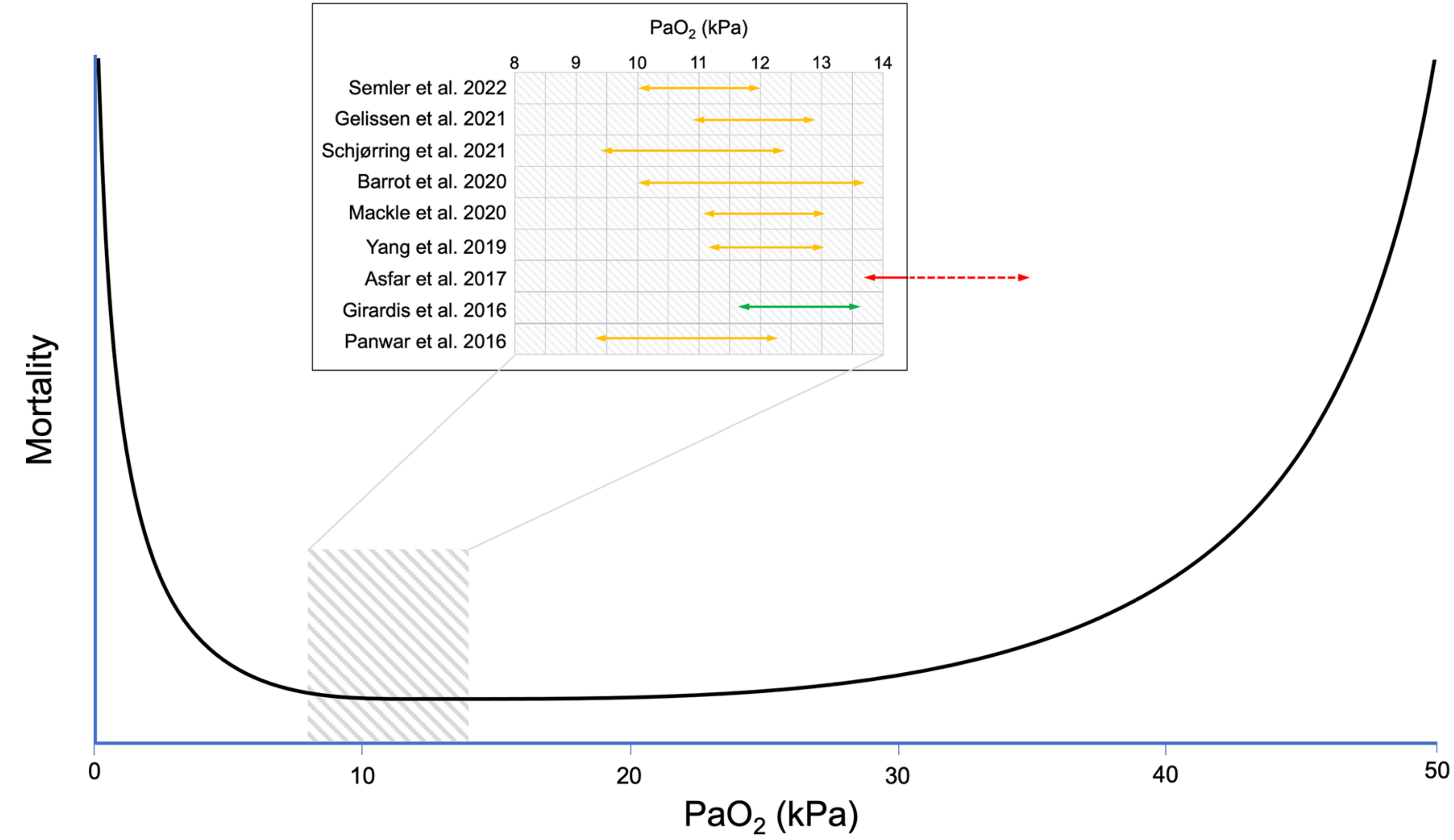


Fig. 1 A conceptual depiction of the proposed U-shaped relationship between arterial oxygenation and mortality in critically ill patients. The curve was adapted from Helmerhorst et al.'s graph of adjusted probability of in-hospital death by mean PaO_2 [6]. Additional findings (within the box) were superimposed from the trials included in a recent systematic review [9–16] and those published subsequently to it [3, 17]. Only trials that enrolled a mixed general ICU population were included. The inset box shows the difference between the reported (or approximated) achieved arterial oxygenation values in the intervention and comparator groups of each trial (represented by each arrow-head). Orange arrows denote trials with no difference in the primary outcome measure between lower and higher oxygenation levels; the green arrow denotes a trial in which lower oxygenation was favourable; the red arrow denotes a trial that was halted early due to safety concerns in the higher oxygenation group

ARDSnet Protocol

- **Ventilation mode**
  - **VCV**
  - No studies demonstrating superiority of PCV (no direct comparison)
  - Positive signals in studies of APRV
    - Only 2 trials comparing APRV and ARMA
    - CCM 2004 = 19 patients pilot study
    - ICM 2017 = 138 patients unicentric trial with sicker patients in control group
  - HFOV in severe subgroups?
    - AJRCCM 2017 = P/F ratio < 65?

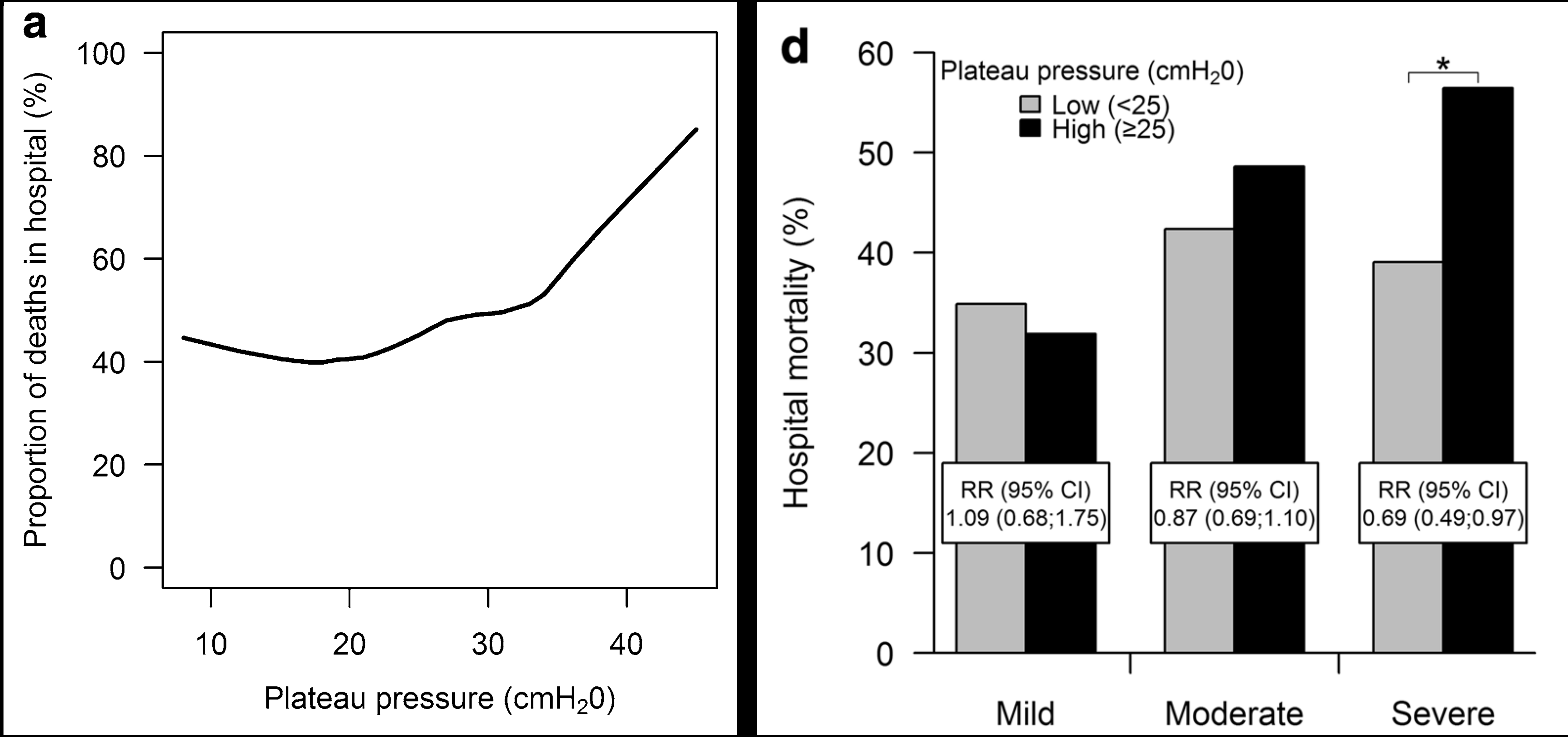
ARDSnet Protocol

- Calculate **ideal body weight**
  - ♂ = 50 + 0.91(height (cm) – 152.4)
  - ♀ = 45.5 + 0.91(height (cm) – 152.4)
  - Adjust Vt accordingly

- *Consider driving pressure and mechanical power?*
  - *PBW-based Vt ignores the lung volume actually available for ventilation*

ARDSnet Protocol

- Start at 8 cc/Kg => decrease to 6 cc/Kg in the following 4 hours
- Pplat q 4 hours (keep < 30 cmH2O)
  - If > 30, then decrease Vt by 1 cc/Kg, minimum 4 cc/Kg
  - If < 25, then increase Vt by 1 cc/Kg, maximum 6 cc/Kg
- If severe dyspnea, then increase Vt to 7-8 cc/Kg IF Pplat < 30 cmH2O
- Pplat > 30 tolerated IF pH < 7.15 OR Vt = 4 cc/Kg


a
100
80
60
40
20
0
Proportion of deaths in hospital (%)
10
20
30
40
Plateau pressure (cmH20)
d
60
50
40
30
20
10
0
Hospital mortality (%)
Plateau pressure (cmH20)
Low (<25)
High (≥25)
*
RR (95% CI)
1.09 (0.68;1.75)
RR (95% CI)
0.87 (0.69;1.10)
RR (95% CI)
0.69 (0.49;0.97)
Mild
Moderate
Severe

ARDSnet Protocol

- **Respiratory rate**
  - Never studied independently
  - Keep < 35/min
  - Aim for pH 7.30-7.45
  - Beware of intrinsic PEEP
    - Dead space and hemodynamic compromise
    - Better oxygenation by alveolar recruitment?
  - Increased RR = **increased mechanical power** = VILI
  - LUNG SAFE (ICM 2016, 42, p. 1865)
    - Increased mortality associated with elevated RR

Permissive Hypercapnia

- **Absolute contra-indications**
  - Pregnancy
  - Head injury and intra-cranial hypertension
  - Severe hemodynamic instability

- No patient in the ARDSnet benefited from NaHCO3 therapy
- Thus efficiency not well documented

Table 3. Respiratory Values during the First Seven Days of Treatment in Patients with Acute Lung Injury and the Acute Respiratory Distress Syndrome.*

Variable	Day 1		Day 3		Day 7	
	Group Receiving Lower Tidal Volumes	Group Receiving Traditional Tidal Volumes	Group Receiving Lower Tidal Volumes	Group Receiving Traditional Tidal Volumes	Group Receiving Lower Tidal Volumes	Group Receiving Traditional Tidal Volumes
Tidal volume (ml/kg of predicted body weight)	6.2±0.9	11.8±0.8	6.2±1.1	11.8±0.8	6.5±1.4	11.4±1.4
No. of patients	387	405	294	307	181	179
Plateau pressure (cm of water)	25±7	33±9	26±7	34±9	26±7	37±9
No. of patients	384	399	294	307	168	173
Peak inspiratory pressure (cm of water)	32±8	39±10	33±9	40±10	33±9	44±10
No. of patients	382	401	295	308	178	177
Mean airway pressure (cm of water)	17±13	17±12	17±14	19±17	17±14	20±10
No. of patients	369	385	288	301	176	173
Respiratory rate (breaths/min)	29±7	16±6	30±7	17±7	30±7	20±7
No. of patients	389	406	296	308	185	181
Minute ventilation (liters/min)	12.9±3.6	12.6±4.5	13.4±3.5	13.4±4.8	13.7±3.8	14.9±5.3
No. of patients	387	401	296	307	182	177
FiO_2	0.56±0.19	0.51±0.17	0.54±0.18	0.51±0.18	0.50±0.17	0.54±0.20
No. of patients	390	406	296	308	185	181
PEEP (cm of water)	9.4±3.6	8.6±3.6	9.2±3.6	8.6±4.2	8.1±3.4	9.1±4.2
No. of patients	390	406	296	308	185	181
$PaO_2:FiO_2$	158±73	176±76	160±68	177±81	165±71	164±88
No. of patients	350	369	284	297	148	160
PaO_2 (mm Hg)	76±23	77±19	74±22	76±23	73±17	75±21
No. of patients	350	369	284	297	148	160
$PaCO_2$ (mm Hg)	40±10	35±8	43±12	36±9	44±12	40±10
No. of patients	351	369	285	297	147	160
Arterial pH	7.38±0.08	7.41±0.07	7.38±0.08	7.41±0.07	7.40±0.07	7.41±0.08
No. of patients	351	369	285	297	148	160

Permissive Hypercapnia

- Potential **solutions** to severe acidosis
  - NaHCO3 infusion
  - THAM
  - Carbicarb (not available in North America)
  - Strategies to minimize CO_2 production
  - Tracheal insufflations of O_2
  - Aim for $pH > 7.15$
  - Extracorporeal CO_2 removal

Association Between Use of Lung-Protective Ventilation With Lower Tidal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome

A Meta-analysis

- JAMA 2012, 308 (16), p. 1651
- 20 trials, 2822 patients

Figure 2. Effect of Ventilation With Smaller Tidal Volume in Patients With Healthy Lungs at the End of the Follow-up Period for Each Study

	High V_T, No.		Low V_T, No.			
	Events	Total	Events	Total	Weight, %	RR (95% CI)
Lung injury						
Gajic et al,[16] 2004	32	100	12	66	18.1	0.47 (0.22-1.00)
Michelet et al,[20] 2006	6	26	3	26	4.6	0.43 (0.10-1.97)
Yilmaz et al,[23] 2007	60	212	17	163	40.7	0.29 (0.16-0.53)
Licker et al,[26] 2009	20	533	5	558	17.7	0.23 (0.09-0.62)
Determann et al,[27] 2010	10	74	2	76	8.6	0.17 (0.04-0.82)
Yang et al,[31] 2011	4	50	1	50	3.4	0.23 (0.03-2.18)
Fernandez-Bustamante et al,[29] 2011	5	75	7	154	5.6	0.67 (0.20-2.17)
Weingarten et al,[32] 2012	1	20	0	20	1.3	0.32 (0.01-8.26)
Subtotal (95% CI)		1090		1113	100.0	0.33 (0.23-0.47)
Total events	138		47			

Heterogeneity: $\chi^2_7=3.74$; $P=.81$, $I^2=0\%$
Test for overall effect: $z=6.06$; $P<.001$

	High V_T, No.		Low V_T, No.			
	Events	Total	Events	Total	Weight, %	RR (95% CI)
Mortality						
Michelet et al,[20] 2006	1	26	2	26	1.0	2.08 (0.18-24.51)
Wolthuis et al,[22] 2007	2	13	3	23	2.5	0.82 (0.12-5.71)
Yilmaz et al,[23] 2007	69	212	27	163	55.7	0.41 (0.25-0.68)
Licker et al,[26] 2009	15	533	13	558	16.7	0.82 (0.39-1.75)
Determann et al,[27] 2010	23	74	24	76	17.7	1.02 (0.51-2.04)
Fernandez-Bustamante et al,[29] 2011	1	75	3	154	1.5	1.47 (0.15-14.38)
Sundar et al,[30] 2011	2	74	1	75	2.2	0.49 (0.04-5.48)
Yang et al,[31] 2011	1	50	0	50	1.7	0.33 (0.01-8.21)
Weingarten et al,[32] 2012	1	20	1	20	1.1	1.00 (0.06-17.18)
Subtotal (95% CI)		1077		1145	100.0	0.64 (0.46-0.86)
Total events	115		74			

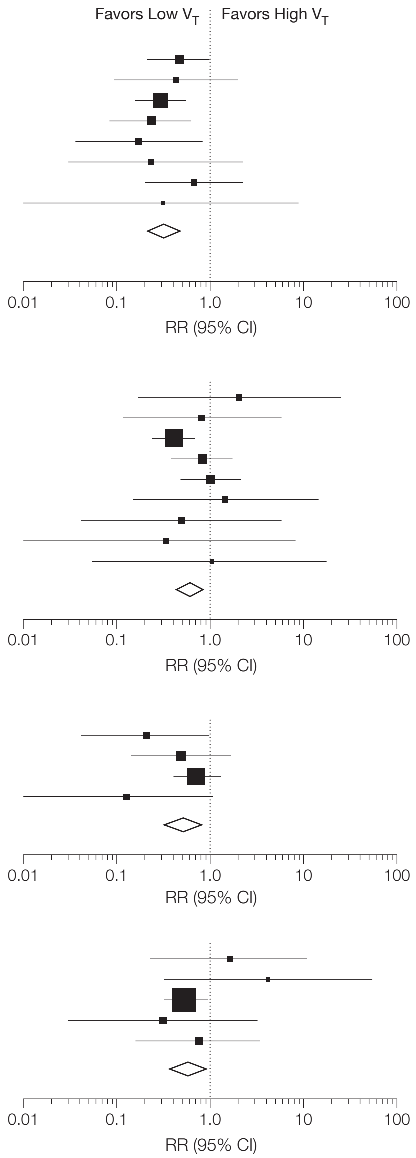
Heterogeneity: $\chi^2_8=6.94$; $P=.54$, $I^2=0\%$
Test for overall effect: $z=2.68$; $P=.007$

	High V_T, No.		Low V_T, No.			
	Events	Total	Events	Total	Weight, %	RR (95% CI)
Pulmonary infection						
Lee et al,[14] 1990	10	56	2	47	16.6	0.20 (0.04-0.99)
Michelet et al,[20] 2006	10	26	6	26	14.6	0.48 (0.14-1.60)
Licker et al,[26] 2009	30	533	23	558	55.8	0.72 (0.41-1.26)
Yang et al,[31] 2011	7	50	1	50	13.0	0.13 (0.01-1.06)
Subtotal (95% CI)		665		681	100.0	0.52 (0.33-0.82)
Total events	57		32			

Heterogeneity: $\chi^2_3=4.39$; $P=.22$, $I^2=32\%$
Test for overall effect: $z=2.79$; $P=.005$

	High V_T, No.		Low V_T, No.			
	Events	Total	Events	Total	Weight, %	RR (95% CI)
Atelectasis						
Lin et al,[25] 2008	2	20	3	20	3.1	1.59 (0.24-10.70)
Cai et al,[21] 2007	5	8	7	8	1.1	4.20 (0.33-53.12)
Licker et al,[26] 2009	47	533	28	558	83.1	0.55 (0.34-0.89)
Yang et al,[31] 2011	3	50	1	50	5.4	0.32 (0.03-3.18)
Weingarten et al,[32] 2012	5	20	4	20	7.3	0.75 (0.17-3.33)
Subtotal (95% CI)		631		656	100.0	0.62 (0.41-0.95)
Total events	62		43			

Heterogeneity: $\chi^2_4=3.76$; $P=.44$, $I^2=0\%$
Test for overall effect: $z=2.18$; $P=.03$



A pooled estimate of risk ratio (RR) was calculated in the individual studies using a fixed-effects model according to Mantel and Haenszel. The size of the data markers indicates the weight of the study in the final analyses. V_T indicates tidal volume.

ORIGINAL ARTICLE

A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery

- IMPROVE trial, NEJM 2013, 369(5), p. 428
- 400 patients
  - > 40 years old
  - Major abdominal surgery of at least 2 hours
  - Risk of pulmonary complications

- Protective vs. non-protective ventilation strategy

Table 3. Results of Unadjusted and Adjusted Outcome Analyses.*

Variable	Nonprotective Ventilation (N=200)	Lung-Protective Ventilation (N=200)	Unadjusted Relative Risk or Between-Group Difference (95% CI)	P Value†	Adjusted Relative Risk or Between-Group Difference (95% CI)‡	P Value
Primary composite outcome — no. (%)						
Within 7 days§	55 (27.5)	21 (10.5)	0.38 (0.24–0.61)	<0.001	0.40 (0.24–0.68)	0.001
Within 30 days	58 (29.0)	25 (12.5)	0.43 (0.28–0.66)	<0.001	0.45 (0.28–0.73)	<0.001
Secondary outcomes — no. (%)						
Pulmonary complication within 7 days¶						
Grade 1 or 2	30 (15.0)	25 (12.5)	0.69 (0.42–1.13)	0.14	0.67 (0.39–1.16)	0.16
Grade ≥3	42 (21.0)	10 (5.0)	0.24 (0.12–0.46)	<0.001	0.23 (0.11–0.49)	<0.001
Atelectasis within 7 days‖	34 (17.0)	13 (6.5)	0.38 (0.21–0.70)	0.001	0.37 (0.19–0.73)	0.004
Pneumonia within 7 days	16 (8.0)	3 (1.5)	0.19 (0.05–0.63)	0.01	0.19 (0.05–0.66)	0.009
Acute lung injury or ARDS within 7 days	6 (3.0)	1 (0.5)	0.17 (0.02–1.37)	0.12	0.21 (0.02–1.71)	0.14
Need for ventilation within 7 days						
Invasive	7 (3.5)	2 (1.0)	0.29 (0.06–1.36)	0.51	0.40 (0.08–1.97)	0.26
Noninvasive	29 (14.5)	9 (4.5)	0.31 (0.15–0.64)	0.006	0.29 (0.13–0.65)	0.002
Extrapulmonary complication within 7 days						
SIRS	100 (50.0)	86 (43.0)	0.86 (0.70–1.06)	0.16	0.87 (0.65–1.17)	0.37
Sepsis	29 (14.5)	13 (6.5)	0.45 (0.24–0.84)	0.04	0.48 (0.25–0.93)	0.03
Severe sepsis or septic shock	9 (4.5)	8 (4.0)	0.89 (0.35–2.26)	0.80	1.48 (0.51–4.32)	0.47
Death within 30 days	7 (3.5)	6 (3.0)	0.86 (0.29–2.51)	0.80	1.13 (0.36–3.61)	0.83
Duration of stay in hospital and ICU — days						
Hospital				0.02		0.006
Median	13	11	−2.25 (−4.04 to −0.47)		−2.45 (−4.17 to −0.72)	
Interquartile range	8–20	8–15				
ICU				0.58		0.69
Median	7	6	−1.48 (−6.87 to 3.91)		−1.21 (−4.98 to 7.40)	
Interquartile range	4–9	4–8				

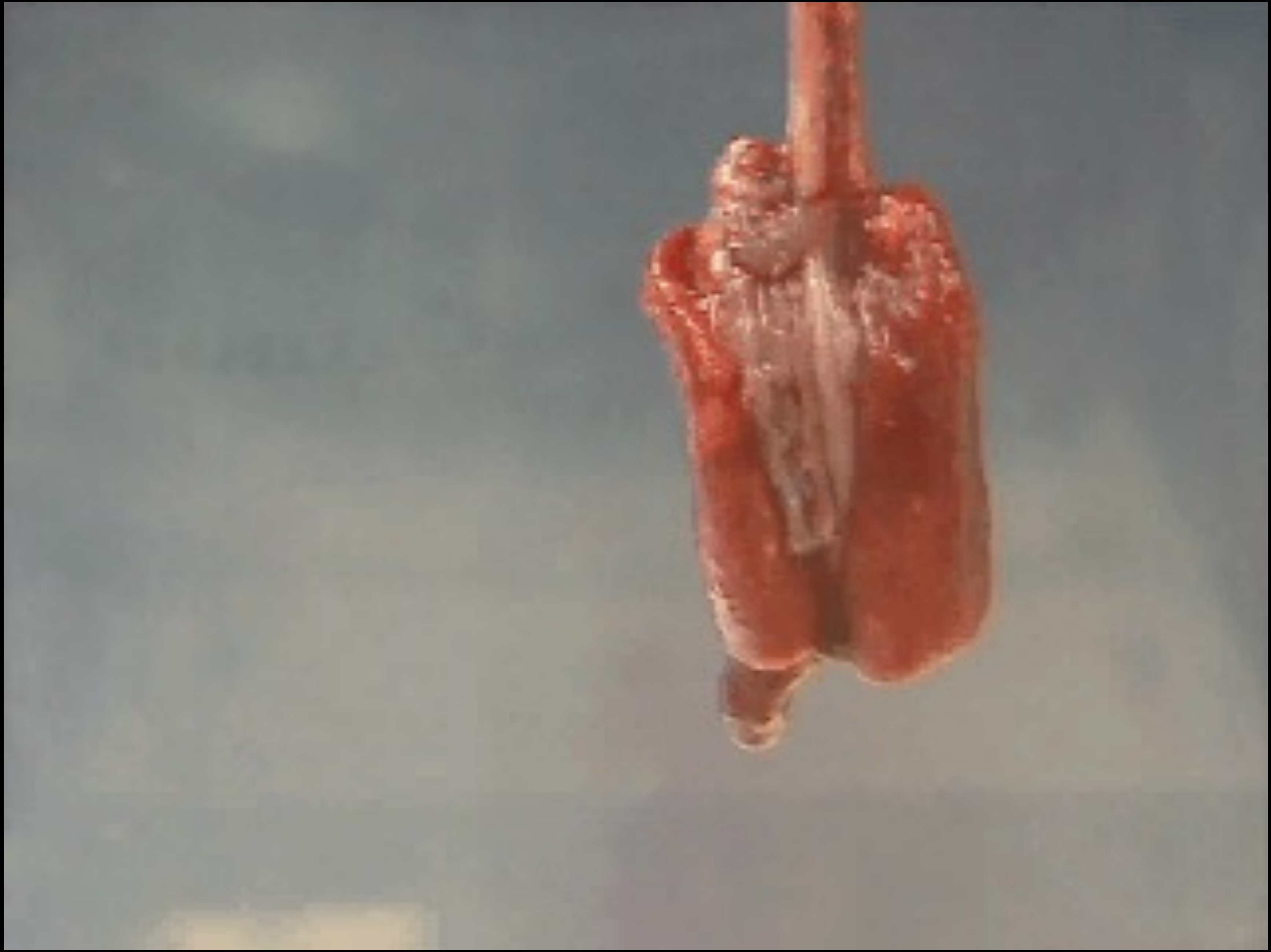
Pierre-Marc Chagnon MD FRCPC

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of a Low vs Intermediate Tidal Volume Strategy on Ventilator-Free Days in Intensive Care Unit Patients Without ARDS

A Randomized Clinical Trial

- PReVENT trial, JAMA 2018, 320 (18), p. 1872
- Multicenter RCT involving 961 non-ARDS patients (> 80% medical admissions)
- Low (4-6 cc/Kg) vs. intermediate (10 cc/Kg) tidal volume
- No difference in primary outcome (21 ventilator free days at 28 days for both groups)
- No differences in secondary outcomes (LOS ICU and hospital, mortality at 28 and 90 days)
- *Lower Vt target (6-8 cc/Kg) in non-ARDS patients, until new evidence challenge this practice*



Pierre-Marc Chagnon MD FRCPC

Recruitment

- Intentional transient increase in transpulmonary pressure = reopening of unstable airless alveoli
- Increased end-expiratory lung volume

- **Numerous ways to do it**
  - Intermittent sighs = increasing tidal volume or PEEP for one of several breaths
  - Sustained increased pressure (ex: PEEP 30 for 30 seconds)
  - Stepwise increase in pressure
  - Supine or prone possible
  - OL-PEEP adjustment after procedure mandatory

Recruitment

- Pressures necessary to open lung units?
  - Few studies in humans with ARDS
  - AJRCCM 2001, 164, p. 131
  - AJRCCM 2006, 174, p. 268

- Opening as measured by CT SCAN
  - Median value 20-30 cmH2O
  - Range from 10-50 cmH2O
  - Only 10% of lung units open above 45 cmH2O = limited functional gain of using pressures > 45 cmH2O
  - Median collapse pressure = 10 cmH2O
  - Some collapse observed at pressures > 20-25 cmH2O

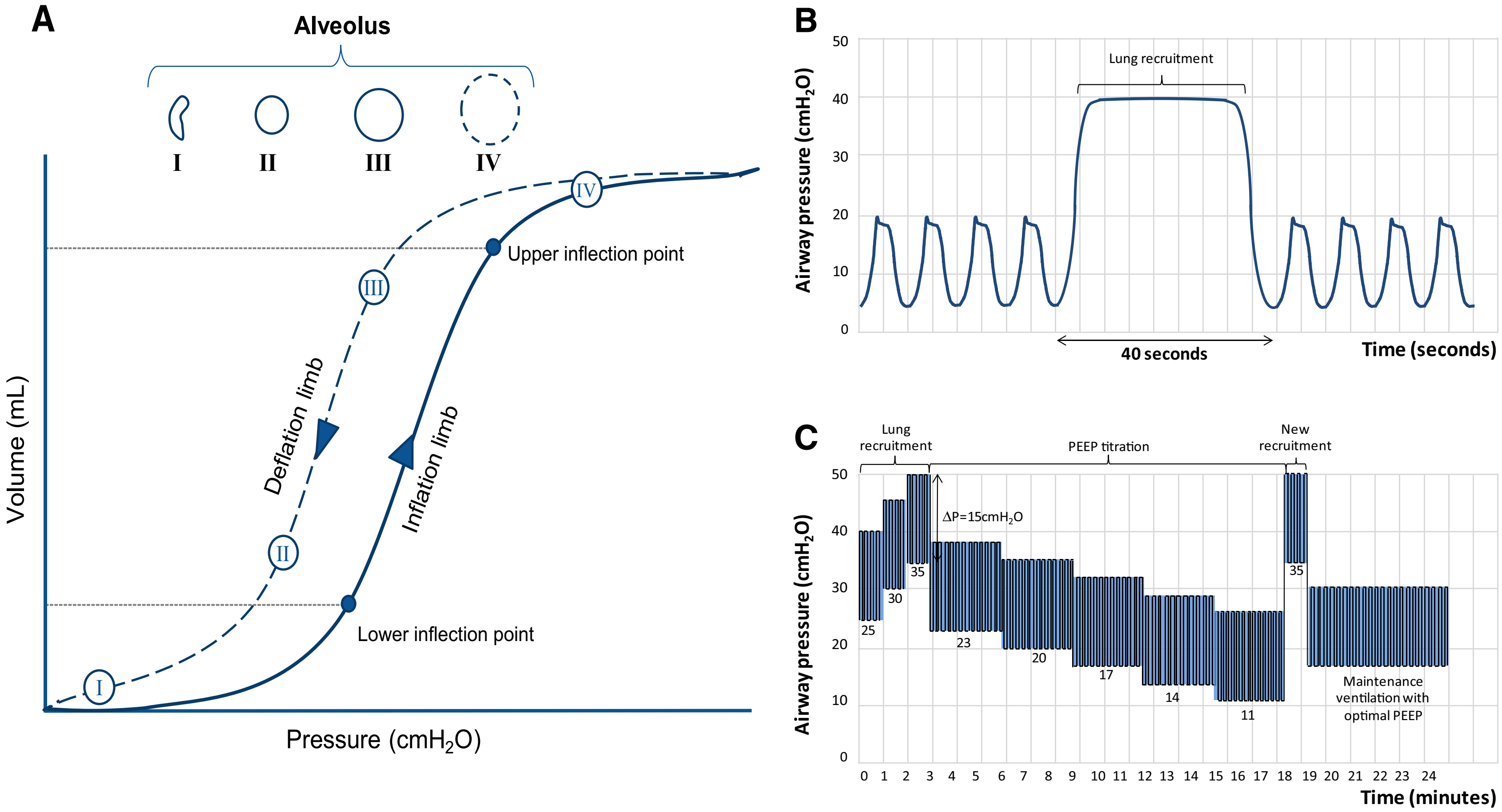


Fig. 1 Pressure–volume curve (**a**). During inflation (*full line*) transpulmonary pressure overcomes the critical opening pressure (upper inflection point). After recruitment maneuver, during deflation (*dotted line*), lung volume is greater at a certain pressure level, and alveoli remain opened as long as positive end-expiratory pressure (PEEP) is kept above a critical pressure level (lower inflection point). Pressure–time (seconds) curve (**b**) showing a sustained inflation recruitment maneuver using continuous positive airway pressure (CPAP) of 40 cmH_2O for 40 s. Pressure–time (minutes) curve showing a stepwise recruitment maneuver (**c**) using both inspiratory pressure and PEEP increases, keeping driving pressure fixed at 15 cmH_2O, achieving peak pressure after recruitment of 50 cmH_2O and PEEP of 35 cmH_2O. After recruitment, figure shows a decremental PEEP titration and a new recruitment maneuver performed after an optimal PEEP is identified (i.e., the PEEP associated with best compliance of respiratory system or best oxygenation). After the new recruitment, PEEP is set 2 cmH_2O above the optimal level

Recruitment

- Bedside methods to **quantify alveolar recruitment**
  - Electrical impedance tomography
  - Lung ultrasound
  - Thoracic SCAN
  - Stress index
  - Objective better static lung compliance
  - Objective better gaseous exchange
    - Better oxygenation
    - Decreased dead space fraction
  - Decreased driving pressure and mechanical power
  - Recruitment / inflation ratio

- The best method remains elusive…

Recruitment

- **Expected benefits**
  - Improved oxygenation
  - Reduced atelectrauma
  - Better recruitment = improved compliance = decreased ΔP for any given Vt
  - Decreased VILI

- **Decreased benefits in**
  - Late ARDS (fibroproliferative)
  - Primary and focal process

Recruitment

- **Risks associated**
  - HD compromise (especially RV dysfunction combined with hypovolemia)
  - Barotrauma (especially primary disease)
  - Increased VILI by overdistension?
  - Increased need for sedation

- **No clear benefits** demonstrated in the literature
  - Heterogeneous ARDS population (primary and secondary / focal and diffuse)
  - Timing, optimal pressure, technique, duration and frequency not defined
  - Co-interventions (especially PEEP adjustments)

Recommendation 6.3

We **recommend against** use of prolonged high-pressure recruitment maneuvers (defined as airway pressure maintained ≥ 35 cmH_2O for at least one minute) to reduce mortality of patients with ARDS.
Strong recommendation; moderate level of evidence against.

This recommendation applies also to ARDS from COVID-19.
Strong recommendation; low level of evidence against for indirectness.

Recommendation 6.4

We **suggest against** *routine* use of brief high-pressure recruitment maneuvers (defined as airway pressure maintained $\geq$ 35 cmH_2O for less than one minute) to reduce mortality in patients with ARDS.
Weak recommendation; high level of evidence of no effect.

This suggestion applies also to ARDS from COVID-19.
Weak recommendation; moderate level of evidence of no effect for indirectness.

Question 4: Should Patients with ARDS Receive Higher Compared with Lower PEEP, with or without LRMs?

Recommendation. We suggest using higher PEEP without LRMs rather than lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low-moderate certainty). We recommend against using prolonged (PEEP $\geqslant$35 cm H_2O for $>$60 s) LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Recruitment

- Consider on an individual basis, especially in patients presenting with life-threatening hypoxemia
  - Patients with lower P/F ratio experiencing significant increase in oxygenation with RM
  - Patients with low respiratory compliance = risks may exceed benefits

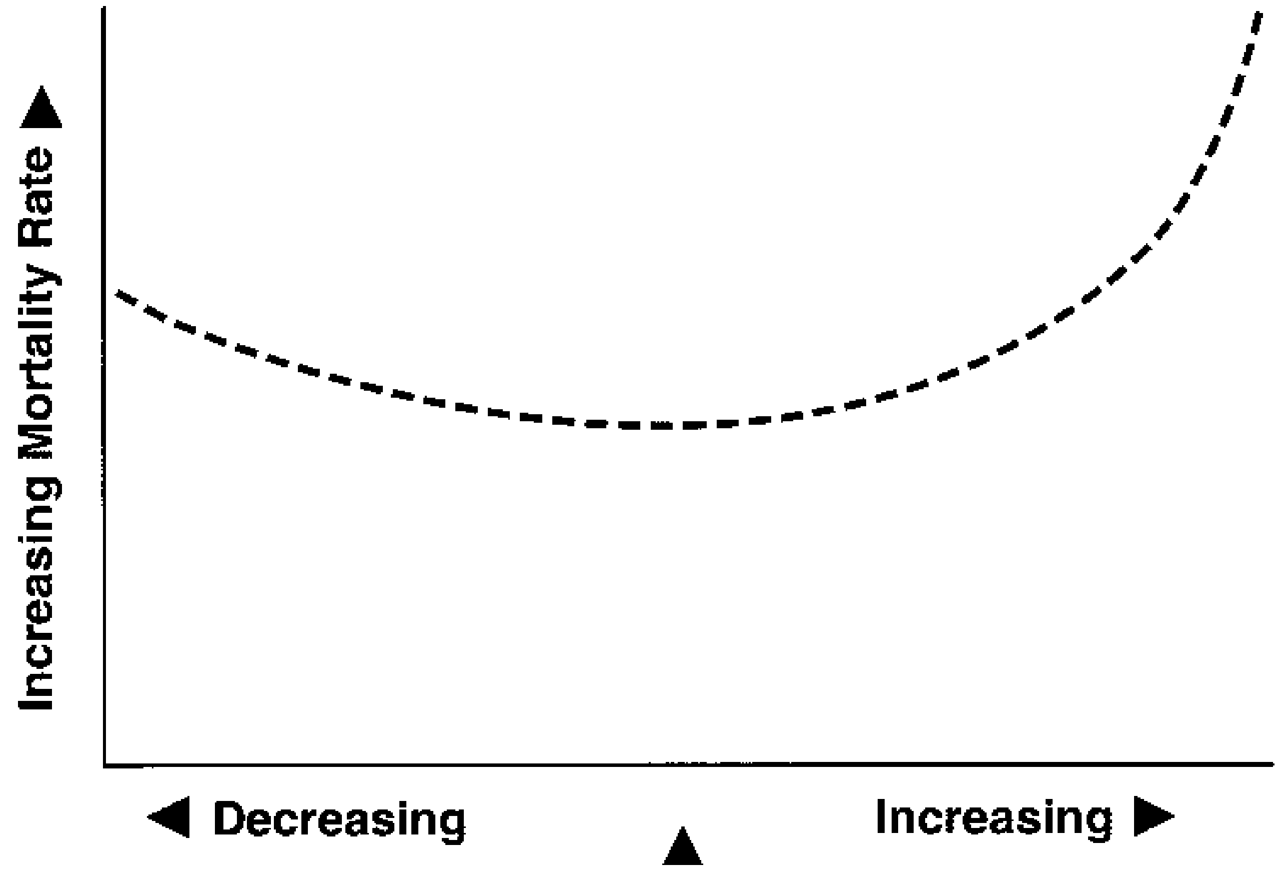
- **Some principles**
  - Institute early
  - Assure adequate volume status and sedation
  - Assess oxygenation and compliance immediately and 6-12 hours after = if no improvement, then do not repeat
  - Investigate OL-PEEP

PEEP in ARDS

- **Beneficial effect = increased oxygenation (decreased FiO2)**
  - Alveolar recruitment = decreased intrapulmonary shunt and better V/Q match
  - Fluid redistribution in the interstitial tissue

- **Beneficial effect = decreased VILI**
  - Alveolar recruitment = increased FRC
  - More homogeneous ventilation
  - Decreased atelectrauma
  - Overall reduced lung stress and strain = decreased mechanical power

- **Potential harmful effects**
  - Decreased cardiac output (decreased venous return and RV stroke volume)
  - Increased dead space (if overdistension)
  - Increased lung stress and strain (if no pulmonary recruitment potential = volutrauma)


Increasing Mortality Rate
Decreasing
Increasing

Setting PEEP in ARDS

According to FiO2 scale
Incremental PEEP (EXPRESS)
Decremental PEEP
Stress Index method
P-V curve
Transpulmonary pressure
Driving pressure and mechanical power
Right ventricular considerations
Recruitment / inflation ratio
Electrical impedance tomography

Higher vs Lower Positive End-Expiratory Pressure in Patients With Acute Lung Injury and Acute Respiratory Distress Syndrome

Systematic Review and Meta-analysis

Table 1. Characteristics of Included Trials

Characteristic	Trial: ALVEOLI,[8] 2004	LOVS,[9] 2008	EXPRESS,[10] 2008
Inclusion criteria	Acute lung injury with PaO_2:FIO_2 ≤300[a]	Acute lung injury with PaO_2:FIO_2 ≤250[a]	Acute lung injury with PaO_2:FIO_2 ≤300[a]
Recruitment period	1999-2002	2000-2006	2002-2005
Recruiting hospitals (country)	23 (United States)	30 (Canada, Australia, Saudi Arabia)	37 (France)
Patients randomized to higher vs lower PEEP	276 vs 273	476 vs 509[b]	385 vs 383[c]
Validity			
Concealed allocation	Yes	Yes	Yes
Follow-up for primary outcome, %	100	100	100
Blinded data analysis	Yes	Yes	Yes
Stopped early	Stopped for perceived futility	No	Stopped for perceived futility
Experimental intervention	Higher PEEP according to FIO_2 chart, recruitment maneuvers for first 80 patients	Higher PEEP according to FIO_2 chart, required plateau pressures ≤40 cm H_2O, recruitment maneuvers	PEEP as high as possible without increasing the maximum inspiratory plateau pressure >28-30 cm H_2O
Control intervention	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP according to FIO_2 chart, required plateau pressures ≤30 cm H_2O, no recruitment maneuvers	Conventional PEEP (5-9 cm H_2O) to meet oxygenation goals
Ventilator procedures	Target tidal volumes of 6 mL/kg of predicted body weight; plateau pressures ≤30 cm H_2O (with exception as above); respiratory rate ≤35/min, adjusted to achieve arterial pH 7.30-7.45; ventilator mode: volume-assist control (except higher PEEP group in LOVS required pressure control); oxygenation goals: PaO_2 55-80 mm Hg and SPO_2 88%-95%; standardized weaning)		

Abbreviations: ALVEOLI, Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury; EXPRESS, Expiratory Pressure Study; FIO_2, fraction of inspired oxygen; LOVS, Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome; PEEP, positive end-expiratory pressure; SPO_2, oxygen saturation.

[a] Acute lung injury defined according to the American-European Consensus Conference.[12]

[b] Includes 2 patients for whom consent was withdrawn prior to protocol initiation, without patient, family, and caregivers being aware of group assignment (ie, 983 patients analyzed).

[c] Includes 1 patient for whom consent was withdrawn prior to protocol initiation, without patient, family, and caregiver awareness of assignment (ie, 767 patients included in the analysis).

Table 4. Clinical Outcomes in All Patients and Stratified by Presence of ARDS at Baseline

Outcomes	All Patients, No. (%) Higher PEEP (n = 1136)	All Patients, No. (%) Lower PEEP (n = 1163)	All Patients Adjusted RR (95% CI)[a]	All Patients *P* Value	With ARDS, No. (%) Higher PEEP (n = 951)	With ARDS, No. (%) Lower PEEP (n = 941)	With ARDS Adjusted RR (95% CI)[a]	With ARDS *P* Value	Without ARDS, No. (%) Higher PEEP (n = 184)	Without ARDS, No. (%) Lower PEEP (n = 220)	Without ARDS Adjusted RR (95% CI)[a]	Without ARDS *P* Value
Death in hospital	374 (32.9)	409 (35.2)	0.94 (0.86 to 1.04)	.25	324 (34.1)	368 (39.1)	0.90 (0.81 to 1.00)	.049	50 (27.2)	44 (19.4)	1.37 (0.98 to 1.92)	.07
Death in ICU[b]	324 (28.5)	381 (32.8)	0.87 (0.78 to 0.97)	.01	288 (30.3)	344 (36.6)	0.85 (0.76 to 0.95)	.001	36 (19.6)	37 (16.8)	1.07 (0.74 to 1.55)	.71
Pneumothorax between day 1 and day 28[c]	87 (7.7)	75 (6.5)	1.19 (0.89 to 1.60)	.24	80 (8.4)	64 (6.8)	1.25 (0.94 to 1.68)	.13	7 (3.8)	11 (5.0)	0.72 (0.37 to 1.39)	.33
Death after pneumothorax[c]	43 (3.8)	40 (3.5)	1.11 (0.73 to 1.69)	.63	41 (4.3)	35 (3.7)	1.20 (0.79 to 1.81)	.39	2 (1.1)	5 (2.3)	0.44 (0.08 to 2.35)[g]	.34
Days with unassisted breathing between day 1 and day 28, median (IQR)[d]	13 (0 to 22)	11 (0 to 21)	0.64 (−0.12 to 1.39)[e]	.10	12 (0-21)	7 (0-20)	1.22 (0.39 to 2.05)[e]	.004	17 (0-23)	19 (5.5-24)	−1.74 (−3.60 to 0.11)[e]	.07
Total use of rescue therapies[f]	138 (12.2)	216 (18.6)	0.64 (0.54 to 0.75)	<.001	130 (13.7)	200 (21.3)	0.63 (0.53 to 0.75)	<.001	8 (4.4)	16 (7.3)	0.60 (0.25 to 1.43)[g]	.25
Death after rescue therapy[f]	85 (7.5)	132 (11.3)	0.65 (0.52 to 0.80)	<.001	82 (8.6)	124 (13.2)	0.66 (0.52 to 0.82)	<.001	3 (1.6)	8 (3.6)	0.37 (0.10 to 1.46)[g]	.15
Use of vasopressors	722 (63.6)	759 (65.3)	0.93 (0.75 to 1.14)[g]	.49	627 (65.9)	647 (68.8)	0.90 (0.72 to 1.13)[g]	.37	95 (51.6)	111 (50.5)	0.92 (0.56 to 1.50)[g]	.72

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure; RR, relative risk.

[a] Multivariable regression with the outcome of interest as dependent variable; PEEP group, age, probability of dying in hospital derived from prognostic scores at baseline, severe sepsis at baseline, and trial as independent variables; and hospital as a random effect.

[b] Patients who died before being discharged from the intensive care unit for the first time up to day 60.

[c] Defined as the need for chest tube drainage.

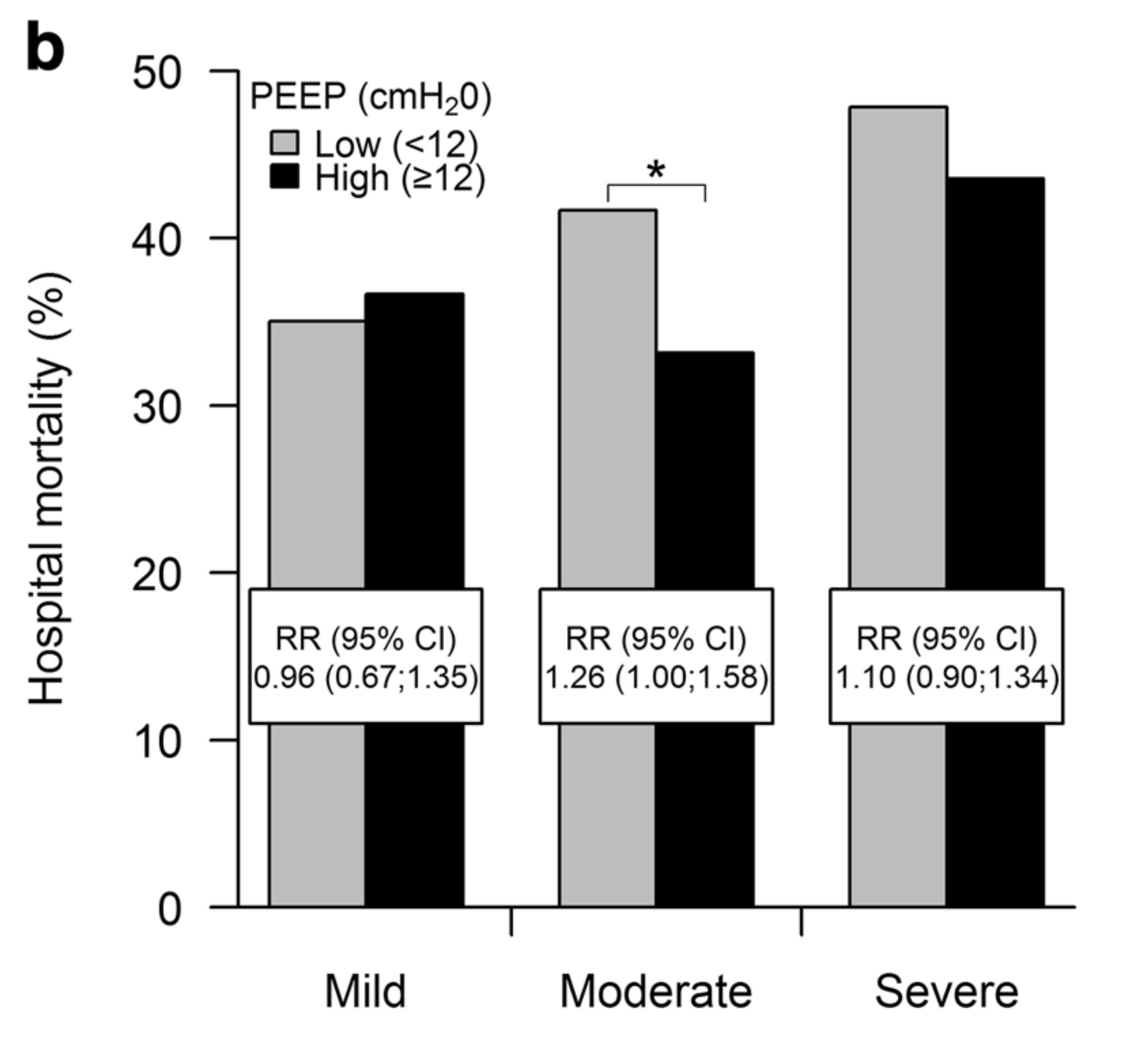
[d] Median number of days of unassisted breathing to day 28 after randomization, assuming a patient survives and remains free of assisted breathing for at least 2 consecutive calendar days after initiation of unassisted breathing.

[e] Coefficient from a corresponding linear regression model using the same independent variables and random effect as the above-described log-binomial model; for example, a coefficient of 1.22 means that patients in the group treated with higher PEEP have, on average, 1.22 days more of unassisted breathing during the first 28 days compared with patients in the group treated with lower PEEP.

[f] As defined in each trial; rescue therapies included in the Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury and the Lung Open Ventilation to Decrease Mortality in the Acute Respiratory Distress Syndrome studies: inhaled nitric oxide, prone ventilation, high-frequency oscillation, high-frequency jet ventilation, extracorporeal membrane oxygenation, partial liquid ventilation, and surfactant therapy. Rescue therapies included in the Expiratory Pressure Study: prone ventilation, inhaled nitric oxide, and almitrine bismesylate.

[g] Adjusted odds ratio substitutes for relative risk, because the corresponding log-binomial model did not converge.

Pierre-Marc Chagnon MD FRCPC



Mortality benefit for higher PEEP in subgroup of patients with more severe ARDS?

Actual trend is to use higher levels of PEEP in more severe ARDS patients

Caution for mild forms (possible harm)

Recommendation. We suggest using higher PEEP without LRMs rather than lower PEEP in patients with moderate to severe ARDS (conditional recommendation, low-moderate certainty). We recommend against using prolonged (PEEP $\geqslant$35 cm H_2O for $>$60 s) LRMs in patients with moderate to severe ARDS (strong recommendation, moderate certainty).

Recommendation 6.1

We are **unable to make a recommendation** for or against routine PEEP titration with a higher PEEP/FiO_2 strategy versus a lower PEEP/FiO_2 strategy to reduce mortality in patients with ARDS.
No recommendation; high level of evidence of no effect.

This statement applies also to ARDS from COVID-19.
No recommendation; moderate level of evidence of no effect for indirectness.

Setting PEEP in ARDS

Setting PEEP in ARDS
According to FiO2 scale
Incremental PEEP (EXPRESS)
Decremental PEEP
Stress Index method
P-V curve
Transpulmonary pressure
Driving pressure and mechanical power
Right ventricular considerations
Recruitment / inflation ratio
Electrical impedance tomography

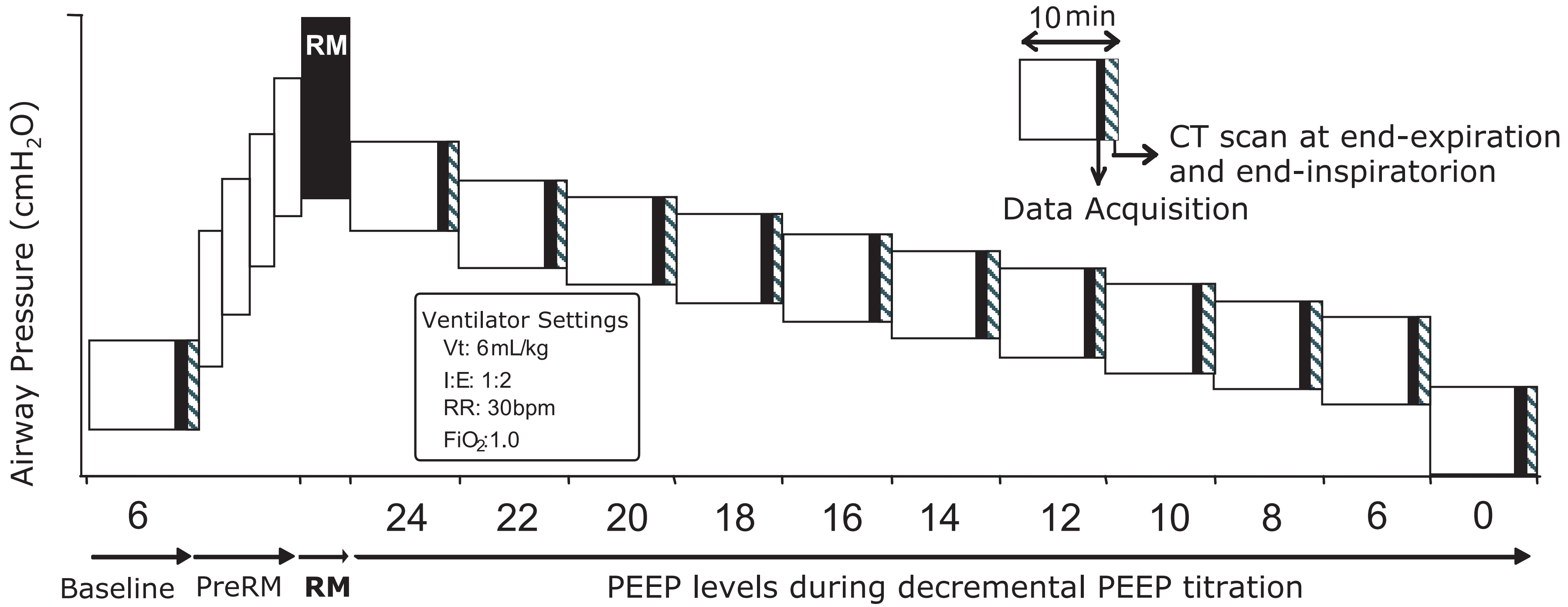


Figure 1. Study protocol. Each box represents a protocol step of 10 mins duration at the end of which a data set and computed tomography (*CT*) scans were obtained. During the recruitment maneuver (*RM*), ventilation settings were changed for 2 mins to pressure controlled at 60 cmH_2O peak inspiratory pressure with 30 cm H_2O of positive end-expiratory pressure (*PEEP*). *Vt*, tidal volume; *I:E*, inspiratory/expiratory ratio; *RR*, respiration rate.

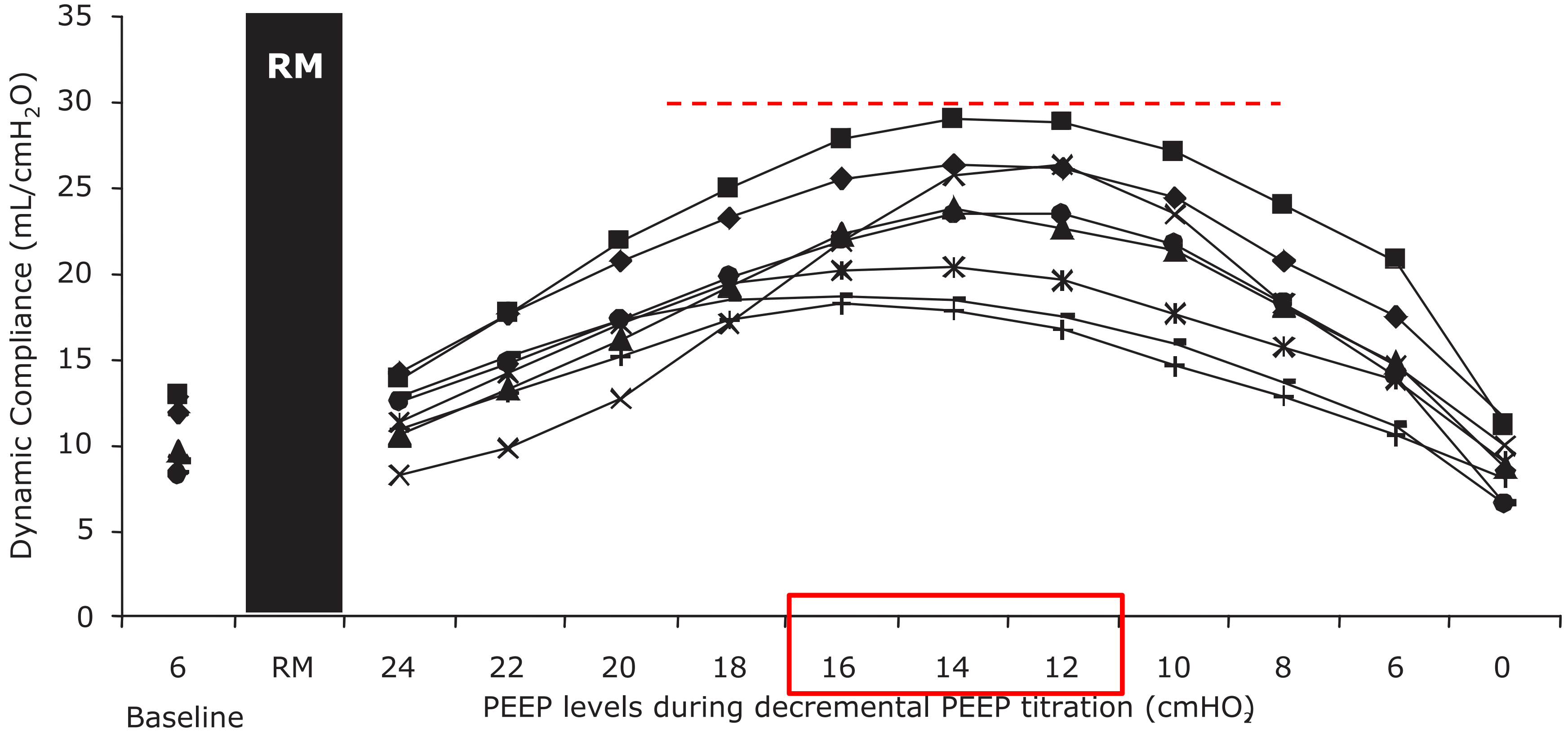


Figure 2. Individual changes in dynamic compliance during the protocol. A biphasic response (i.e., a first increment and a subsequent decrement with a visually identifiable maximum) was observed in all animals. Each symbol represents an individual animal. *RM*, recruitment maneuver; *PEEP*, positive end-expiratory pressure.

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Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome

A Randomized Clinical Trial

- ART trial, JAMA 2017, 318 (14), p. 1335
- Multicenter RCT
- 1010 moderate to severe ARDS patients
- Lung recruitment and PEEP titration according to best-Crs (501 patients) vs. ARDSnet (509 patients)

Table 2. Outcomes Among Patients Treated With Lung Recruitment Maneuver With Positive End-Expiratory Pressure (PEEP) vs Low-PEEP Strategy

Outcome	Lung Recruitment Maneuver With PEEP Titration Group (n = 501)	Low-PEEP Group (n = 509)	Type of Effect Estimate	Effect Estimate (95% CI)	*P* Value
Primary Outcome					
Death ≤28 d, No. of events/total No. (%)	277/501 (55.3)	251/509 (49.3)	HR	1.20 (1.01 to 1.42)	.041
Secondary Outcomes					
Death, No. of events/total No. (%)					
In intensive care unit	303/500 (60.6)	284/509 (55.8)	RD	4.8 (-1.5 to 11.1)	.13
In hospital	319/500 (63.8)	301/508 (59.3)	RD	4.5 (-1.7 to 10.7)	.15
Within 6 mo[a]	327/501 (65.3)	305/509 (59.9)	HR	1.18 (1.01 to 1.38)	.04
Length of stay, d					
Intensive care unit, mean (SD)	18.2 (22.4)	19.2 (25.9)	MD	-1.0 (-4.0 to 2.0)	.51
Median (IQR)	12.0 (5.0 to 23.0)	14.0 (7.0 to 23.0)			
Hospital, mean (SD)	25.5 (32.3)	26.2 (31.7)	MD	-0.7 (-4.6 to 3.3)	.74
Median (IQR)	15.0 (5.0 to 32.0)	18.0 (7.0 to 35.0)			
No. of ventilator-free d from d 1 to d 28, mean (SD), d	5.3 (8.0)	6.4 (8.6)	MD	-1.1 (-2.1 to -0.1)	.03
Median (IQR)	0.0 (0.0 to 11.0)	0.0 (0.0 to 14.0)			
Pneumothorax requiring drainage ≤7 d, No./total No. (%)	16/501 (3.2)	6/509 (1.2)	RD	2.0 (0.2 to 3.8)	.03
Barotrauma ≤7 d, No./total No. (%)	28/501 (5.6)	8/509 (1.6)	RD	4.0 (1.5 to 6.5)	.001
Exploratory Outcomes, No./Total No. (%)					
Death					
Within 7 d	160/501 (31.9)	130/509 (25.5)	RD	6.4 (0.6 to 12.2)	.03
With refractory hypoxemia ≤7 d[b]	45/501 (9.0)	51/509 (10.0)	RD	-1.0 (-4.9 to 2.8)	.59
With refractory acidosis ≤7 d[c]	68/501 (13.6)	56/509 (11.0)	RD	2.6 (-1.7 to 6.8)	.25
With barotrauma ≤7 d[d]	7/501 (1.4)	0/509 (0.0)	RD	1.4 (0.2 to 2.6)	.007
Cardiorespiratory arrest on day 1[e]	5/501 (1.0)	2/509 (0.4)	RD	0.6 (-0.6 to 1.8)	.28
Need of commencement or increase of vasopressors or hypotension (MAP <65 mm Hg) within 1 h	174/500 (34.8)	144/508 (28.3)	RD	6.5 (0.5 to 12.4)	.03
Refractory hypoxemia (Pa_{O_2}<55 mm Hg) ≤1 h	8/496 (1.6)	10/506 (2.0)	RD	-0.4 (-2.2 to 1.5)	.81
Severe acidosis (pH<7.10) ≤1 h	65/496 (13.1)	55/506 (10.9)	RD	2.2 (-2.0 to 6.5)	.29

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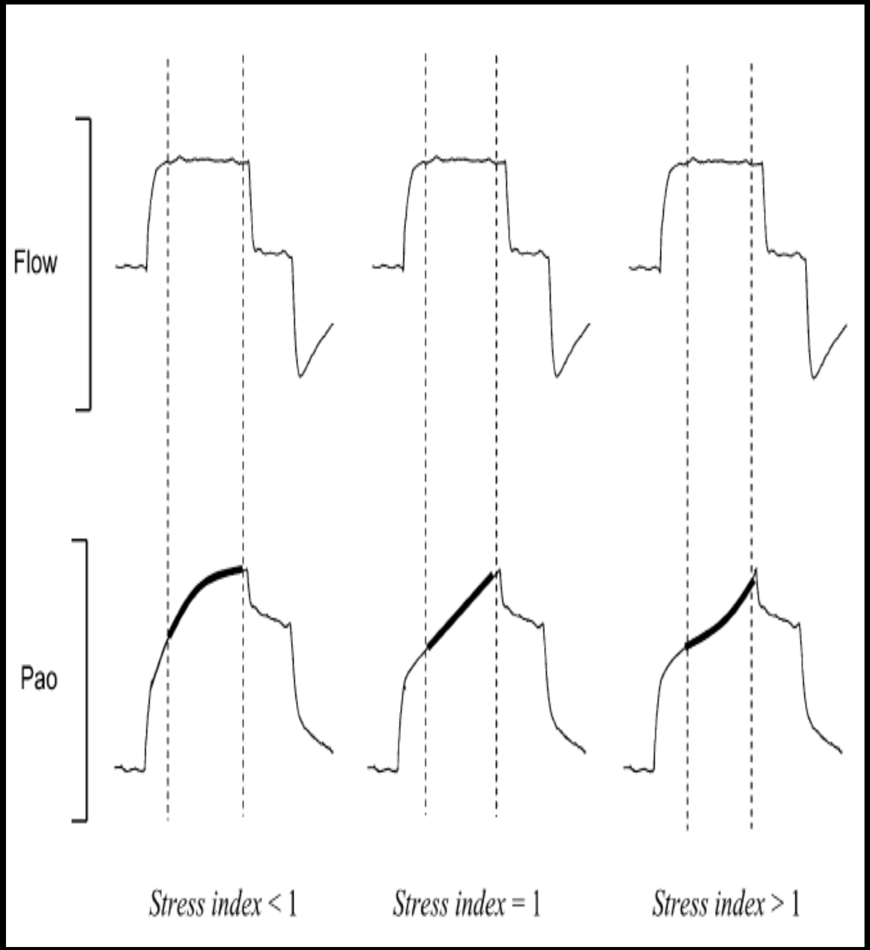
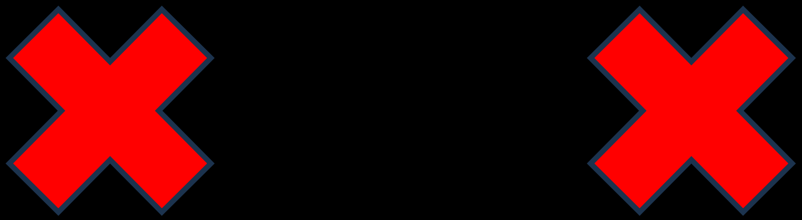
ART Trial

- Baseline characteristics
  - 2/3 of patients with **septic shock**
  - 62% **primary ARDS**
- Injurious protocol
  - modified after 555 patients enrolled
  - 3 cardiac arrest following recruitment manoeuvres
  - Pressure levels not seen in the previous literature (ad 45 cmH2O for 2 minutes)
- Lack of external validity (mainly South America)
- No blinding possible
- *Open lung strategy according to ART not recommended*

Setting PEEP in ARDS
According to FiO2 scale
Incremental PEEP (EXPRESS)
Decremental PEEP
Stress Index method
P-V curve
Transpulmonary pressure
Driving pressure and mechanical power
Right ventricular considerations
Recruitment / inflation ratio
Electrical impedance tomography

Paw = (El X Vt) + (R X Q) + PEEPtot





Index < 1 = convexity Continuous decrease in elastance

Index > 1 = concavity Continuous increase in elastance

Index 0.9-1.1 = linear Elastance remains stable throughout inflation

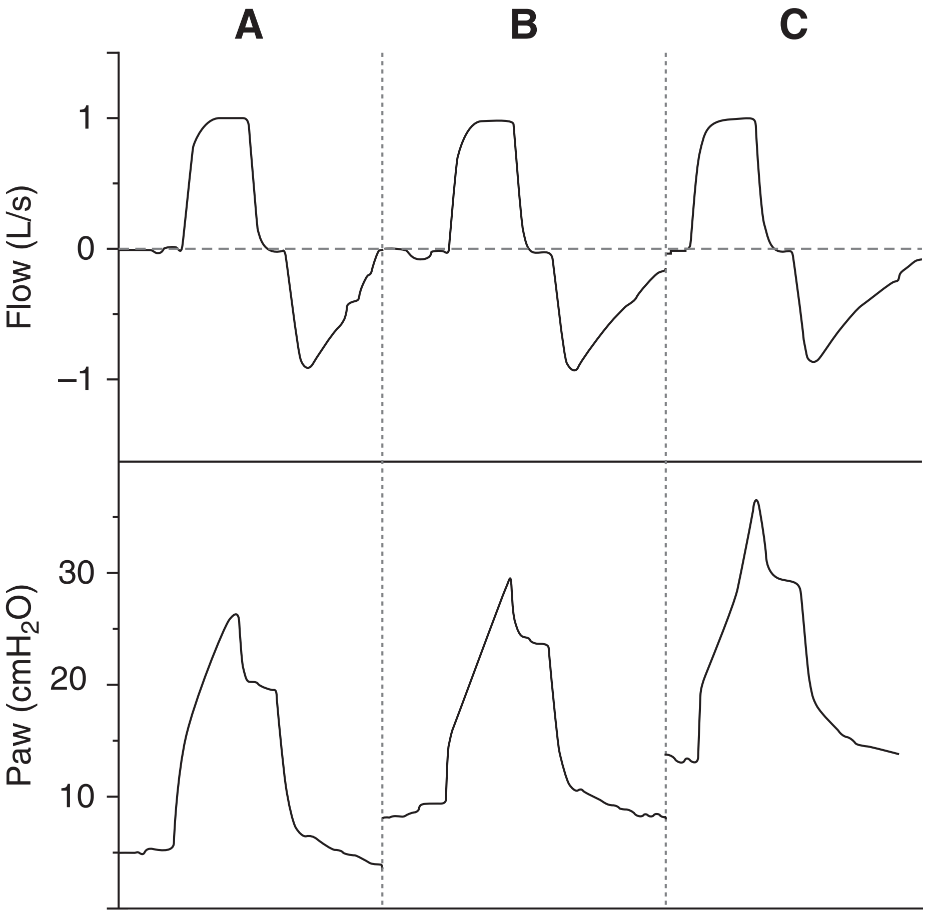


Figure 4. Stress index. Examination of the late portion of the inspiratory pressure–time curve may provide information on the effect of positive end-expiratory pressure (PEEP) on tidal recruitment. (*A*) Demonstration of a convex shape, consistent with a stress index less than 1, on a PEEP of 5 cm H_2O. (*B*) Demonstration of a flat shape, consistent with a stress index of 1, on a PEEP of 10 cm H_2O. (*C*) Demonstration of a concave shape, consistent with a stress index greater than 1, on a PEEP of 15 cm H_2O. These patterns are correlated with intratidal alveolar recruitment, stable alveolar mechanics, and tidal hyperinflation, respectively. Paw = airway pressure.

Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury

Salvatore Grasso, MD; Pierpaolo Terragni, MD; Luciana Mascia, MD, PhD; Vito Fanelli, MD; Michel Quintel, MD; Peter Herrmann, PhD; Goran Hedenstierna, MD; Arthur S. Slutsky, MD; V. Marco Ranieri, MD

- **Stress index method**
  - Grasso et al., CCM 2004, 32 (4), p. 1018
  - Constant flow (square wave) assist-control ventilation
  - PEEP adjusted for stress index values between 0.9-1.1
  - Vs. ARMA

Stress Index

1) Less PEEP

2) Same P/F ratio

3) Small derecruitment (but no consequence on oxygenation)

4) Decreased elastance

5) Decrease in inflammatory markers

6) Decrease in PCO2

TABLE 2. VENTILATORY PARAMETERS, PARTITIONED STATIC ELASTANCE, AND GAS EXCHANGE PARAMETERS AT THE END OF EACH STUDY PERIOD

	ARDSnet	Stress Index	*P* Value
$PEEP_{external}$, cm H_2O	13.2 ± 2.4	6.8 ± 2.2	<0.01
$PEEP_{i,st}$, cm H_2O	0.9 ± 1.1	1.1 ± 1.6	NS
V_T, ml	420 ± 80	440 ± 60	NS
RR, breaths/min	23 ± 5	22 ± 4	NS
Minute ventilation, L/min	8.6 ± 2.8	9 ± 3.1	NS
Est_{rs}, cm H_2O/L	34.7 ± 6.6	31.2 ± 7.4	<0.01
Est_L, cm H_2O/L	28.6 ± 6.7	26.3 ± 7.1	<0.01
Est_{cw}, cm H_2O/L	5.9 ± 2.4	6.2 ± 2.4	NS
F_{IO_2}	0.75 ± 0.14	0.76 ± 0.13	NS
pH	7.397 ± 0.1	7.408 ± 0.1	NS
Pa_{O_2}/F_{IO_2}	122 ± 44	110 ± 32	NS
Pa_{CO_2}, mm Hg	45.6 ± 6.1	41.8 ± 6.3	<0.01

Definition of abbreviations: Est_{cw} = static elastance of chest wall; Est_L = static elastance of lung; Est_{rs} = static elastance of respiratory system; NS = not significant; PEEP = positive end-expiratory pressure; $PEEP_{external}$ = PEEP at end expiration; $PEEP_{i,st}$ = static intrinsic PEEP; RR = respiratory rate.

Data are mean ± SD.

Stress Index

ARMA patients

- More PEEP (13 vs. 7)
- Increased elastance
- Increased PCO2
- Increased inflammatory markers
- Increased PVR
- Decreased CO

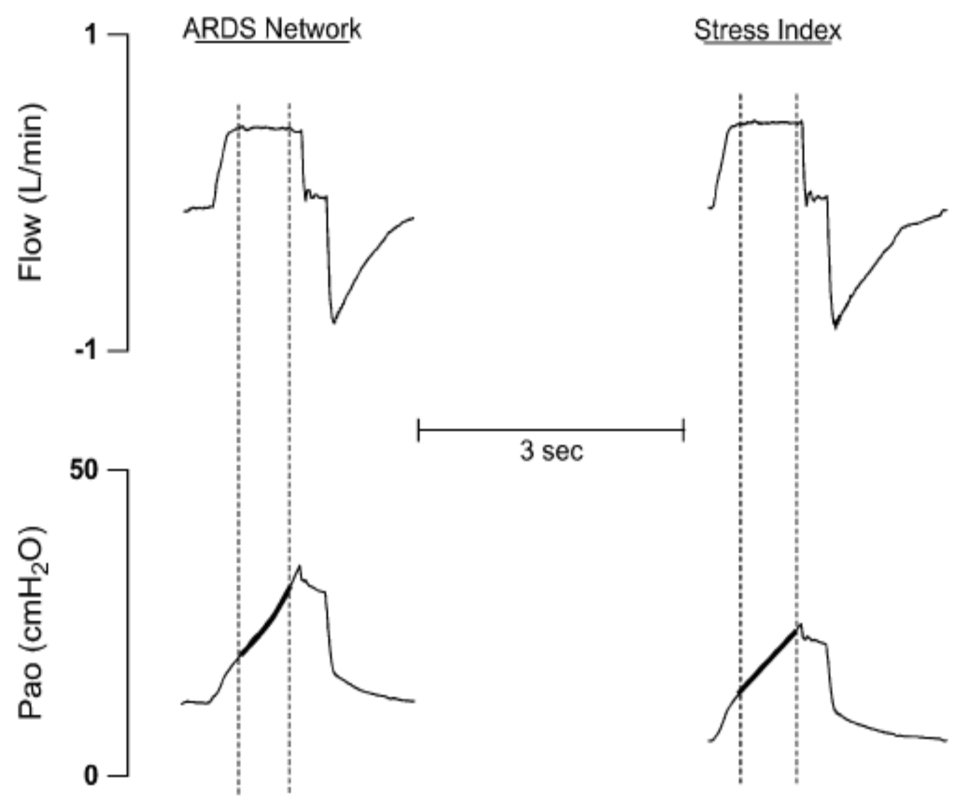
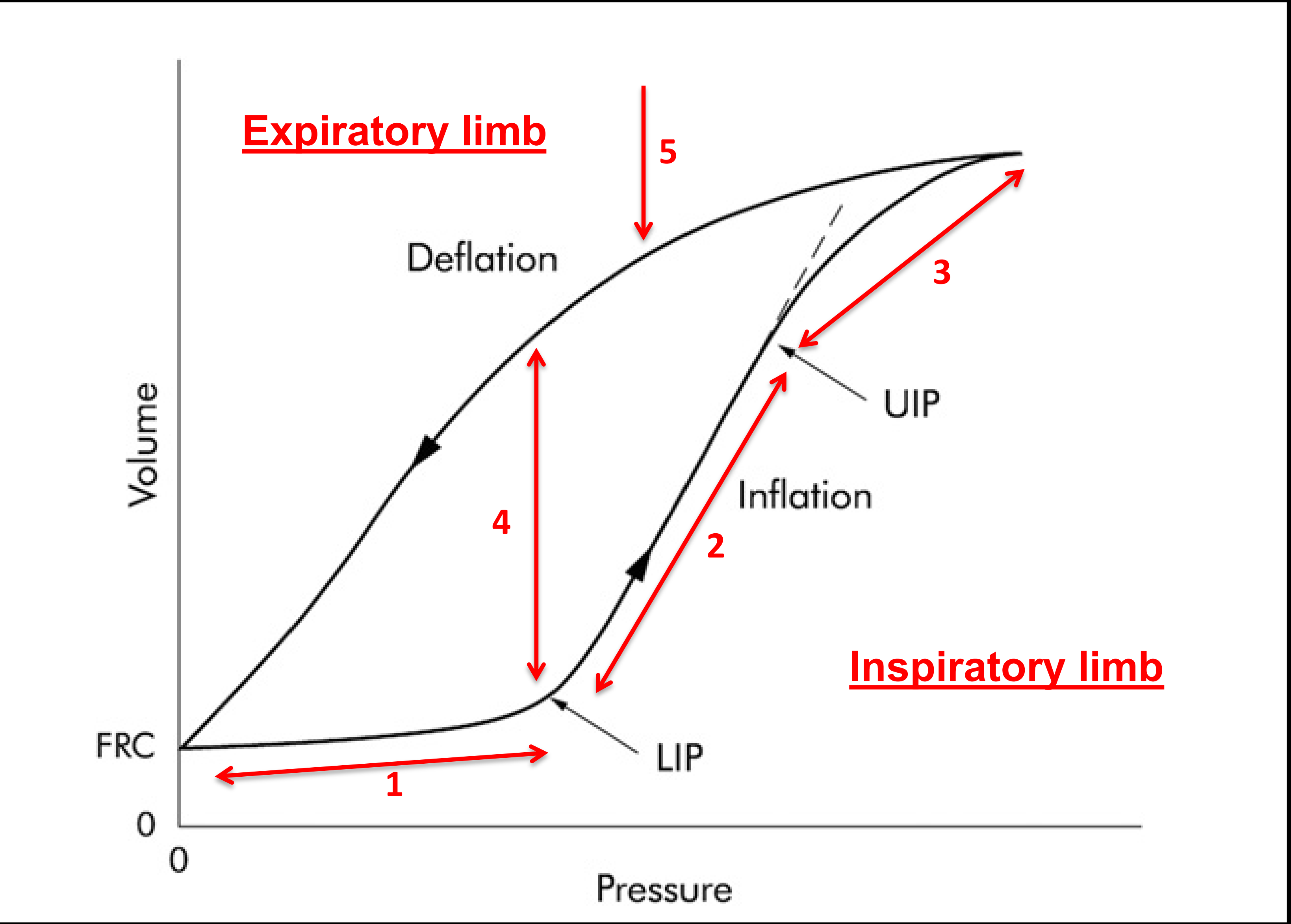


Figure 3. Experimental record showing flow and airway opening pressure (Pao) traces obtained in a representative patient during the two experimental conditions. *Dotted lines* identify the portion of constant-flow inflation and the *bold lines* the corresponding segment of Pao on which the software fits the power equation for the stress index calculation. During the ARDSnet strategy, the stress index value was 1.233, with a positive end-expiratory pressure (PEEP) level of 12 cm H_2O, whereas it was reduced to 1.006 during the stress index strategy, with a PEEP level of 5 cm H_2O.

Setting PEEP in ARDS

Setting PEEP in ARDS
According to FiO2 scale
Incremental PEEP (EXPRESS)
Decremental PEEP
Stress Index method
P-V curve
Transpulmonary pressure
Driving pressure and mechanical power
Right ventricular considerations
Recruitment / inflation ratio
Electrical impedance tomography


Expiratory limb
5
Deflation
3
UIP
Volume
4
Inflation
2
Inspiratory limb
FRC
LIP
1
0
0
Pressure

Setting PEEP in ARDS

- **Limitations**
  - Starting at LIP, progressive recruitment occurs… When to stop?
    - PMC or MH?
  - Recruitment occurs past UIP
    - Significance?
  - PV curve influenced by altered chest wall compliance
    - Elevated pleural and abdominal pressures
  - Time consuming
    - Constant Slow-flow (< 10L/min)
    - Pressure-step changes
  - Patient must be sedated and passive
  - Important inter-observer variability in finding LIP and UIP
    - Up to 11 cmH2O according to some studies

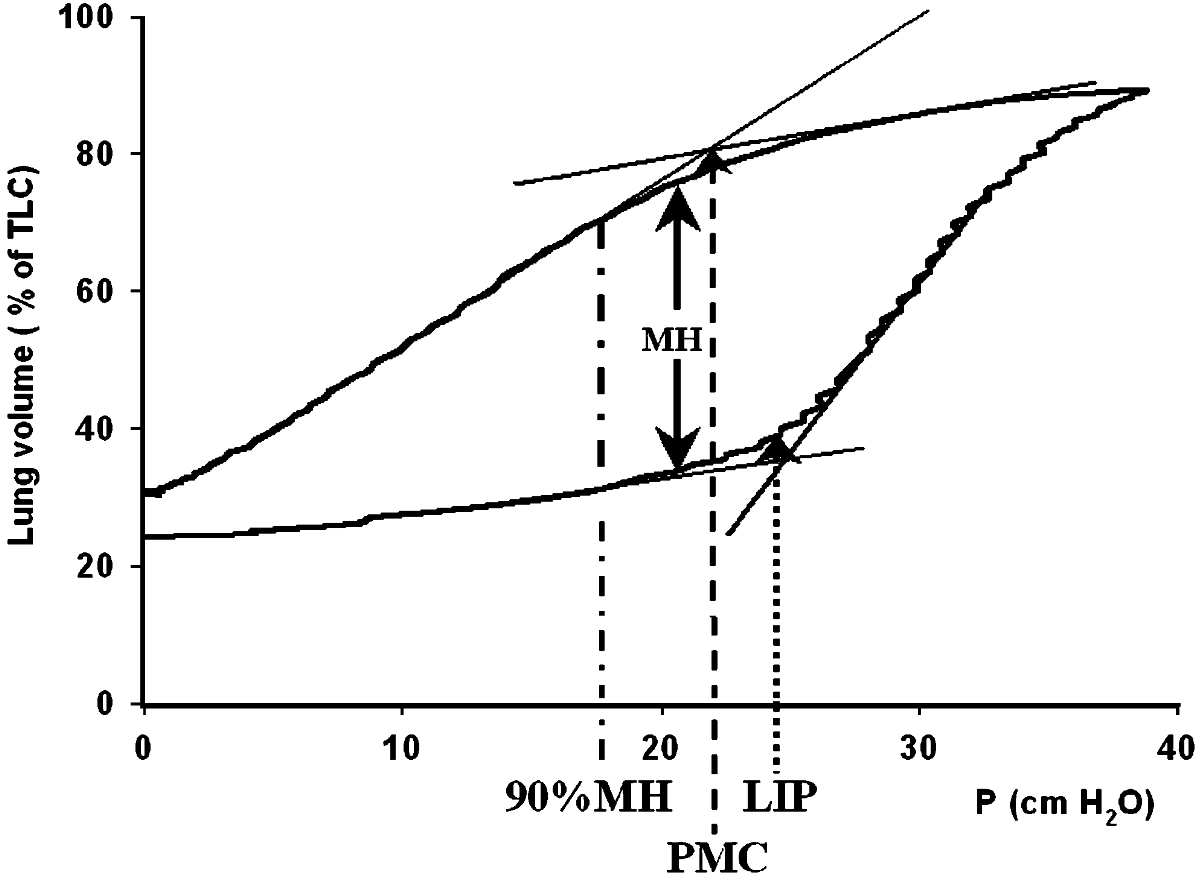


Fig. 1. A pressure–volume loop from an animal after lung lavage. The methods for obtaining lower inflexion point (LIP), point of maximum curvature (PMC) and 90% of maximal hysteresis (90%MH) are depicted.

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Transpulmonary Pressure

- Paw ≠ transpulmonary pressure (PL)
  - Increase in chest wall elastance (oedema, kyphoscoliosis, abdominal hypertension)
  - Right shift in pressure-volume curve (obesity)
  - Resultant increase in airway pressure without an increase in lung stress
  - Inadequate PEEP to achieve lung recruitment (because of concerns about high airway plateau pressure)

- PL = pressure gradient from the airway to the pleural space
  - PL = Paw – Ppl
  - More accurate reflection of the stress on the lung parenchyma, independent of the chest wall
  - End-inspiratory PL vs. standard plateau pressure
    - PLplat within tolerable limits (< 25?) = consider exceeding conventional airway plateau pressure limits
  - End-expiratory PL in positive range (0-10 cmH2O)
    - Adjust PEEP accordingly to prevent cyclic alveolar collapse

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.

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Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure–Guided Strategy vs an Empirical High PEEP-F_{IO_2} Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome

A Randomized Clinical Trial

Setting PEEP in ARDS
According to FiO2 scale
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DRIVING PRESSURE

- Normalizing VT to Crs and using the ratio as an index indicating the 'functional' size of the lungs
  - $\Delta P_{el,rs} = \Delta V \times E_{rs}$ => $\Delta P = V_t / C_{rs}$
  - Crs directly related to the size of the lung participating in ventilation
  - Thus ΔP describes the relationship between Vt and the lung volume available to receive a breath (size of tidal volume in relation to the aerated lung)
  - In patients not making any respiratory efforts => $\Delta P = P_{plat} - PEEP_{tot}$

- May better reflect mechanical power and thus pulmonary stress and strain
  - ΔP = amount of cyclic parenchymal deformation imposed on opened lung units

DRIVING PRESSURE

- Decreasing ΔP via
  - Decrease in Vt
  - Increase in Crs (via increased PEEP)
- For a constant Vt, titrating PEEP to minimize ΔP is equivalent to titrating PEEP to maximize Crs
- Evaluation of lung recruitability?
  - Decreased ΔP vs. increased PEEP
- Prognostic marker?

SPECIAL ARTICLE

Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

- NEJM 2015, 372 (8), p. 747
- Can a change in ΔP resulting from a specific change in ventilator settings be linked to survival?
  - Better *predictor of outcome?*

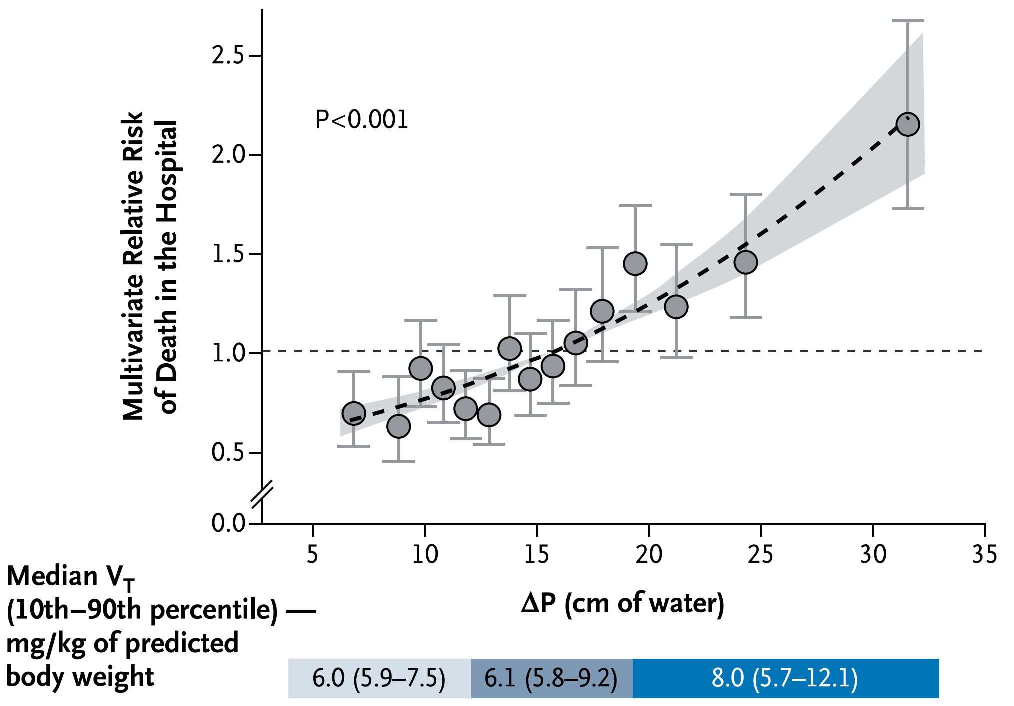


Figure 2. Relative Risk of Death in the Hospital versus ΔP in the Combined Cohort after Multivariate Adjustment.

The combined cohort (with 1249 death events) was partitioned into 15 quantiles of ΔP, and the relative risk for each quantile was calculated in relation to the mean risk of the combined population (assumed to be 1). The mean risk and 95% confidence intervals (error bars) for each percentile were calculated after multivariate adjustment at the patient level (Cox proportional-hazards model) for the five covariates (trial, age, risk of death according to APACHE or SAPS, arterial pH at entry, and Pa_{O_2}:F_{IO_2} at entry) specified in model 1. The gray zone represents the 95% confidence interval for the Cox regression (dashed line) across the whole population when ΔP is considered as a continuous variable.

Pierre-Marc Chagnon MD FRCPC

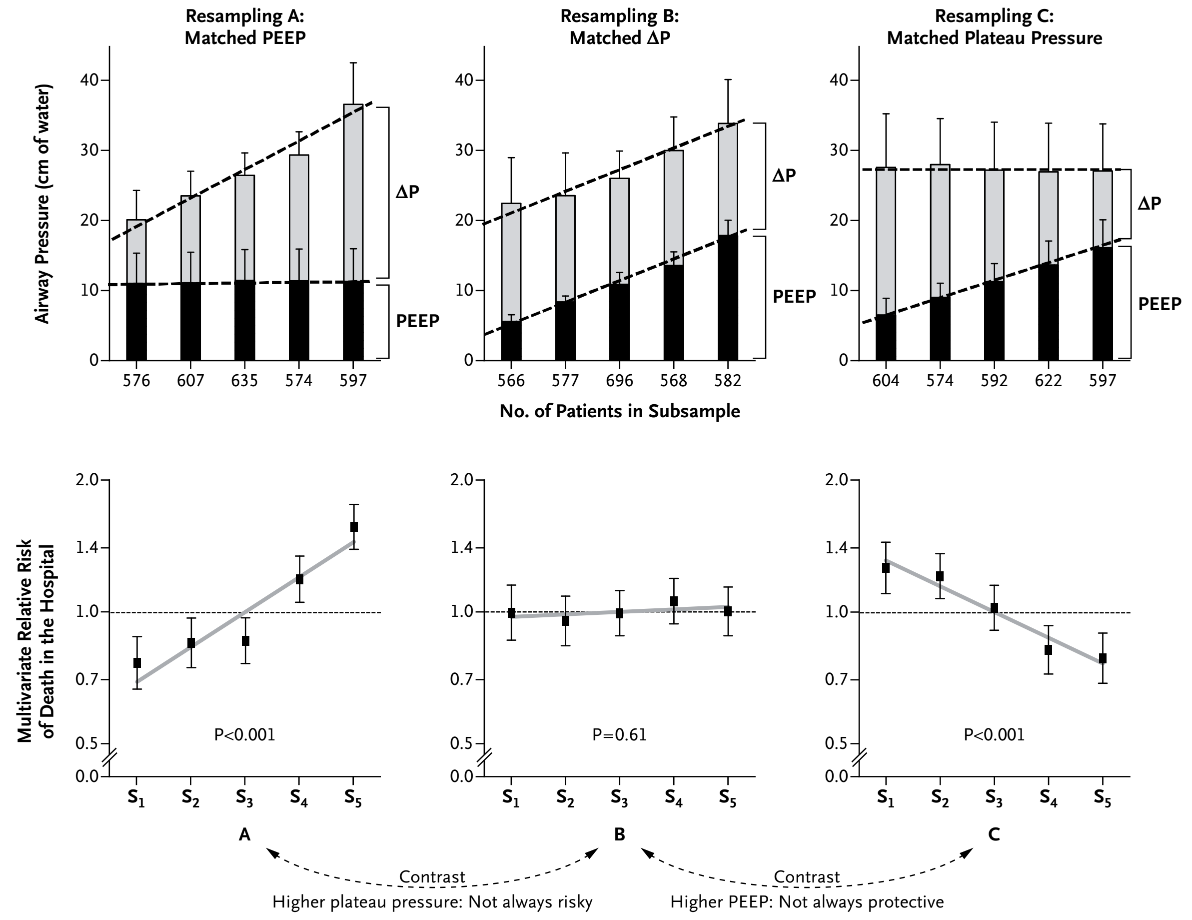
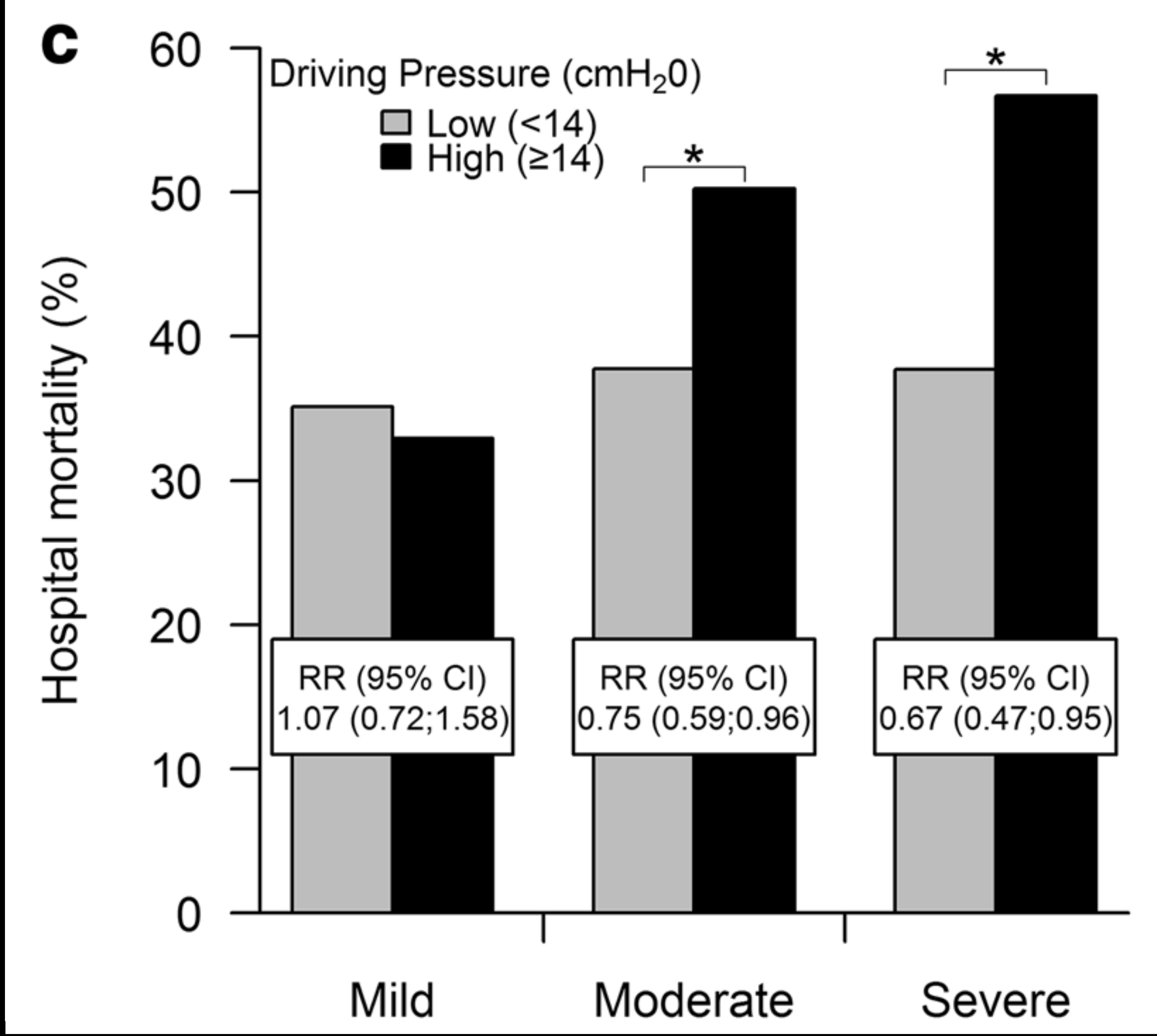


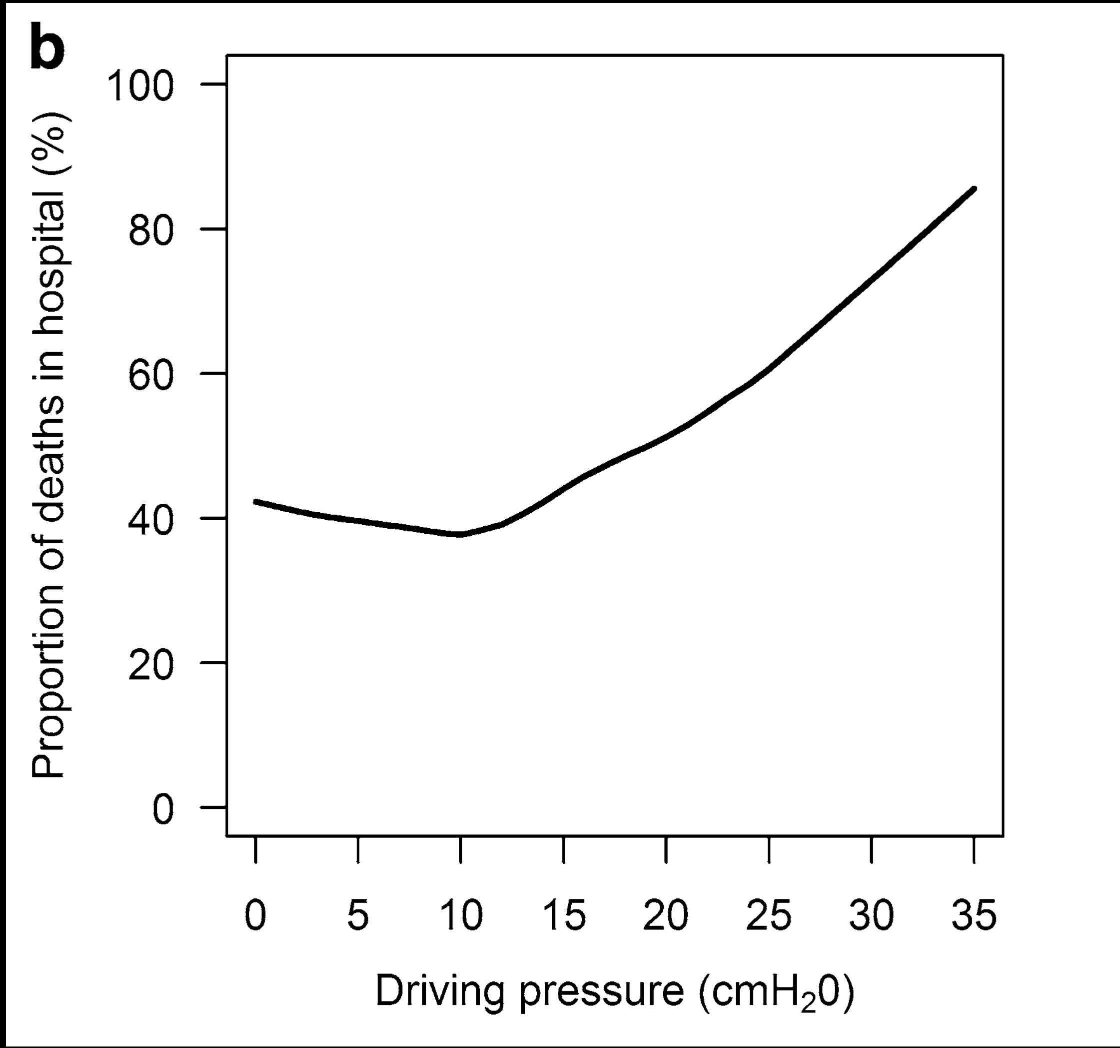
Figure 1. **Relative Risk of Death in the Hospital across Relevant Subsamples after Multivariate Adjustment — Survival Effect of Ventilation Pressures.**

Using double stratification procedures (obtaining subgroups of patients with matched mean levels for one variable but very different mean levels for another ranking variable; see Section III.3 in the Supplementary Appendix for details), we partitioned our data set into five distinct subsamples (each including approximately 600 patients with the acute respiratory distress syndrome [ARDS]) and calculated the relative risk (adjusted mortality) for each subsample in comparison with the mean risk in the combined population. The upper stacked-bar diagrams illustrate the mean values for positive end-expiratory pressure (PEEP), plateau pressure, and driving pressure (ΔP) observed in each subsample. The error bars represent 1 standard deviation. Each resampling (A, B, and C) produced subsamples with similar mean values for one ventilator variable but very distinct values for the two other variables. At the bottom, the respective relative risks for death in the hospital are shown, calculated for each subsample after multivariate adjustment (at the patient level) for the five covariates (trial, age, risk of death according to the Acute Physiology and Chronic Health Evaluation [APACHE] or Simplified Acute Physiology Score [SAPS], arterial pH at entry, and Pa_{O_2}:F_{IO_2} at entry) specified in model 1. Error bars represent 95% confidence intervals. A relative risk of 1 represents the mean risk of the pooled population, which had an adjusted survival rate of 68% at 60 days. Note that a lower survival rate was observed among patients with higher ΔP and higher survival was observed among patients with lower ΔP, independent of concomitant variations in PEEP and plateau pressure.

DRIVING PRESSURE

- Higher Vt and plateau pressure associated with increased mortality only if higher ΔP
- Protective effect of higher PEEP only if associated with decreased ΔP
- Positive association between ΔP and survival even though all the ventilator settings were protective
- Survival benefits in the low Vt trials were proportional to reductions in ΔP
- ΔP thus looks like a critical mediator of the benefits of various interventions
- Future trials could be designed to link ventilator changes to changes in ΔP


c
Driving Pressure (cmH$_2$0)
Low (<14)
High (≥14)
Hospital mortality (%)
60
50
40
30
20
10
0
*
*
RR (95% CI)
1.07 (0.72;1.58)
RR (95% CI)
0.75 (0.59;0.96)
RR (95% CI)
0.67 (0.47;0.95)
Mild
Moderate
Severe


b
Proportion of deaths in hospital (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
Driving pressure (cmH$_2$0)

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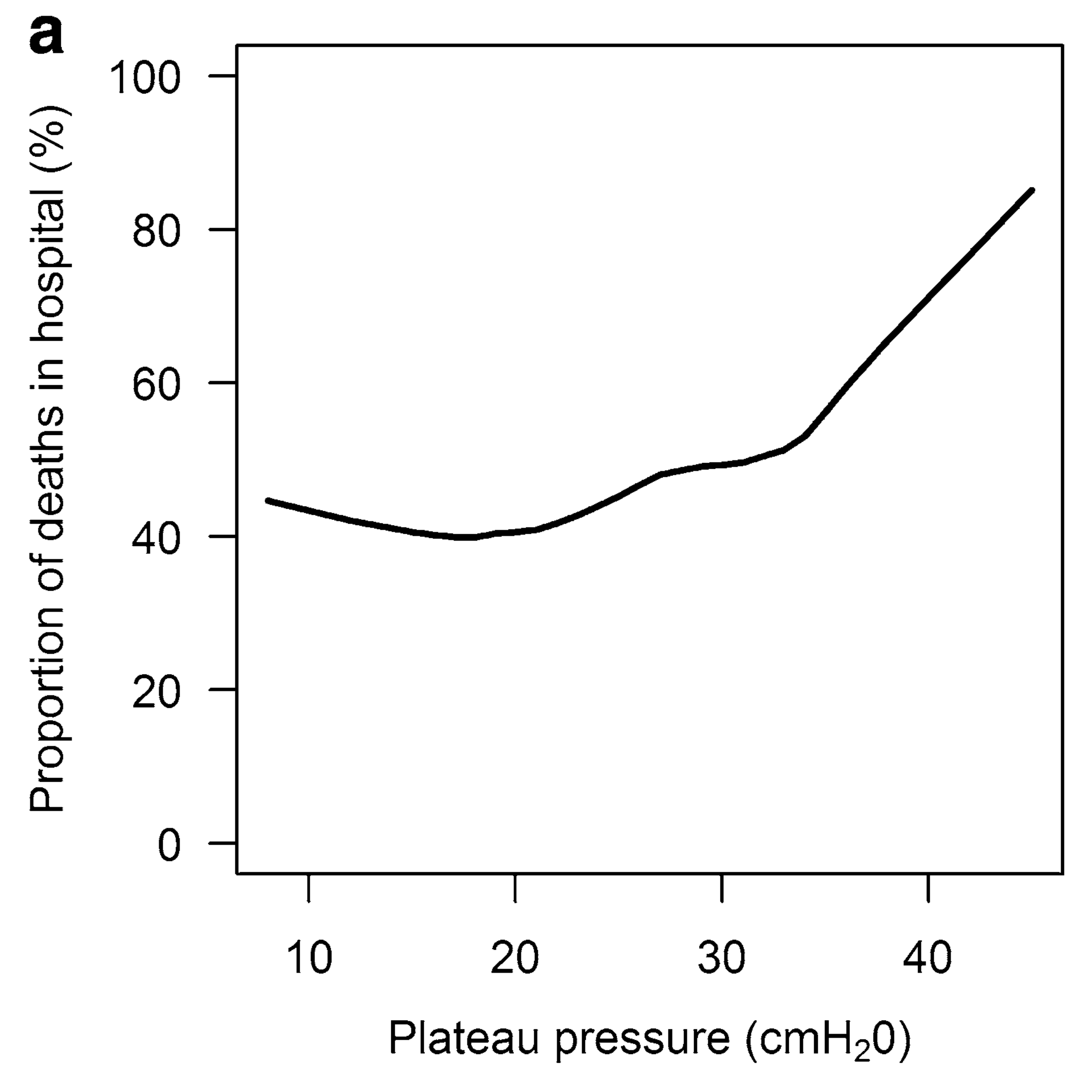
François Jardin
Antoine Vieillard-Baron

Is there a safe plateau pressure in ARDS? The right heart only knows

- ICM 2007, 33, p. 444
  - Before protective ventilation = acute cor pulmonale (ACP) = frequent and associated with a poor prognosis
  - ACP rare if Pplat < 27 cmH2O
  - Linear relationship between Pplat and ACP incidence
  - Pplat > 27 cmH2O + ACP = increased mortality
  - Pplat < 27 => mortality similar whether ACP present or not



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RV Function and Ventilation

- Should we aim for smaller Pplat in the presence of ACP?
- If Pplat > 27 and ACP, consider decreasing Vt < 6 cc/Kg
- Consider TEE for RV monitoring in severe ARDS
- Consider early prone positioning if ACP (even if P/F ratio > 150 mmHg?)

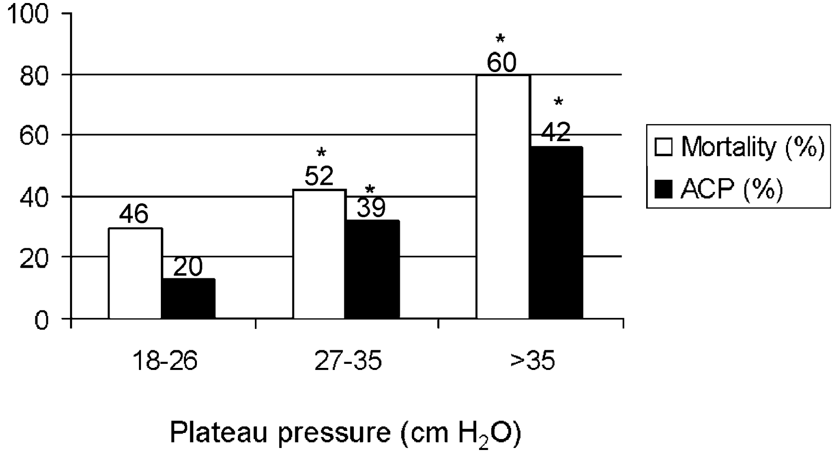

Fig. 1 Mortality rate and incidence of acute cor pulmonale (*ACP*) are plotted against three ranges of plateau pressure (see text). Figures are the exact number of patients concerned. $^*p < 0.05$, when compared with the preceding range

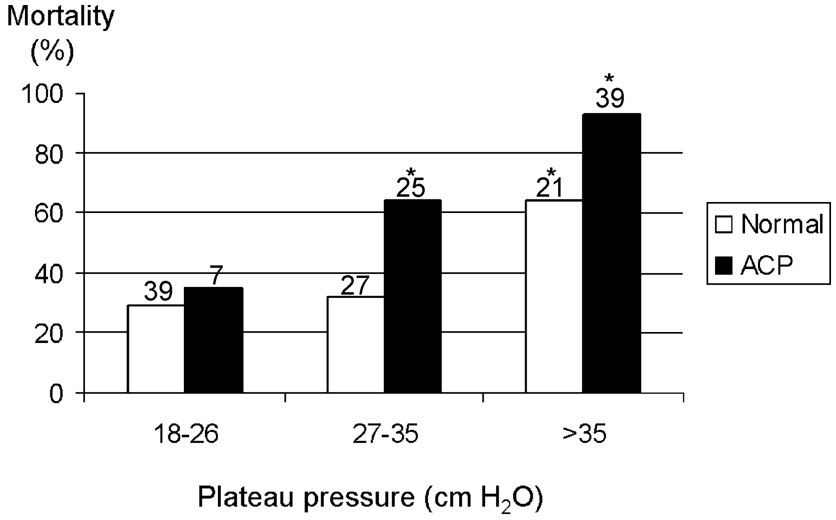

Fig. 2 Mortality rate is plotted against three ranges of plateau pressure (see text), after separating patients with normal bedside echocardiographic findings (normal), and patients exhibiting acute cor pulmonale (*ACP*) detected by echocardiography. Figures are the exact number of patients concerned. $^*p < 0.05$, when compared with the preceding range

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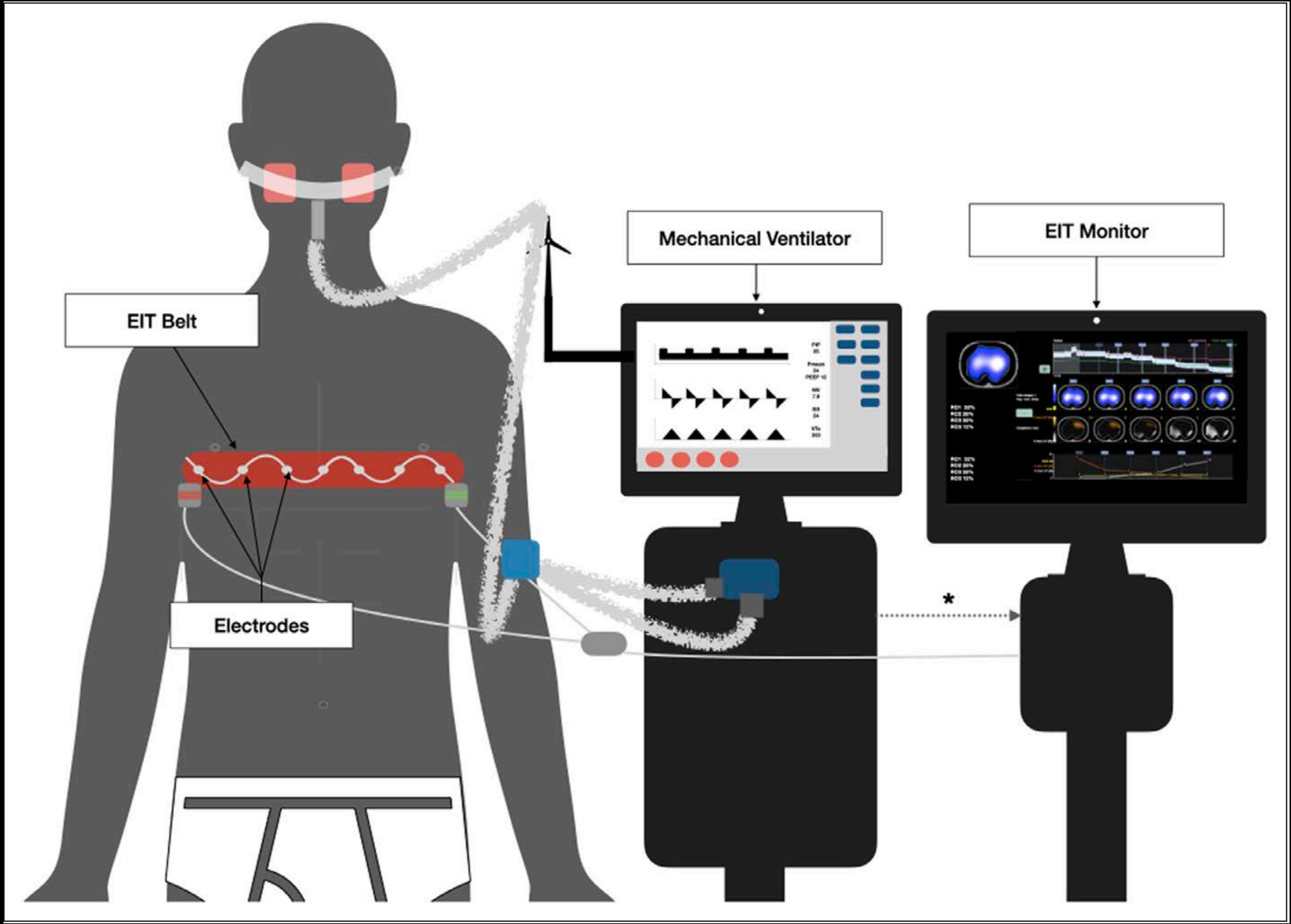

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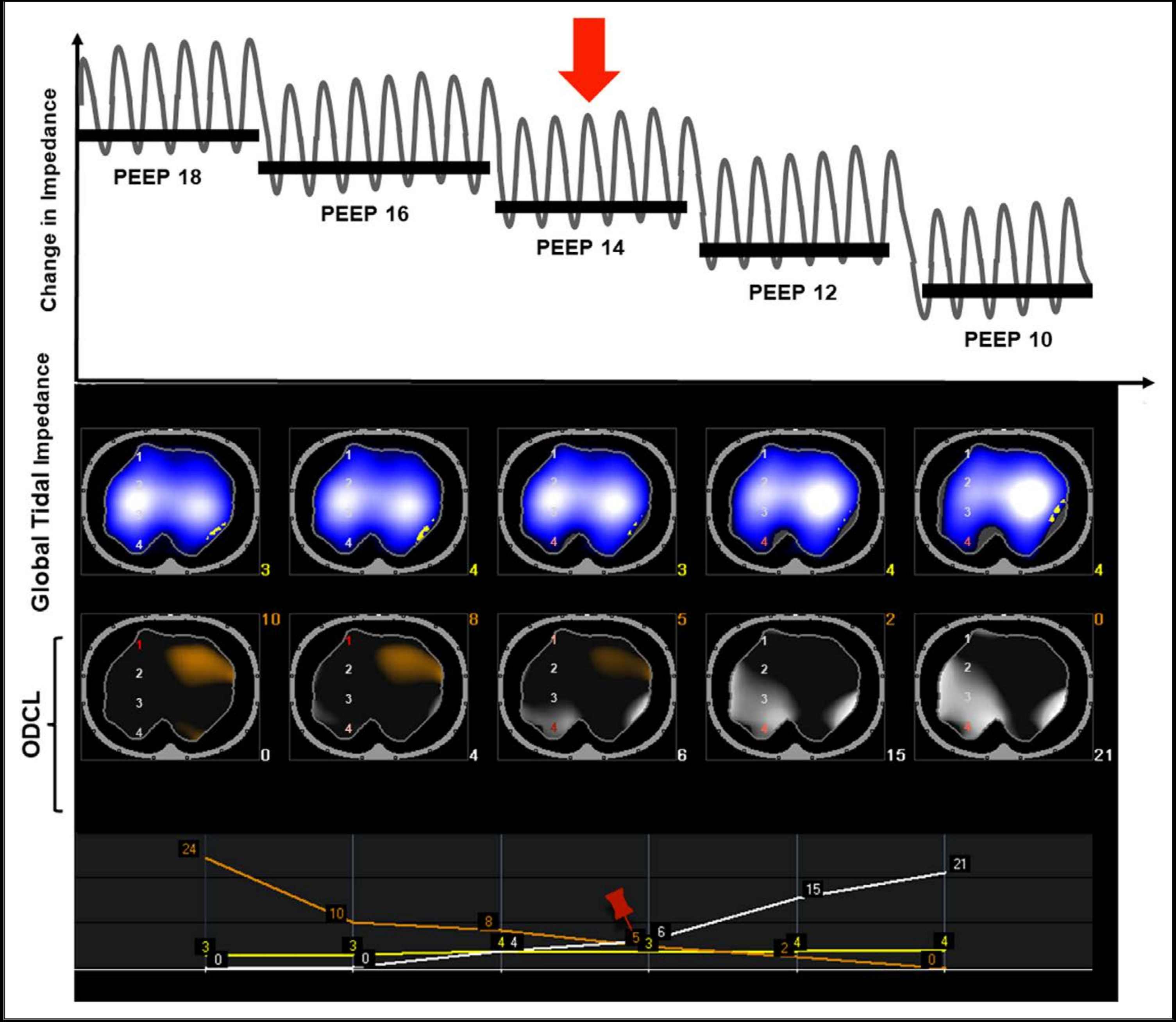

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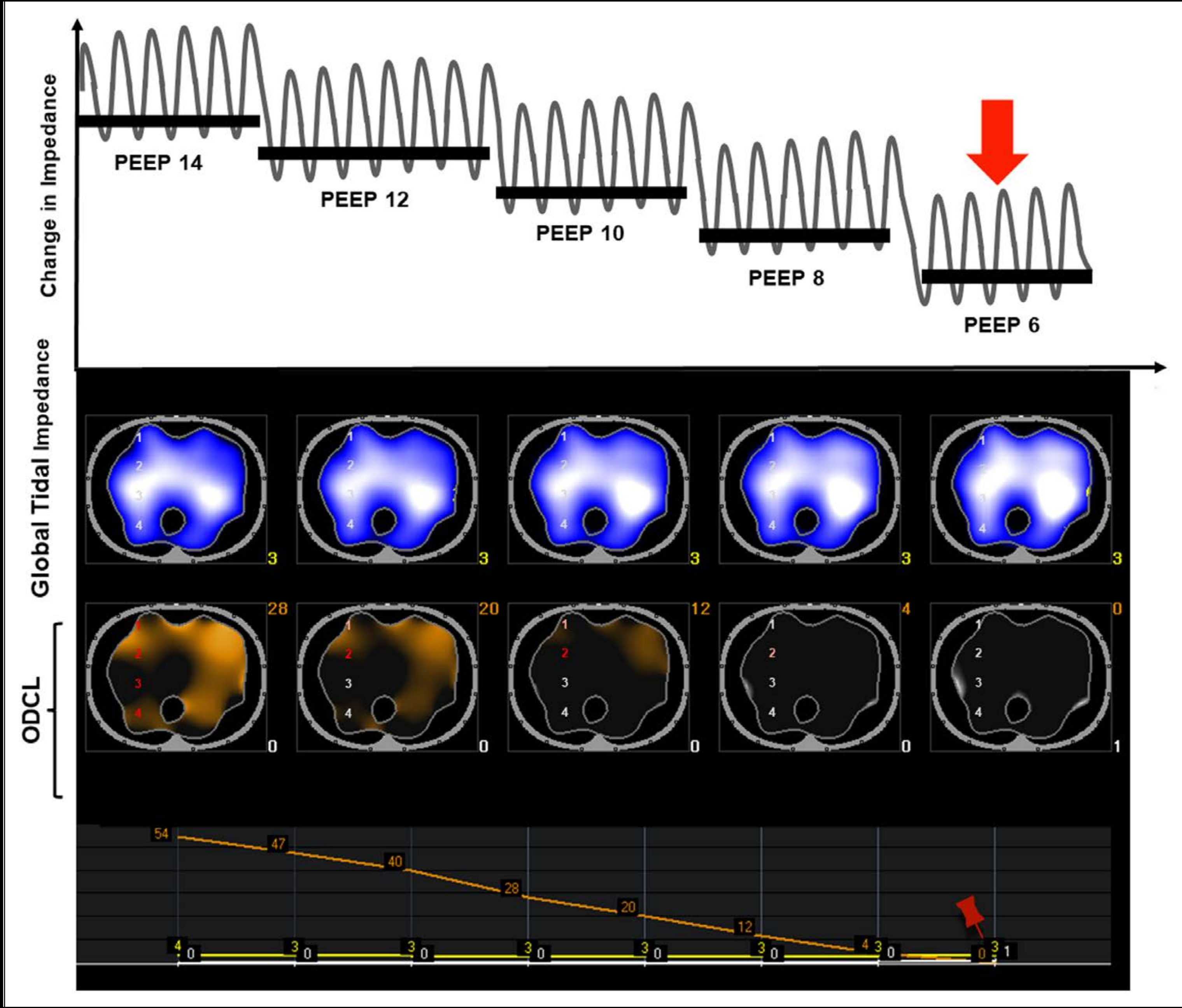

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Recruitment / Inflation ratio

- R/I ratio reflects the proportion of volume distributed into the recruited lung to that into the baby lung when PEEP is changed (high ΔVrec for ΔPrec (high – low))
  - R/I ratio = Crec to the compliance of the baby lung (Crs) – Crec/Crs
  - The lower the R/I ratio, the greater the volume that will be distributed into the already aerated baby lung = the greater risk of hyperinflation
  - Cut-off value = 0.5

- R/I ratio = new method to titrate PEEP in ARDS
  - Indicator for atelectrauma = setting PEEPlow in high recruiters
  - Indicator for hyperinflation = setting PEEPhigh in low recruiters

- Setting PEEPhigh greater than AOP is necessary to use the recruitability test

Pierre-Marc Chagnon MD FRCPC