PEEP: AMICA E NEMICA

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Conflicts of interest

- Payment for lectures from Getinge, Draeger Medical, Pfizer, Fisher & Paykel, MSD
- Travel/accommodation/congress registration support from Biotest, Getinge

POSITIVE PRESSURE RESPIRATION AND ITS APPLICATION TO THE TREATMENT OF ACUTE PULMONARY EDEMA *

By Alvan L. Barach, M.D., F.A.C.P., John Martin, M.D., and Morris Eckman, B.S., *New York, N. Y.*

The purpose of this paper is to present observations we have made which provide a physiologic basis for the use of positive pressure respiration in the treatment of acute pulmonary edema. For the most part positive pressure has been thought of as a method of resuscitation such as that accomplished by the pulmotor in accidental asphyxia. The function of pressure in the respired air has, however, a broad physiological significance, being employed by the human organism itself as a compensatory mechanism as well as lending itself to therapeutic application in inhalational therapy. We wish to present the subject from the following points of view: (1) A critical discussion of the pertinent literature. (2) Animal experimentation on the development and treatment of acute pulmonary edema. (3) Physiological studies on the effect of positive pressure respiration in human subjects. (4) The clinical results of treatment with positive pressure in patients with acute pulmonary edema.

Barach et al, Ann Intern Med 1938

ACUTE RESPIRATORY DISTRESS IN ADULTS

DAVID G. ASHBAUGH
M.D. Ohio State
ASSISTANT PROFESSOR OF SURGERY

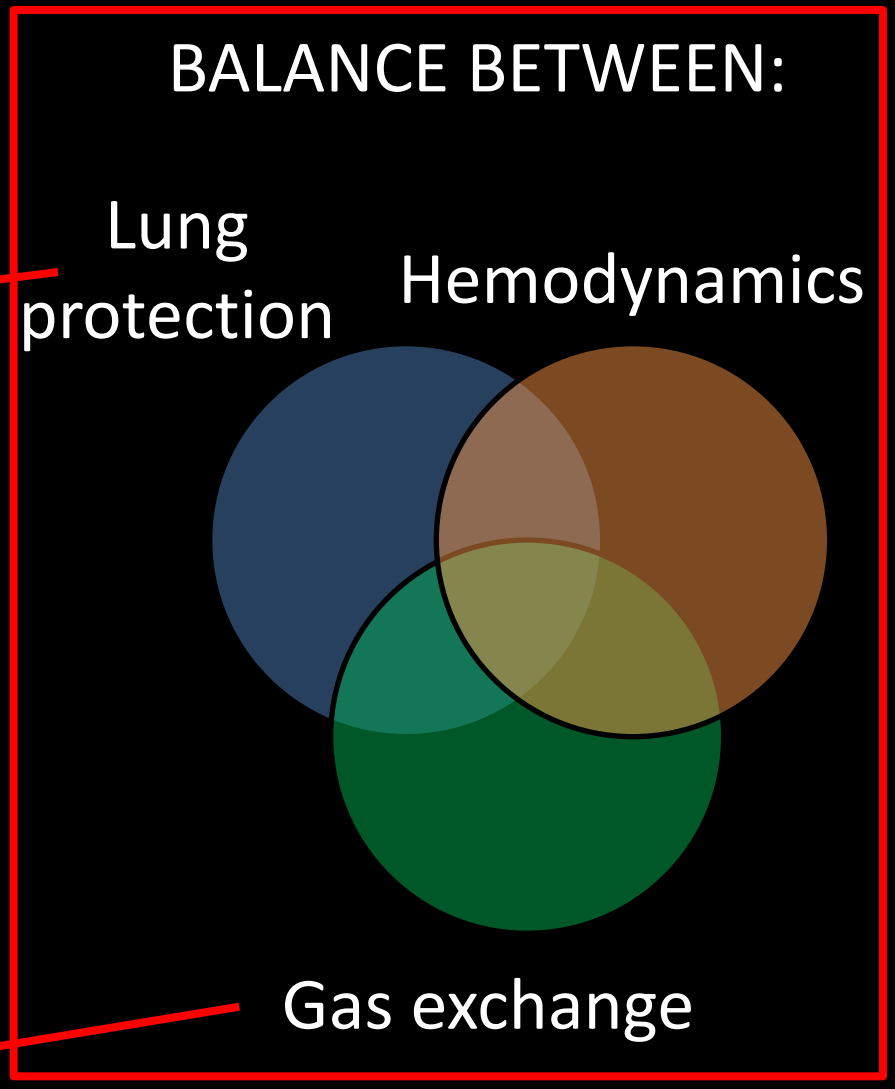
Summary The respiratory-distress syndrome in 12 patients was manifested by acute onset of tachypnœa, hypoxæmia, and loss of compliance after a variety of stimuli; the syndrome did not respond to usual and ordinary methods of respiratory therapy. The clinical and pathological features closely resembled those seen in infants with respiratory distress and to conditions in congestive atelectasis and postperfusion lung. The theoretical relationship of this syndrome to alveolar surface active agent is postulated. Positive end-expiratory pressure was most helpful in combating atelectasis and hypoxæmia. Corticosteroids appeared to have value in the treatment of patients with fat-embolism and possibly viral pneumonia.

Ashbaugh et al, Lancet 1967

Experimental Pulmonary Edema due to Intermittent Positive Pressure Ventilation with High Inflation Pressures. Protection by Positive End-Expiratory Pressure[1-4]

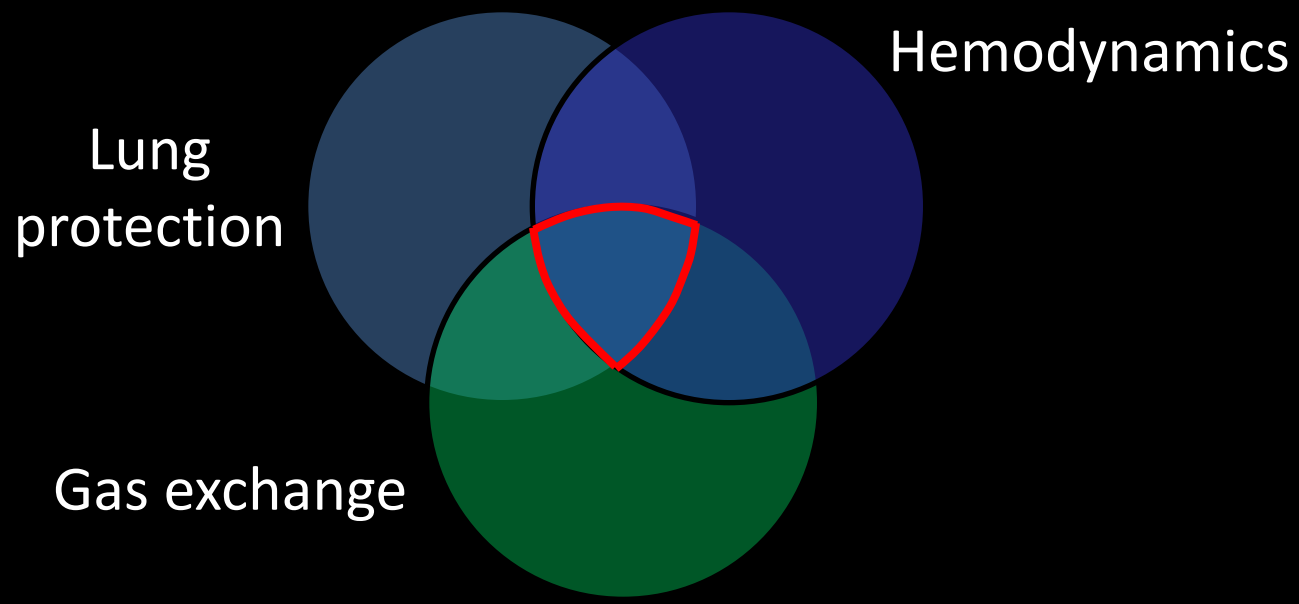
Webb and Tierney Am Rev Resp Dis 1974

Mechanical ventilation can harm the lung: Ventilator-Induced Lung Injury (VILI)



- Oxygenation: FiO_2 + positive airway pressure
- CO_2 removal: ventilation

PEEP adjustment



POSITIVE EFFECTS

- Prevent derecruitment
- Promote recruitment
- Improve oxygenation
- Improve ventilation distribution
- Reduced alveolar V_D

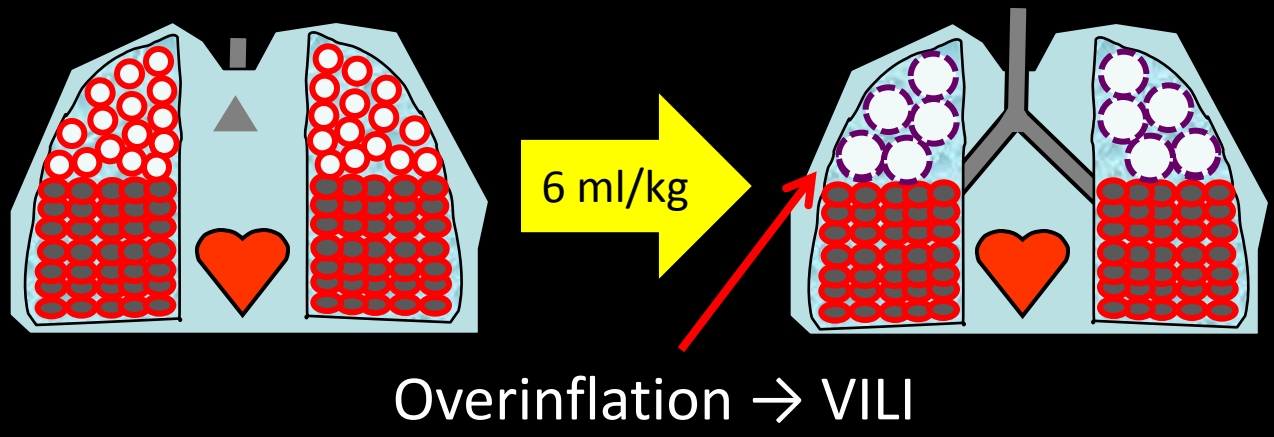
NEGATIVE EFFECTS

- Overinflation
- Cardiac output impairement
- Worsening of oxygenation
- Worsening of perfusion distribution
- Increased alveolar V_D

PEEP and recruitment

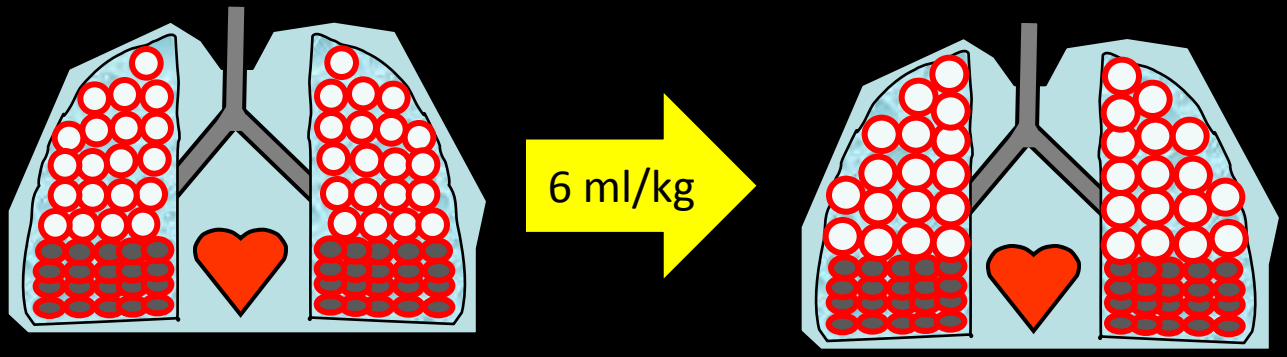
Low PEEP:
derecruitment

$\underline{Cpl_{rs}\ low}$



Higher PEEP :
keeps lungs
recruited

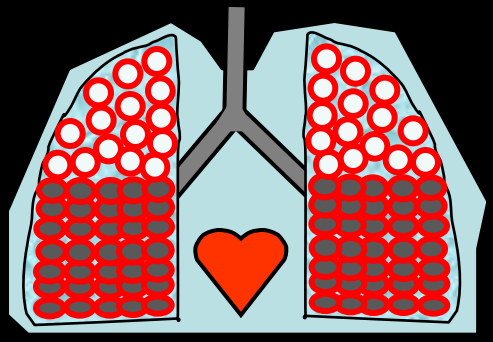
$\underline{Cpl_{rs}\ improved}$



Gas exchange

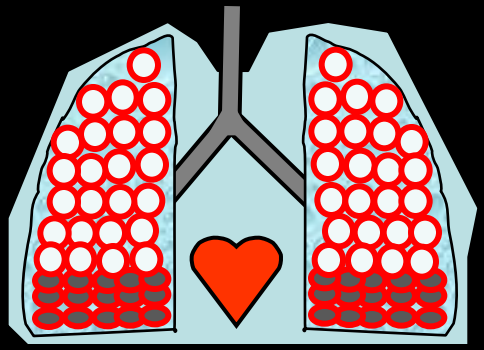
- **Shunt → hypoxemia**
- **Shunt-dependent increased Vd/Vt → hypercapnia**

Low PEEP:
derecruitment



High shunt
Low PaO_2

HigherPEEP:
keeps lungs
recruited



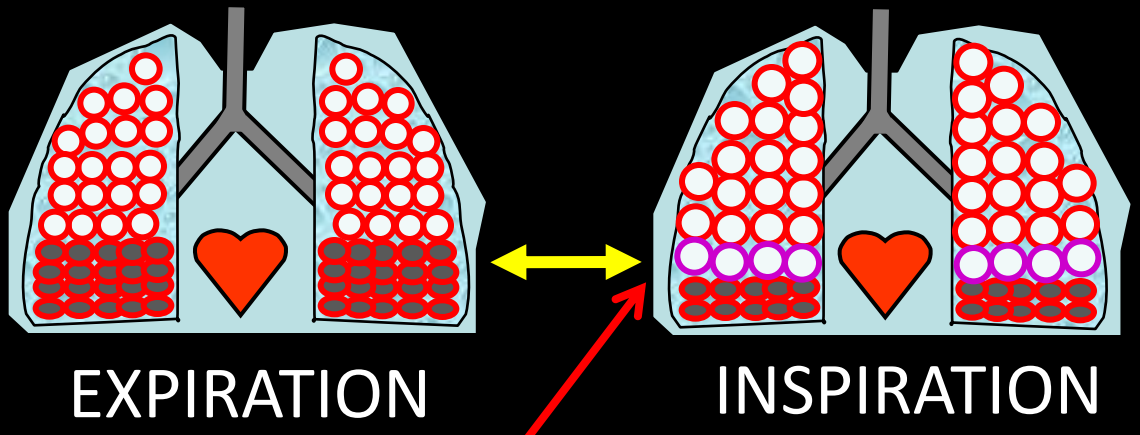
Low shunt
Higher PaO_2

Shunt decrease → Vd/Vt reduction

Lower $PaCO_2$

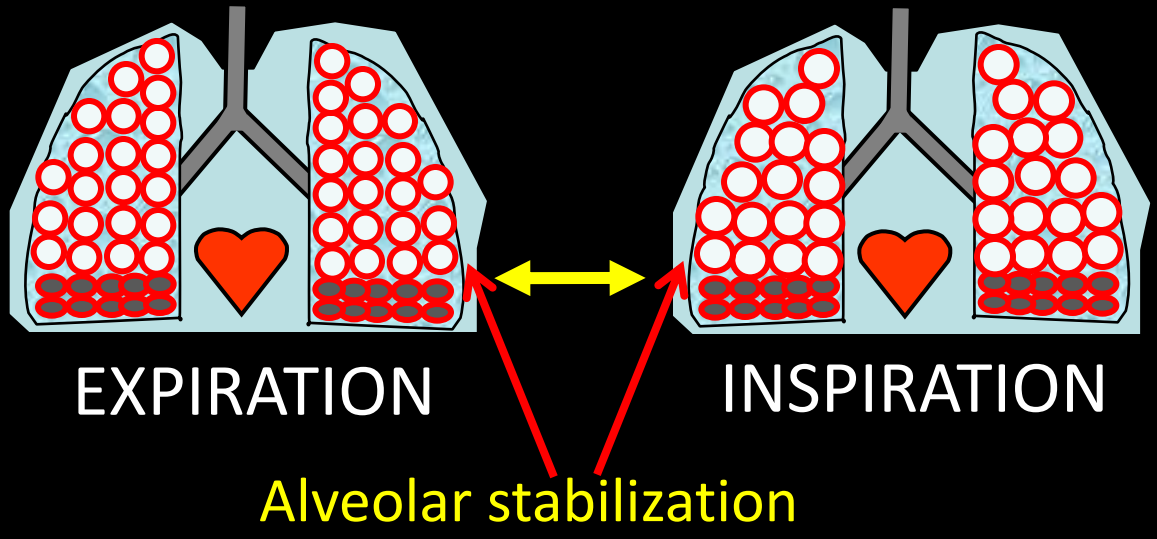
PEEP and lung protection

Low PEEP



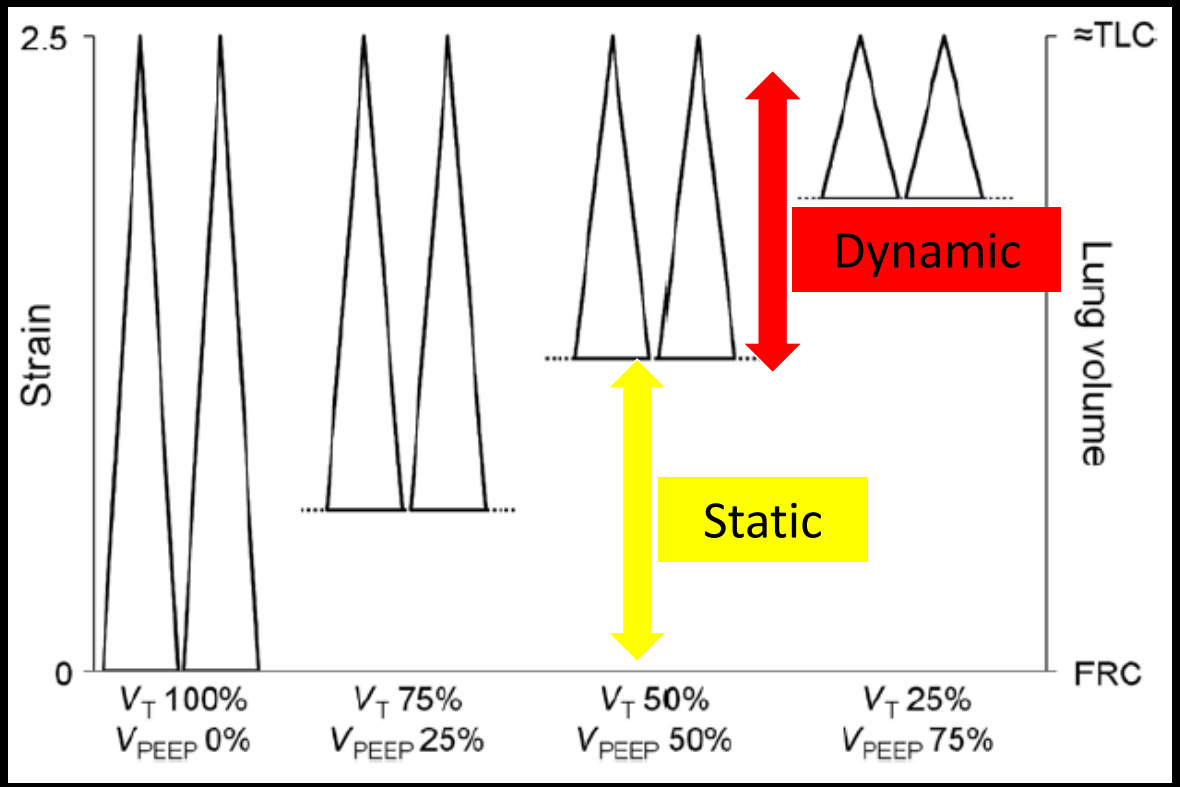
Cyclic alveolar opening and closing: atelectrauma → VILI

Higher PEEP



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];



When dynamic strain decreases

- ↓ mortality
- ↑ oxygenation
- ↓ histological damage and BAL IL-6

Protti et al, CCM 2013

«It remains unclear whether PEEP is protective per se or whether its putative benefit is due to the associated reduction in tidal volume, driving pressure and atelectrauma»

Collino et al, Anesthesiology 2019

Mechanical power: a «unifying hypothesis»?

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

DISTEND THE LUNG | **MOVE THE AIR** | **KEEP OPEN**

- Amount of energy applied to the lung
- Takes into account also the effect of flow and rate
- Obtained from the equation of motion, multiplying total pressure by the changes in volume and rate

Why is PEEP included?

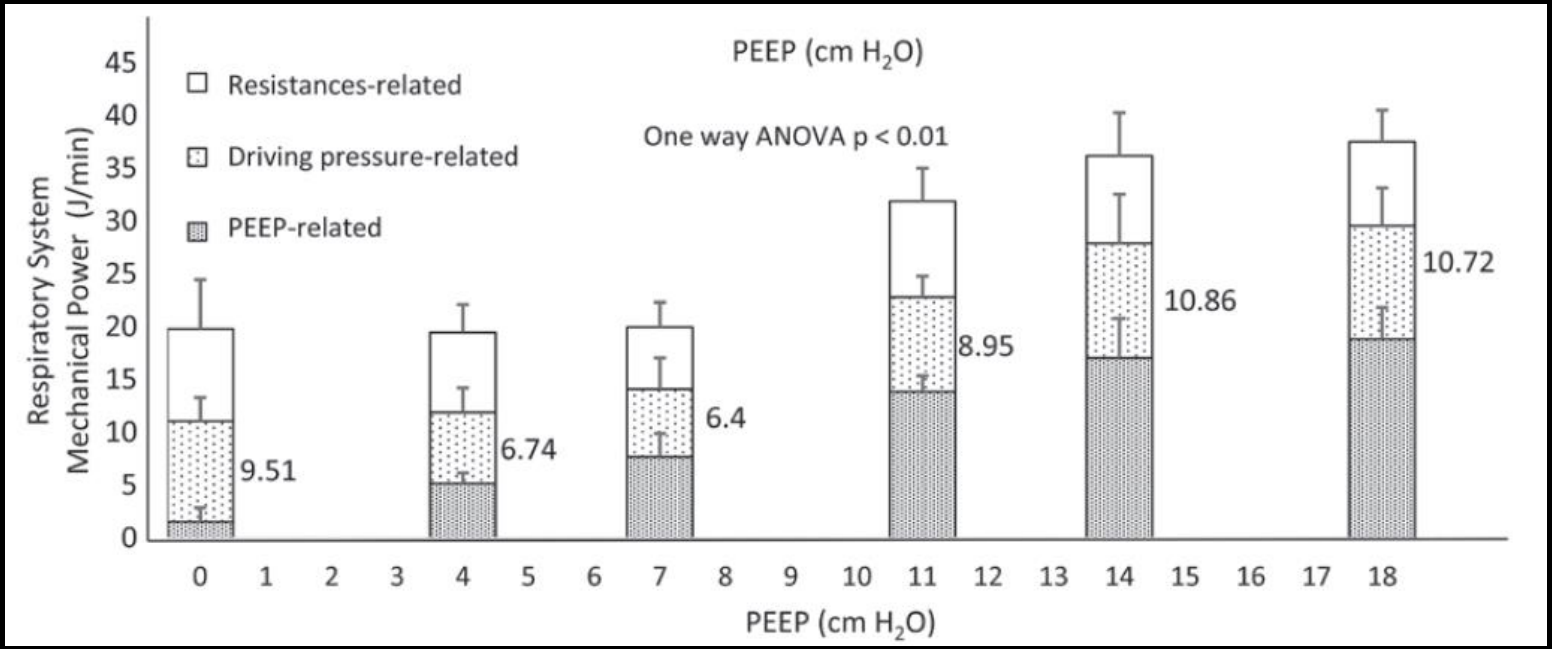
- PEEP increases lung volume above FRC → *static* increase in end-exp stress and strain
- This pressure is stored in lung structures as potential energy
- Tidal lung inflation requires a further increase in transpulmonary pressure (*dynamic* strain)
- The effect of MP on the respiratory system depends on lung recruitability: if PEEP leads to a decrease in ΔP and elastance, MP will decrease

ANESTHESIOLOGY

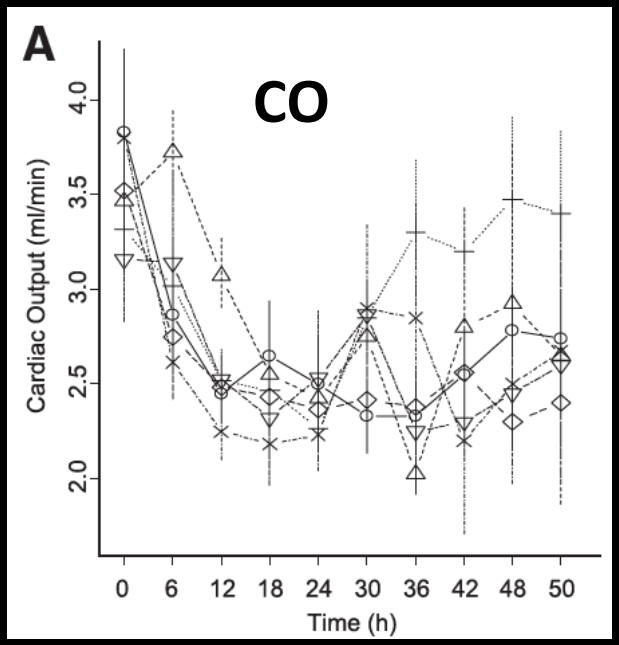
Positive End-expiratory Pressure and Mechanical Power

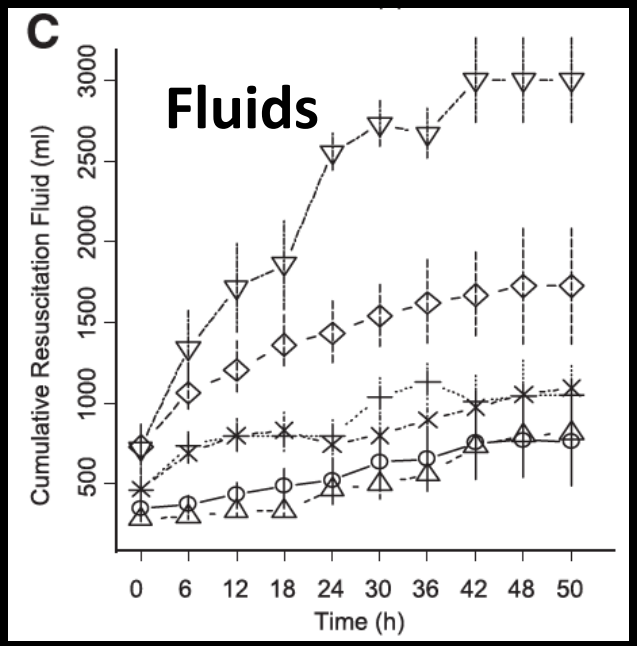
- Hypothesis: PEEP, together with Vt, respiratory rate and gas flow, contributes to the mechanical power required to ventilate the lungs
- Animal model: healthy piglets, ventilated for 50 hrs with a Vt = FRC (strain 1) and RR = 30/min
- Six levels of PEEP (0-4-7-11-14-18) applied

Collino et al, Anesthesiology 2019



- MP similar between 0 and 7 cmH_2O of PEEP, then increased linearly with PEEP
- Lung elastance, atelectasis and inflammation decreased from 0 to 7 cmH_2O PEEP, but increased progressively with higher PEEP





- At high PEEP levels severe hemodynamic impairment
- Mortality 0% with PEEP 0-11 cmH_2O → 33% with PEEP 14 cmH_2O → 50% with PEEP 18 cmH_2O

PEEP and lung protection

- PEEP will raise total stress in all pts, but its application can result in predominant alveolar recruitment, alveolar overdistention or a combination of both
- The net effect of PEEP on recruitment, overdistention and hemodynamics depend on the level of PEEP and on the size of the associated TV

↓

LUNG RECRUITABILITY IS A CRUCIAL DETERMINANT OF THE EFFECT OF PEEP

Lung Recruitment in Patients with the Acute Respiratory Distress Syndrome

Luciano Gattinoni, M.D., F.R.C.P., Pietro Caironi, M.D., Massimo Cressoni, M.D., Davide Chiumello, M.D., V. Marco Ranieri, M.D., Michael Quintel, M.D., Ph.D., Sebastiano Russo, M.D., Nicolò Patroniti, M.D., Rodrigo Cornejo, M.D., and Guillermo Bugedo, M.D.

- 68 pts with ALI/ARDS
- CT scan at 5-15-45 cmH_2O to assess the percentage of potentially recruitable lung
- High variability in the potential for recruitment
- Pts with higher recruitability had: greater lung weight, lower P/F, lower Crs, higher Vd/Vt, higher Qs/Qt and higher mortality

Gattinoni et al, NEJM 2006

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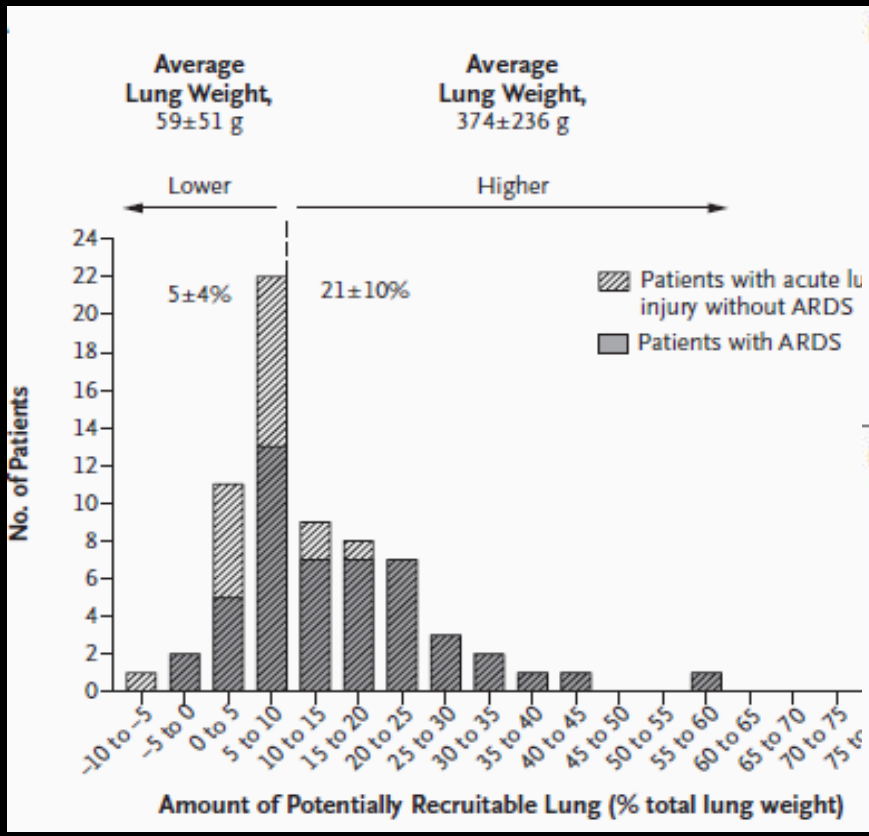

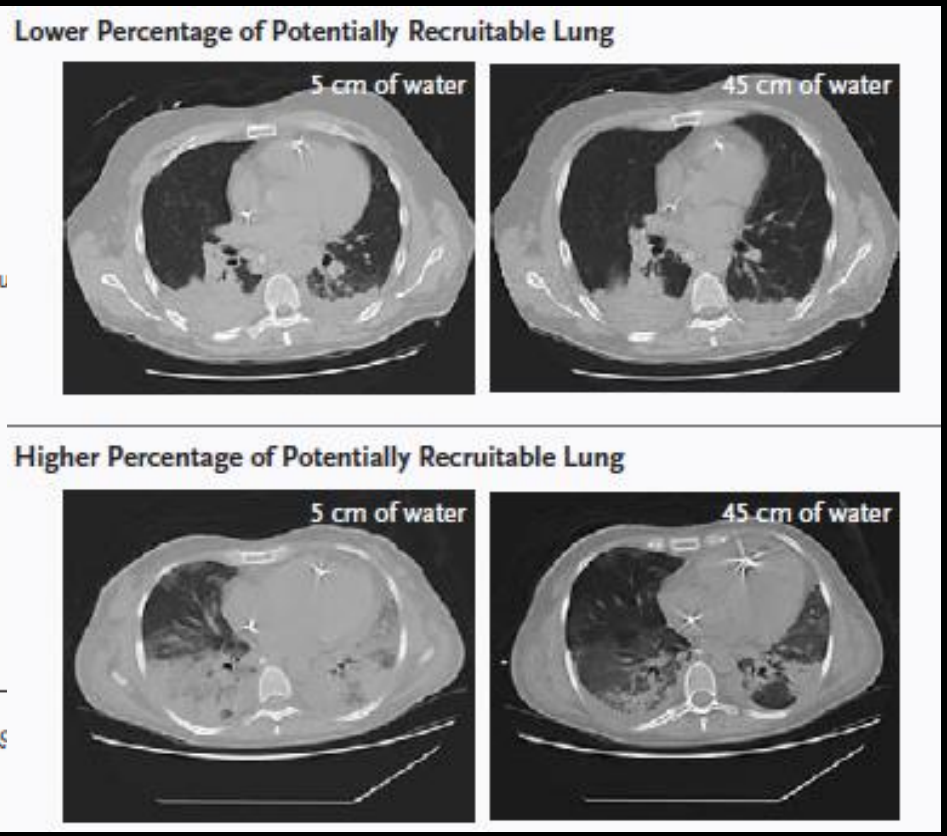

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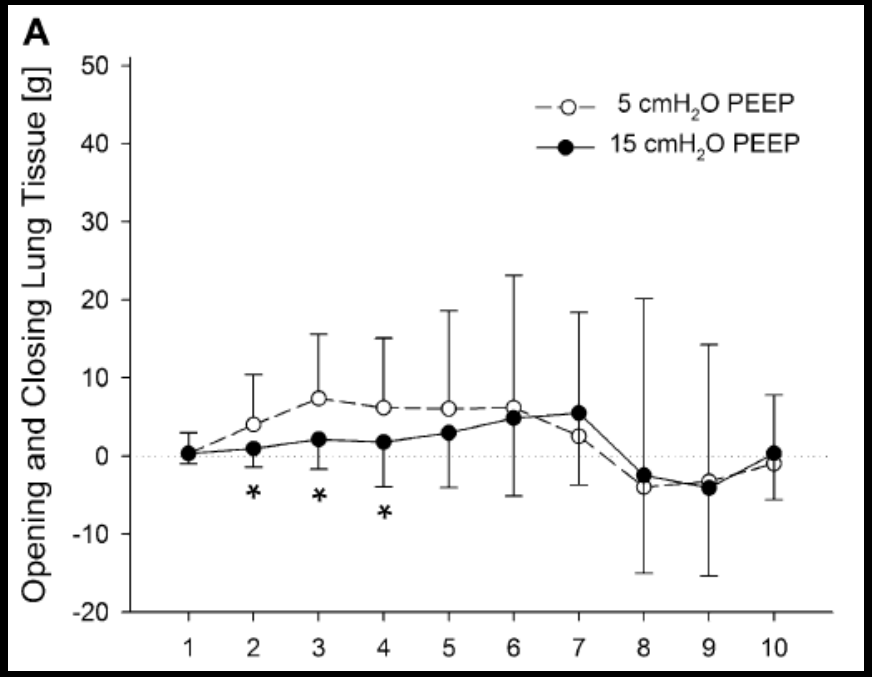
- Strong correlation between the percentage of potentially recruitable lung and the response to PEEP increase from 5 to 15 cmH_2O
- Bedside estimate of the percentage of potentially recruitable lung: at least 2 of the following
  - P/F < 150 @ PEEP 5
  - a decrease in Vd/Vt or an increase in Crs when PEEP is increased from 5 to 15 cmH_2O

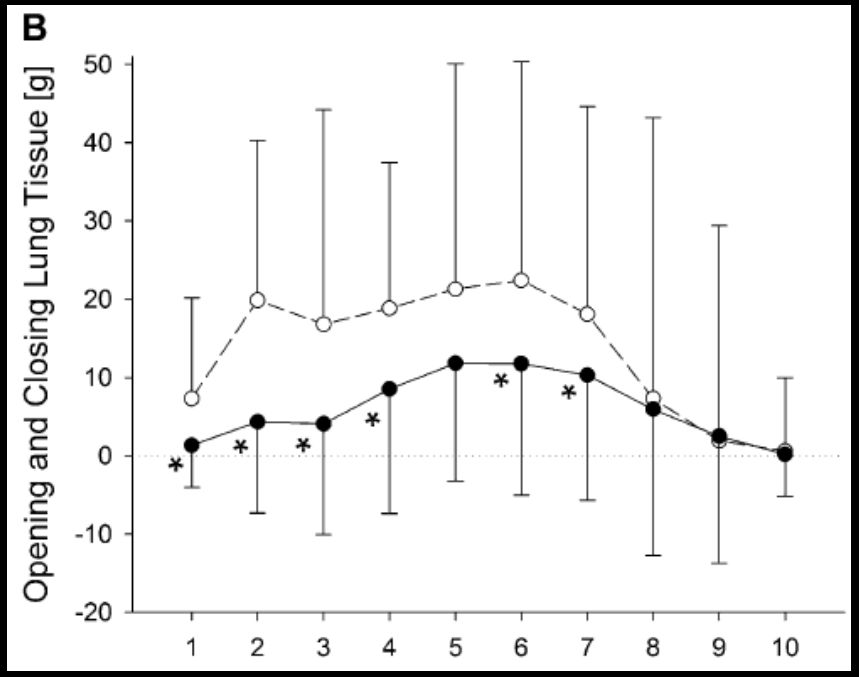
Gattinoni et al, NEJM 2006

Lung Opening and Closing during Ventilation of Acute Respiratory Distress Syndrome

Pietro Caironi[1,2], Massimo Cressoni[1], Davide Chiumello[2], Marco Ranieri[3], Michael Quintel[4], Sebastiano G. Russo[4], Rodrigo Cornejo[5], Guillermo Bugedo[5], Eleonora Carlesso[1], Riccarda Russo[2], Luisa Caspani[2], and Luciano Gattinoni[1,2]



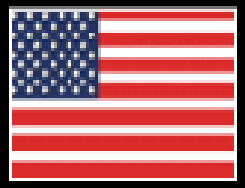
lower recruitability



higher recruitability

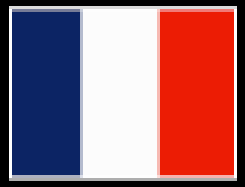
Caironi et al, AJRCCM 2010

High (15) vs low (9) PEEP: RCTs



« Alveoli » The NEW ENGLAND JOURNAL of MEDICINE 2004

« Lovs » JAMA® 2008

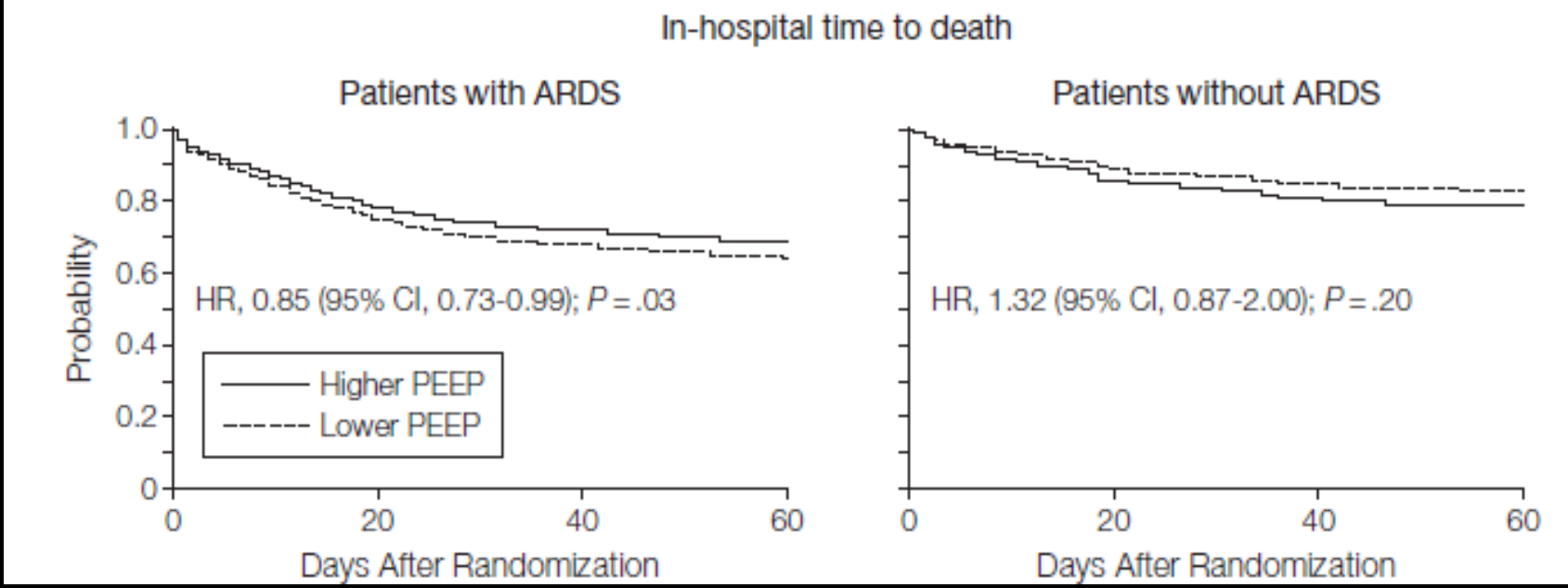


« ExPress » JAMA® 2008

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

Systematic Review and Meta-analysis

JAMA



High PEEP 34 % vs low PEEP 39 % ($p<0.05$)

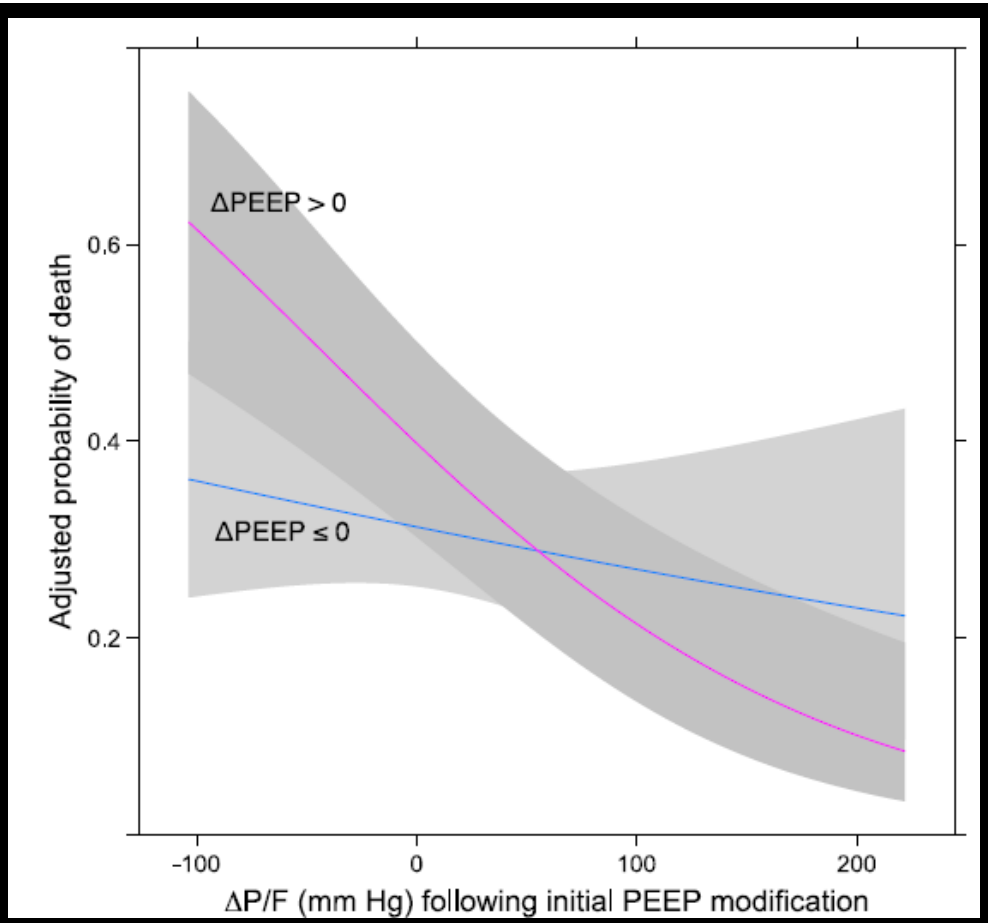
High PEEP 27 % vs low PEEP 19 % ($p=0.07$)

Briel et al, JAMA 2010

Oxygenation Response to Positive End-Expiratory Pressure Predicts Mortality in Acute Respiratory Distress Syndrome

A Secondary Analysis of the LOVS and ExPress Trials

Ewan C. Goligher[1,2,3,4], Brian P. Kavanagh[1,5,6], Gordon D. Rubenfeld[1,2,7], Neill K. J. Adhikari[1,2,7], Ruxandra Pinto[7], Eddy Fan[1,2,4], Laurent J. Brochard[1,2,8], John T. Granton[1,2,4], Alain Mercat[9], Jean-Christophe Marie Richard[10], Jean-Marie Chretien[11], Graham L. Jones[12], Deborah J. Cook[12,13], Thomas E. Stewart[1,2,4], Arthur S. Slutsky[1,2,4], Maureen O. Meade[12,13], and Niall D. Ferguson[1,2,3,4]



- After an increase in PEEP, an increase in P/F strongly associated with a decrease in mortality
- Association stronger for pts with baseline P/F < 150

Goligher et al, AJRCCM 2014

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

- 120 ICUs, 9 Countries, from 2011-2017
- 1010 pts with moderate-severe ARDS (less than 72 hrs) randomized to
  1. OLA (n = 501)
  2. Conventional ventilation (n = 509): ARDSnet low PEEP – low TV

Cavalcanti et al, JAMA 2017

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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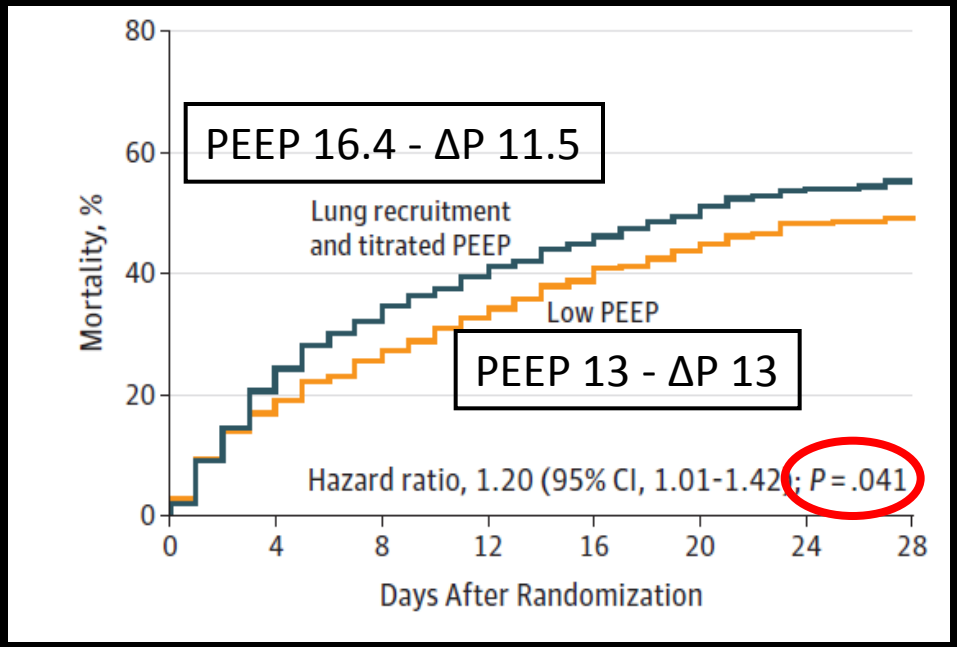


- Higher mortality in the experimental group: 55.3 vs 49.3%
- Higher risk of barotrauma
- Higher need for vasopressors
- 5 episodes of CA (!)

Cavalcanti et al, JAMA 2017

Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials

	Phenotype 1 (n=404)		Phenotype 2 (n=145)		
	Low PEEP (n=202)	High PEEP (n=202)	Low PEEP (n=71)	High PEEP (n=74)	p value*
Mortality at 90 days	33 (16%)	48 (24%)	36 (51%)	31 (42%)	0·049
Ventilator-free days	20 (10–25)	21 (3–24)	2 (0–21)	4·5 (0–20)	0·018
Organ failure free-days	22 (11–26)	22 (9–26)	4 (0–18)	6·5 (0–21)	0·003

- Data from ARMA and ALVEOLI trials → 1022 pts
- Hypoinflammatory (1) and hyperinflammatory (2) phenotypes
- Different phenotypes had different outcomes and response to PEEP

Calfee CS, Lancet Resp Med 2014

Oxygenation to predict PEEP effect

- Gattinoni: P/F < 150 at PEEP 5 has PPV of 76% for estimating response to PEEP increase (5 → 15)
- Briel: higher PEEP beneficial if baseline P/F < 200
- Goligher: association between P/F improvement with higher PEEP and mortality

MEASURES OF OXYGENATION MAY PREDICT CLINICAL RESPONSE TO HIGHER PEEP

Oxygenation to predict PEEP effect

- BUT oxygenation does not depend only on recruitment…
  - effect on cardiac output
  - extrapulmonary shunt
  - efficiency of HPV
  - FiO_2 setting

Oxygenation to predict PEEP effect

- BUT oxygenation does not depend only on recruitment…
  - effect on cardiac output
  - extrapulmonary shunt
  - efficiency of HPV
  - FiO_2 setting

At a glance

ZEEP

PEEP

Hemodynamic effects of PPV

1. Caused by changes in lung volume and by increase in ITP («transmission» of airway pressure)
2. Magnitude depends on:
   - volume status
   - lung and chest wall compliance

$$\Delta Ppl = PEEP \times C_L/(C_L+C_W)$$

In practice

Stiff lung
Soft chest wall

(Ex. primary ARDS)

LOWER HEMODYNAMIC EFFECT OF PEEP

Soft lung
Stiff chest wall

(Ex. obese COPD)

HIGHER HEMODYNAMIC EFFECT OF PEEP

Hemodynamic effects of PEEP

- Reduction of RV preload (decreased gradient for VR?) → net effect: CO decrease
- No direct effect on cardiac contractility
- Differential effect on RV and LV function
- Effect on PVR (RV afterload) again depends on the balance between recruitment and overdistention

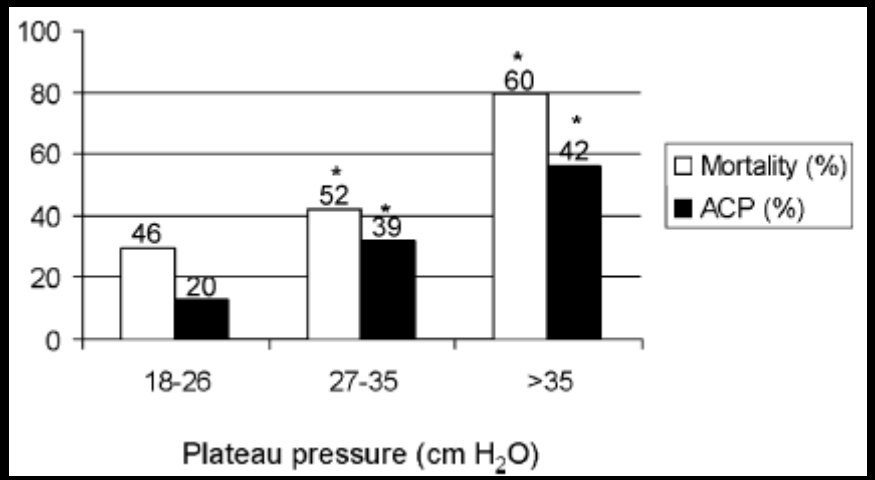
ARDS and RV dysfunction (ACP)

- Incidence RVD (ACP) ≈ 25%
- Caused by increase in PVR
  - alveolar damage and microvascular occlusions
  - hypoxemia and hypercapnia→ vasoconstriction and arteriolar remodeling
  - positive pressure ventilation
- ↑ afterload → imbalance between O_2 supply and demand → RV ischemia

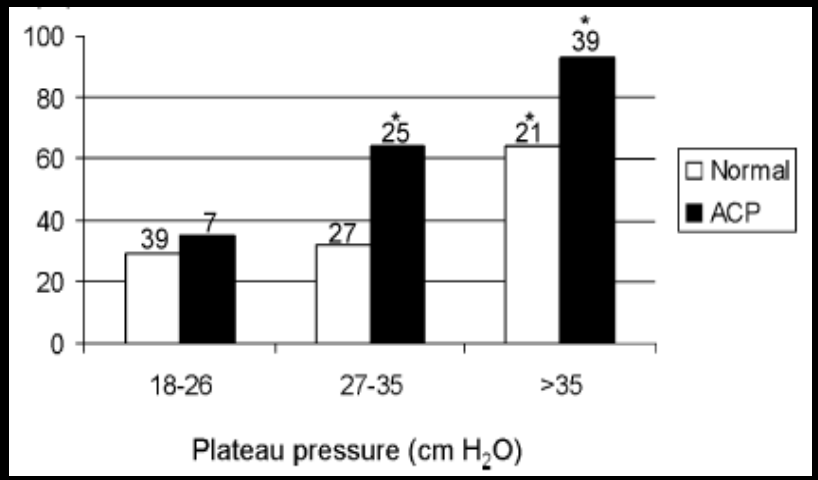
ARDS and RV dysfunction (ACP)

François Jardin
Antoine Vieillard-Baron

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



Incidence vs Pplat



Mortality and US findings

Jardin F, ICM 2007

Conclusions

- Higher PEEP levels more likely to be beneficial in pts with higher potential for recruitment
- PEEP level selected based on its effect on gas exchange, respiratory mechanics, hemodynamics
- Remember to monitor hemodynamic impact