RESCARE17
6-8 October 2017
IMA HALL -KOCHI

# Ventilator induced lung injury Pathophysiology and prevention

DR. J.V. PETER, MD, DNB, MAMS, FRACP, FCICM, FICCM
MEDICAL ICU, CHRISTIAN MEDICAL COLLEGE, VELLORE

The lungs of one man may bear, without injury, as great a force as those of another man can exert; which by the bellows cannot always be determined

**John Fothergill, 1745**

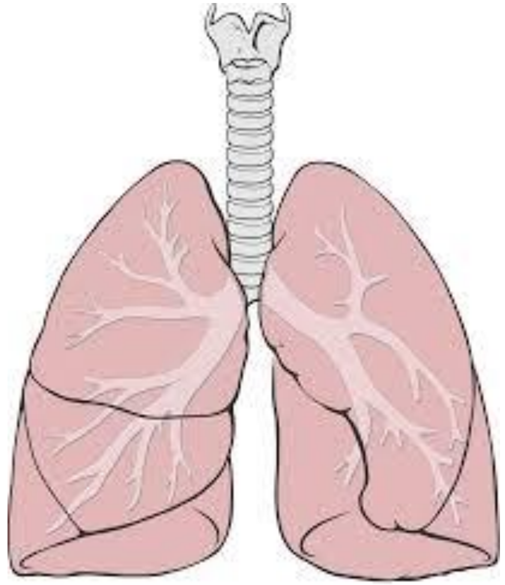
**Fothergill J. Observation on a case published in the last volume of the medical essays, and c. of recovering a man dead in appearance, by distending the lungs with air. Philos Trans R Soc Lond 1745;43:275-81.**

# Outline

- Introduction and terminology
- Mechanisms of lung injury
- Prevention of lung injury
- Concluding remarks

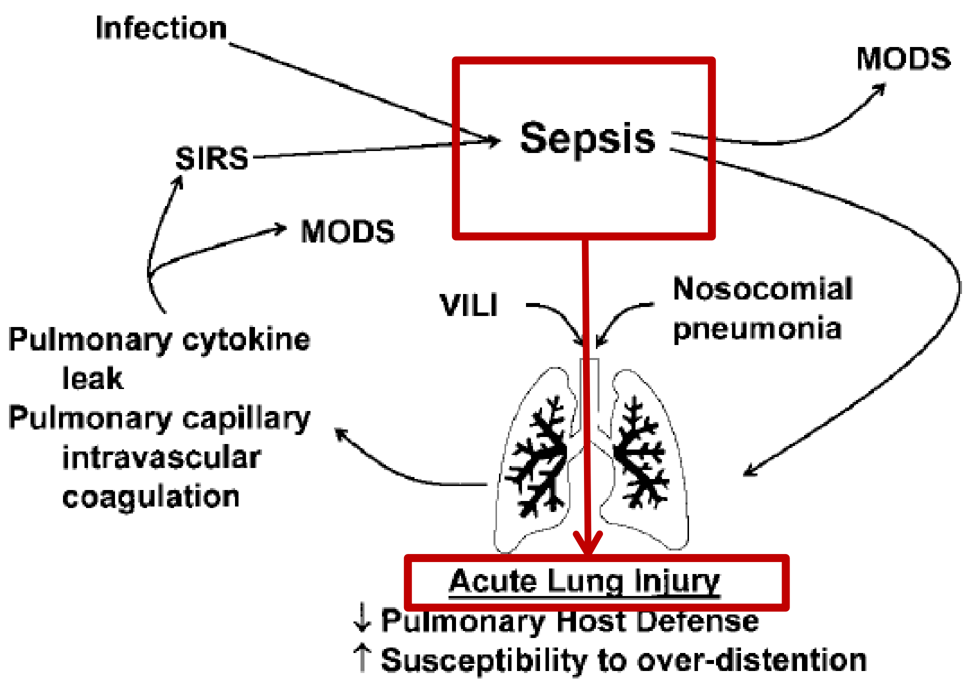
# Introduction

- Vital organ responsible for gas exchange
- Weighs about 1.3 kg; dual blood circulation
- 300-500 million alveoli, 2400 km
- Entire blood volume circulates through the lung
- Ideal for participation in all activities

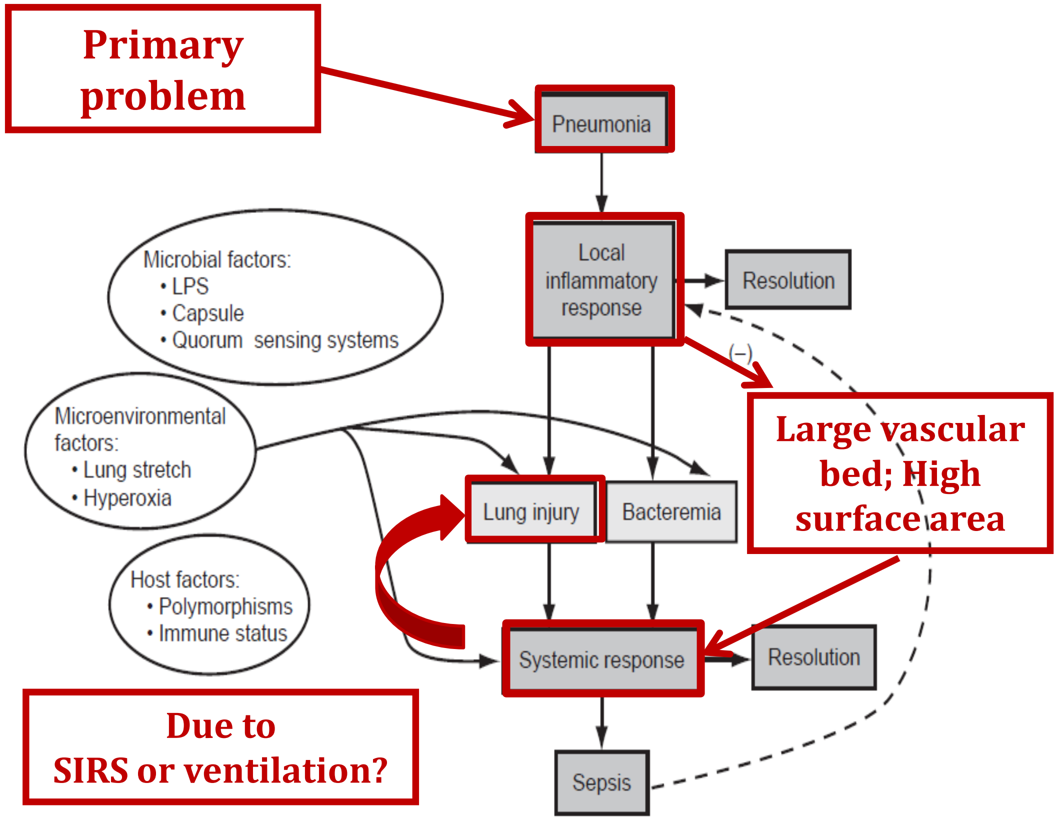


# Silent spectator or active propagator

RESCARE17
6-8 October 2017
IMA HALL -KOCHI



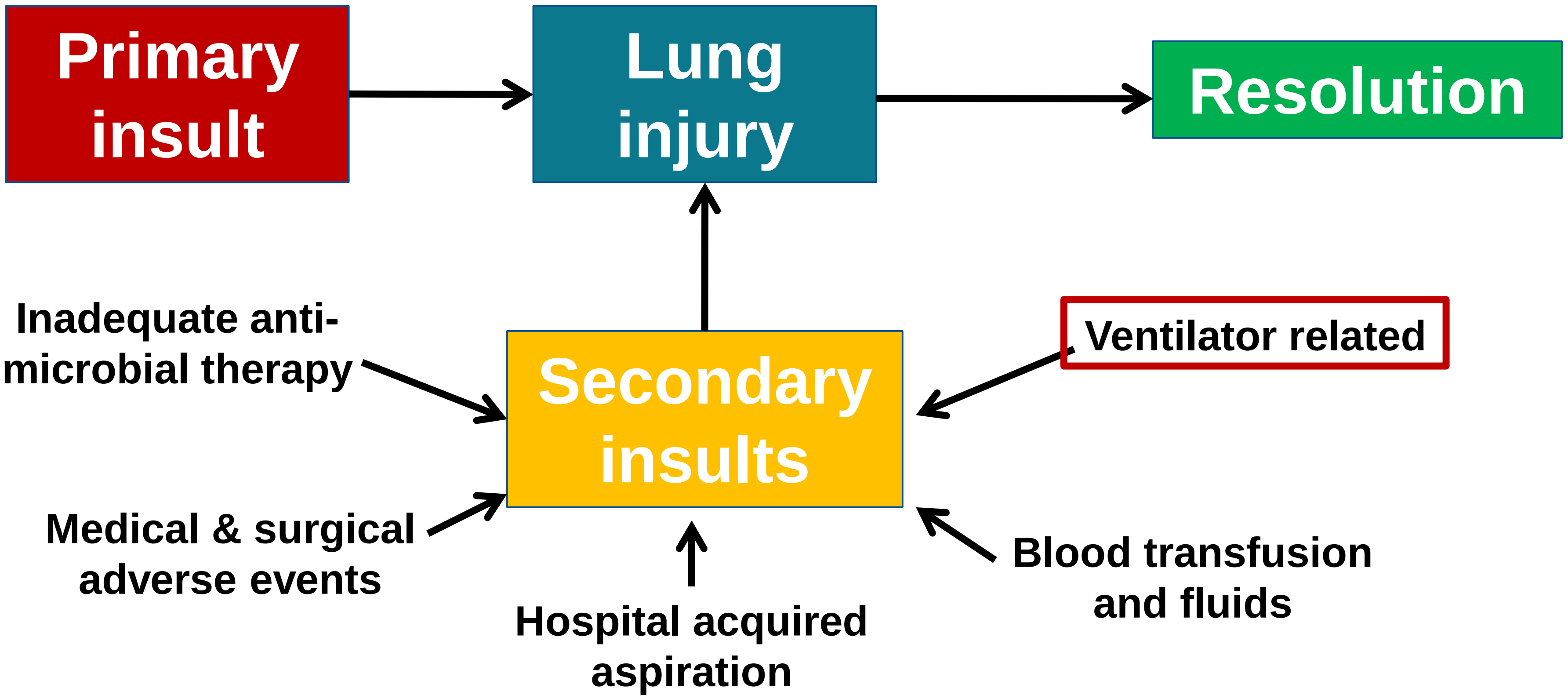

Silent spectator?




Active propagator?

# First and second hits






Ahmed AH et al. The role of potentially preventable hospital exposures in the development of acute respiratory distress syndrome: a population-based study. Crit Care Med 2014; 42: 31-9.

# Terminology

- Ventilator induced lung injury (VILI) introduced in 1970s
- Used concurrently with Ventilator associated lung injury (VALI)
- Terms not inter-changeable
- VALI – existing lung injury exacerbated by ventilation
- VILI – injury to previously normal lungs

# Ventilator induced lung injury



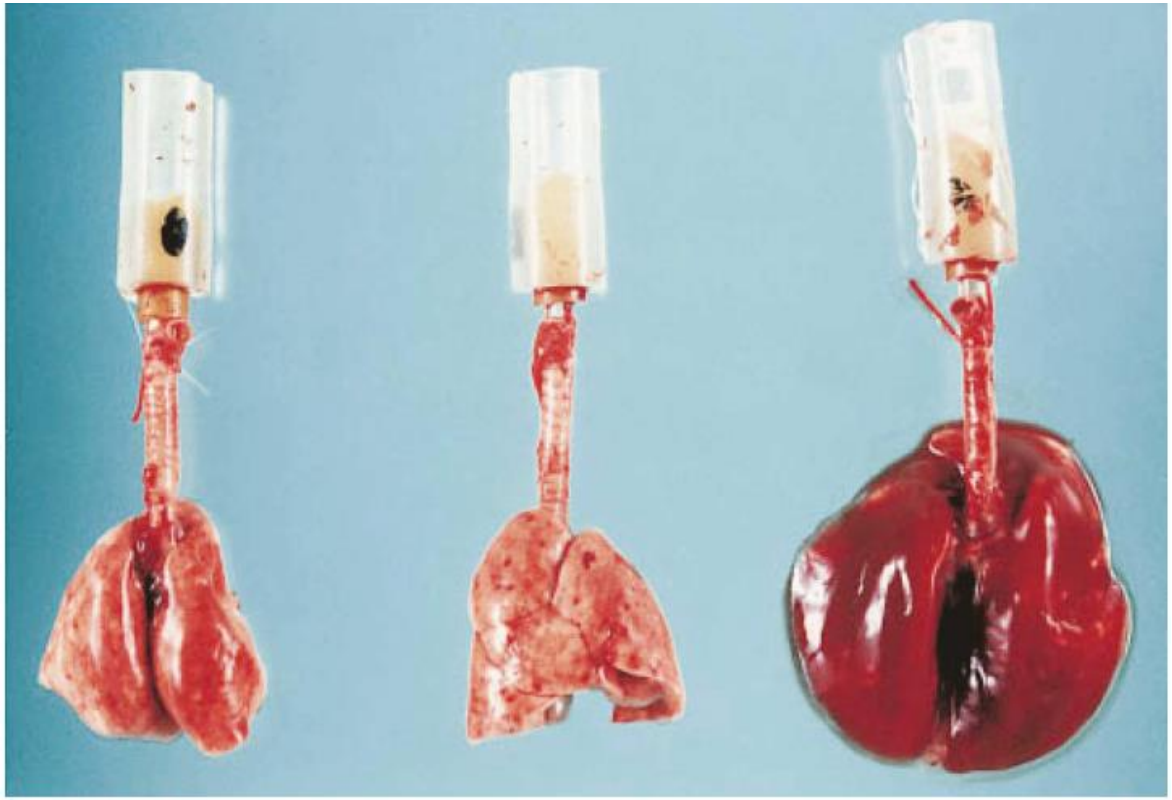


**Figure 1 Macroscopic aspect of rat lungs after mechanical ventilation at 45 cm $H_2O$ peak airway pressure.** *Left*: normal lungs; *middle*: after 5 min of high airway pressure mechanical ventilation. Note the focal zones of atelectasis (in particular at the left lung apex); *right*: after 20 min, the lungs were markedly enlarged and congestive; edema fluid fills the tracheal cannula. Used with permission. From Dreyfuss et al. [15].

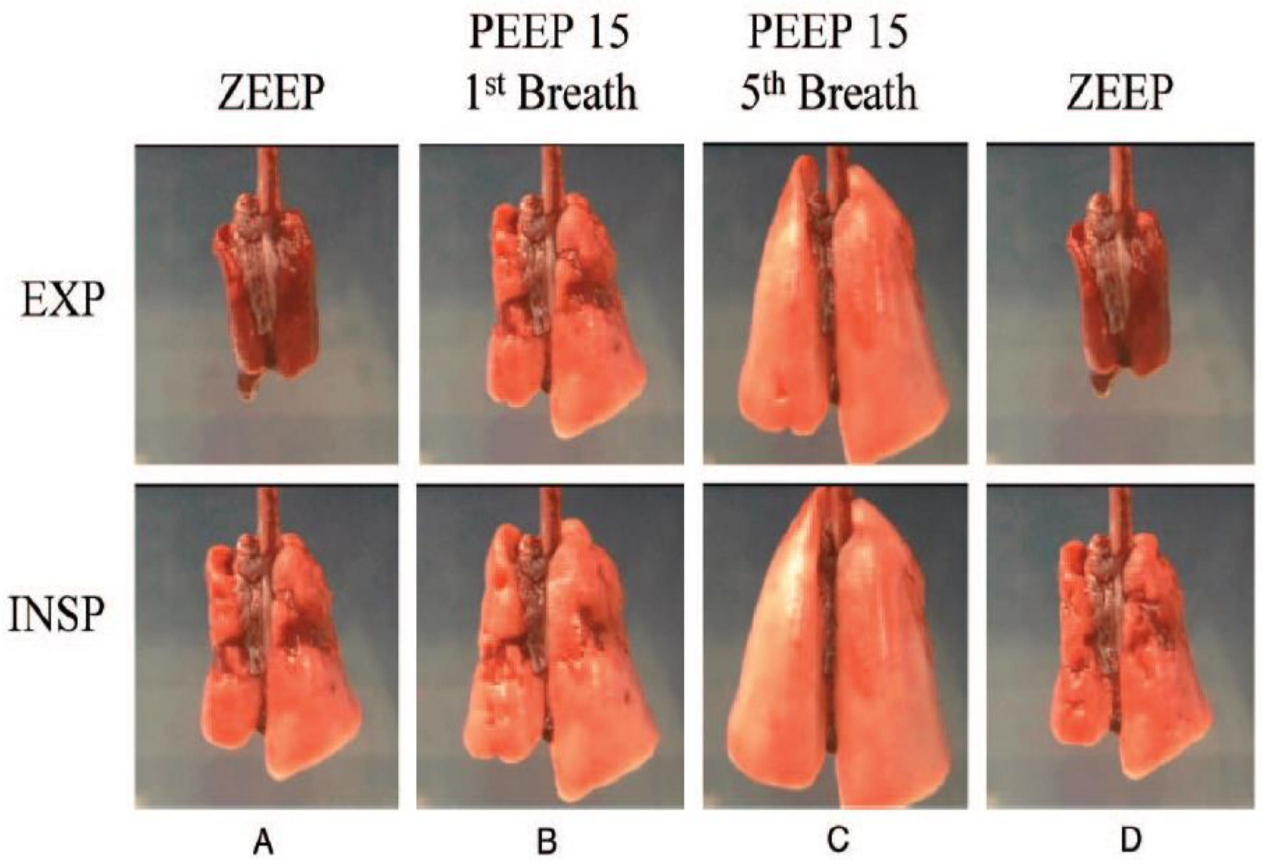
- Rat normal lungs
- Subject to MV @ 45 cm PAP
- Enlarged and congested lungs

**Apply high pressure**
**To normal lungs**
**Lung injury**

**Prost N. Ventilator induced lung injury; historical perspectives and clinical implications. Annals of Intensive Care 2011; 1: 28**

# ZEEP ventilation and injury

RESCARE17
6-8 October 2017
IMA HALL -KOCHI




- ZEEP ventilation
- Collapsed lung
- Increased shear
- ARDS like picture rats

Slutsky AS. Ventilator induced lung injury – from barotrauma to biotrauma. Respir Care 2005; 50: 646-59

# ZEEP and cytokines

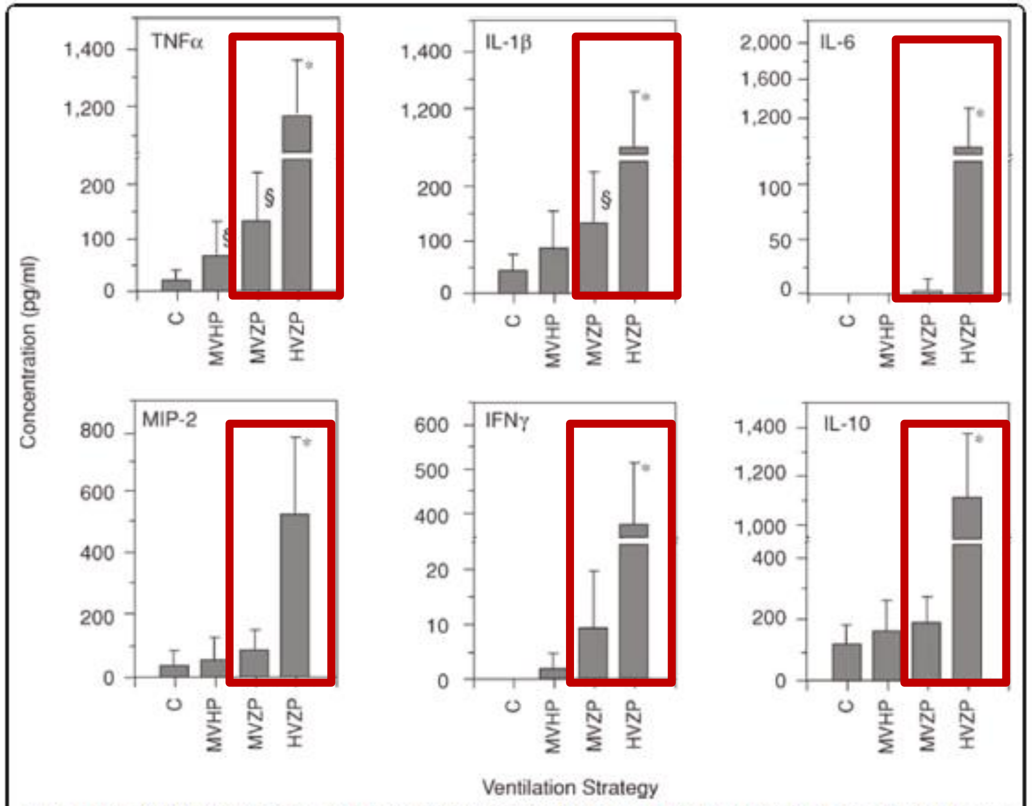



**Figure 8 Effect of different ventilator strategies on cytokine concentrations in lung lavage of isolated unperfused rat lungs**. Four ventilator settings were used: controls (*C* = normal tidal volume), moderate tidal volume + high PEEP (*MVHP*), moderate tidal volume + zero PEEP (*MVZP*), high tidal volume + zero PEEP (*HVZP*) resulting in the same end-inspiratory distension as MVHP. Major increases in cytokine concentrations were observed with HVZP. Used with permission. From Tremblay et al. [57].

- Significantly higher cytokine
- With ZEEP ventilation
- Worse with high tidal volumes

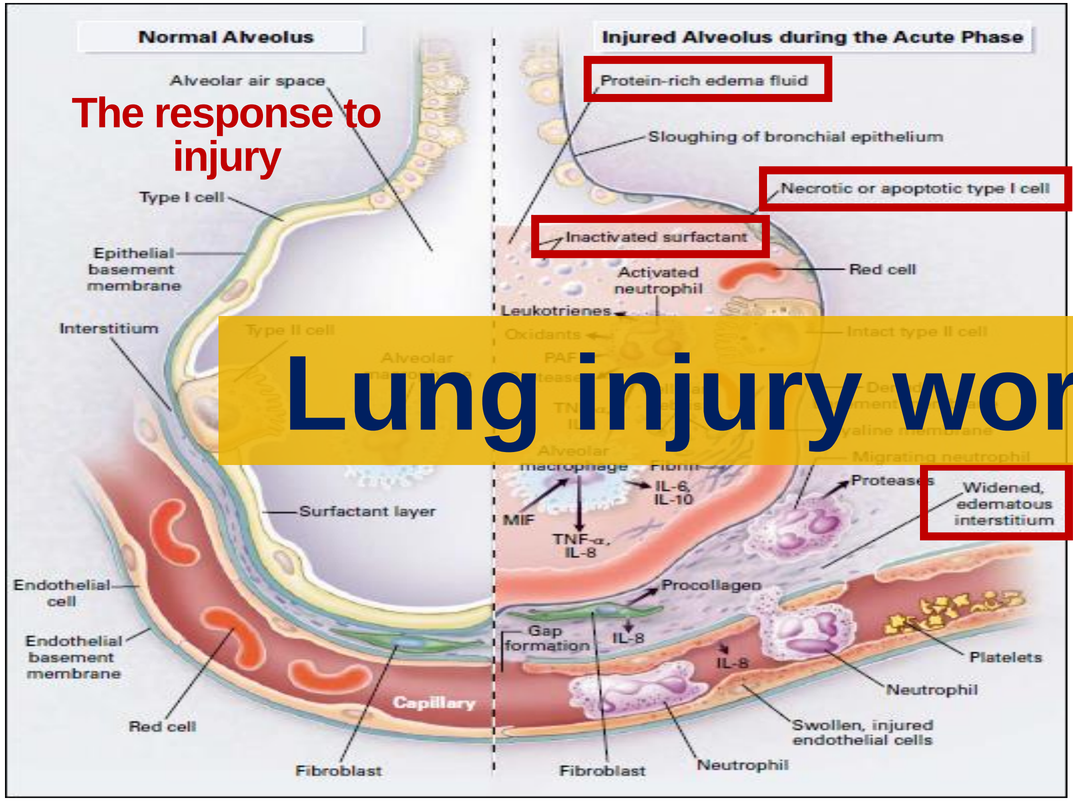
Prost N. Ventilator induced lung injury; historical perspectives and clinical implications. Annals of Intensive Care 2011; 1: 28

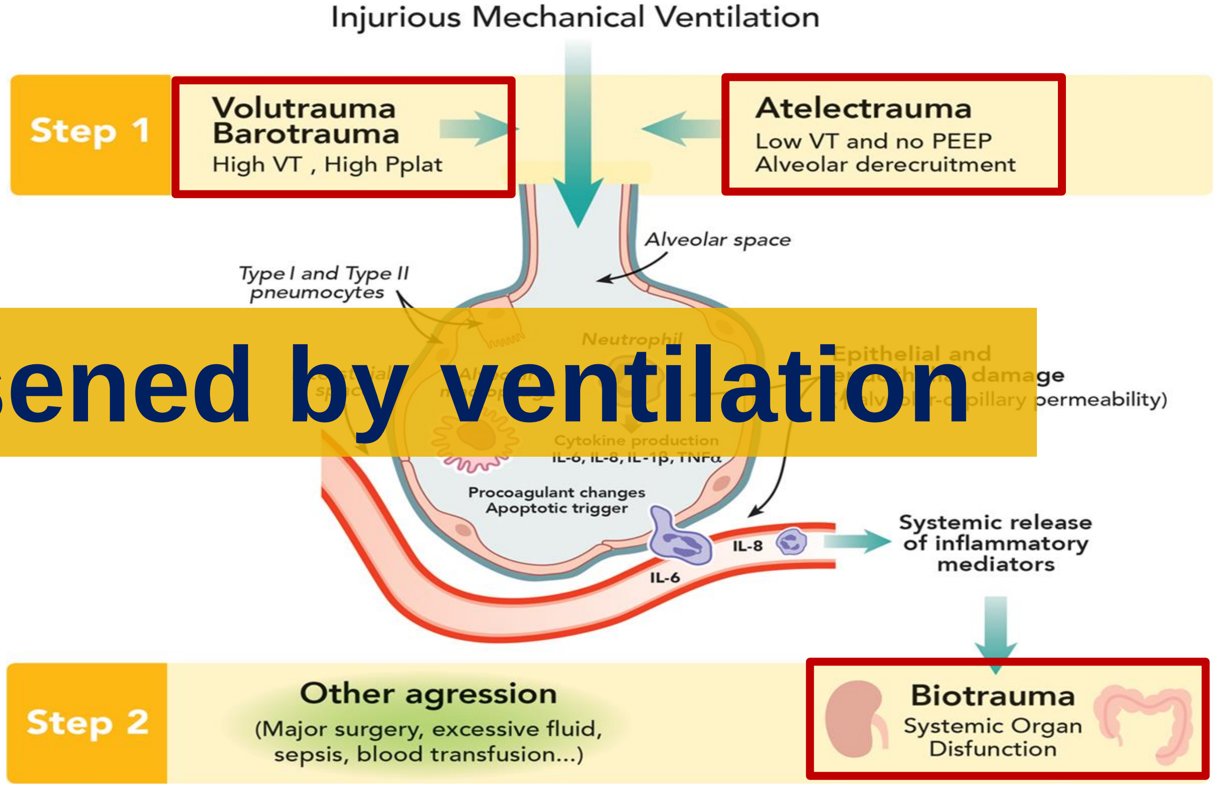
# Implications



- Lung injury even in “normal lungs”
- Take care as to how you ventilate
- Improper settings can result in lung injury
- Consequences can be significant


# Ventilator associated lung injury




## Lung injury worsened by ventilation

## Lung injury already present

Ware LB, et al. The acute respiratory distress syndrome. N Engl J Med 2000; 342: 1334-49.

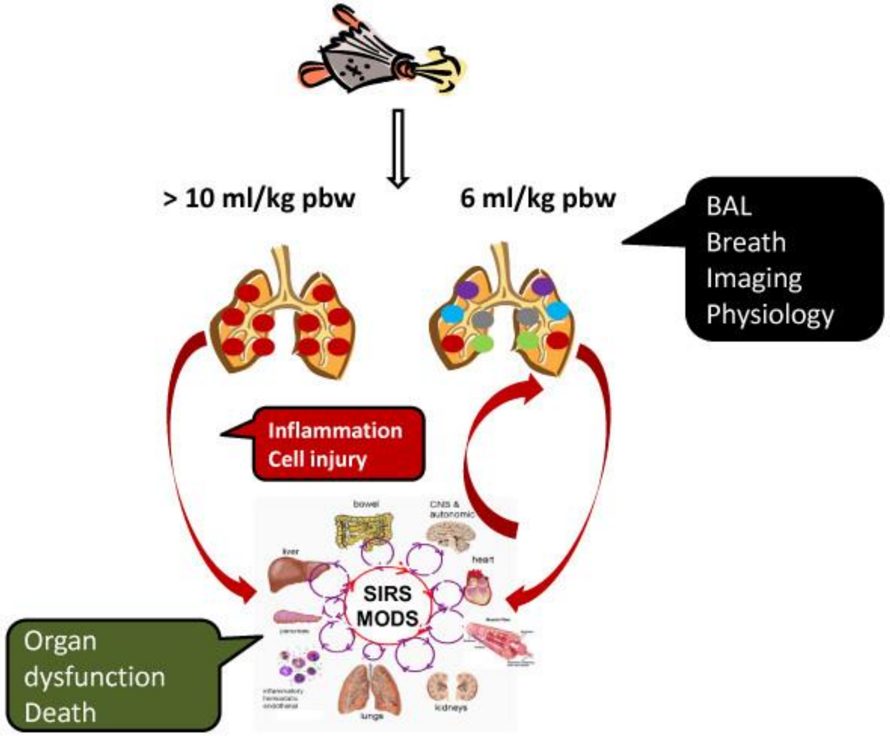
## Further injury by ventilation

Futier T et al. Perioperative positive pressure ventilation: an integrated approach to improve pulmonary care. Anesthesiology 2014; 121 400-8.

# Components of VALI



- Volutrauma
- Barotrauma
- Atelectotrauma or atelectrauma
- Biotrauma
- Oxygen toxic effects

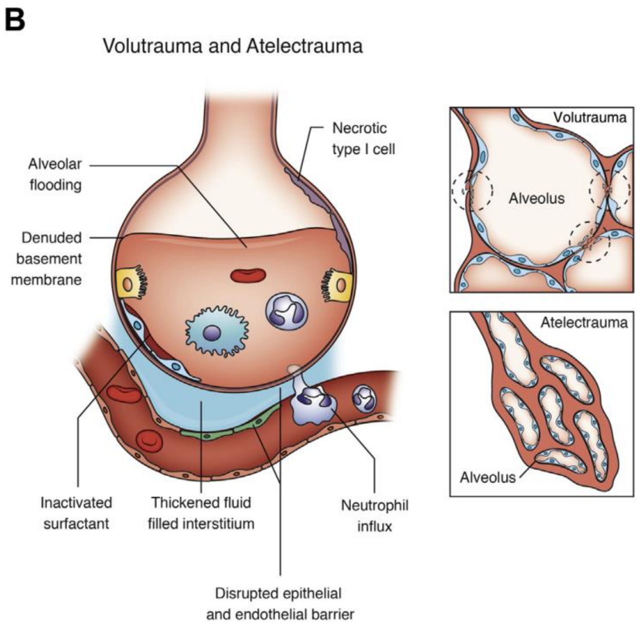



Pinhu L. Ventilator associated lung injury. Lancet 2003; 361: 332-40

# Volutrauma



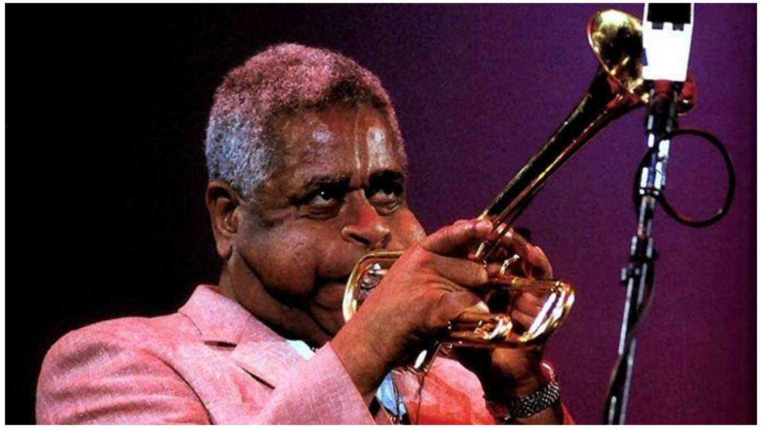
- Damage caused by over-distension
- High volume or high end-inspiratory volume injury
- Rats tidal volume limited by chest straps
- No lung injury in response to high pressure
- Variables influencing peak pressures (resistance, compliance)




Curley GF. Biotrauma and ventilator-induced lung injury. Clinical implications. Chest 2016; 150: 1109-1117

# Barotrauma

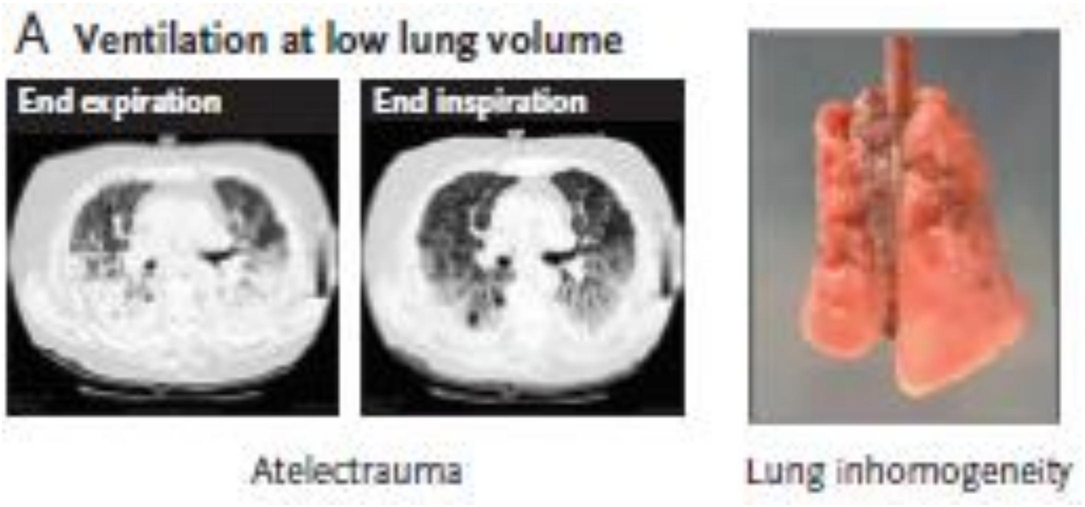
- Lung injury due to high pressure
- Rats high pressure ventilation, lung injury
- Trumpet players 150 cm water pressure
- No lung injury



# Atelectrauma



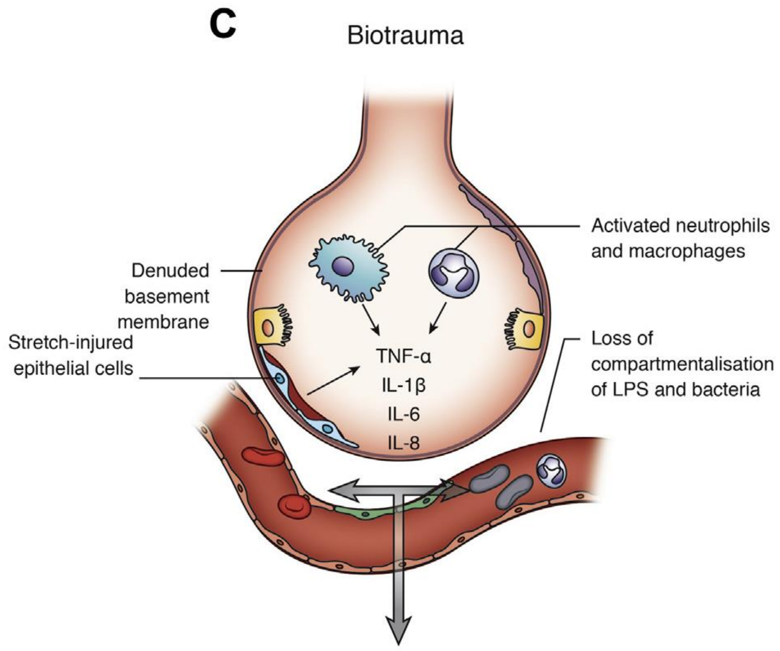
- With repeated recruitment and collapse
- Low volume or low end-expiratory volume injury
- Prevented by using PEEP above lower inflection point



# Biotrauma



- Pulmonary and systemic inflammation
- Caused by released of mediators
- From lungs subjected to ventilation




Curley GF. Biotrauma and ventilator-induced lung injury. Clinical implications. Chest 2016; 150: 1109-1117

# Oxygen toxic effects

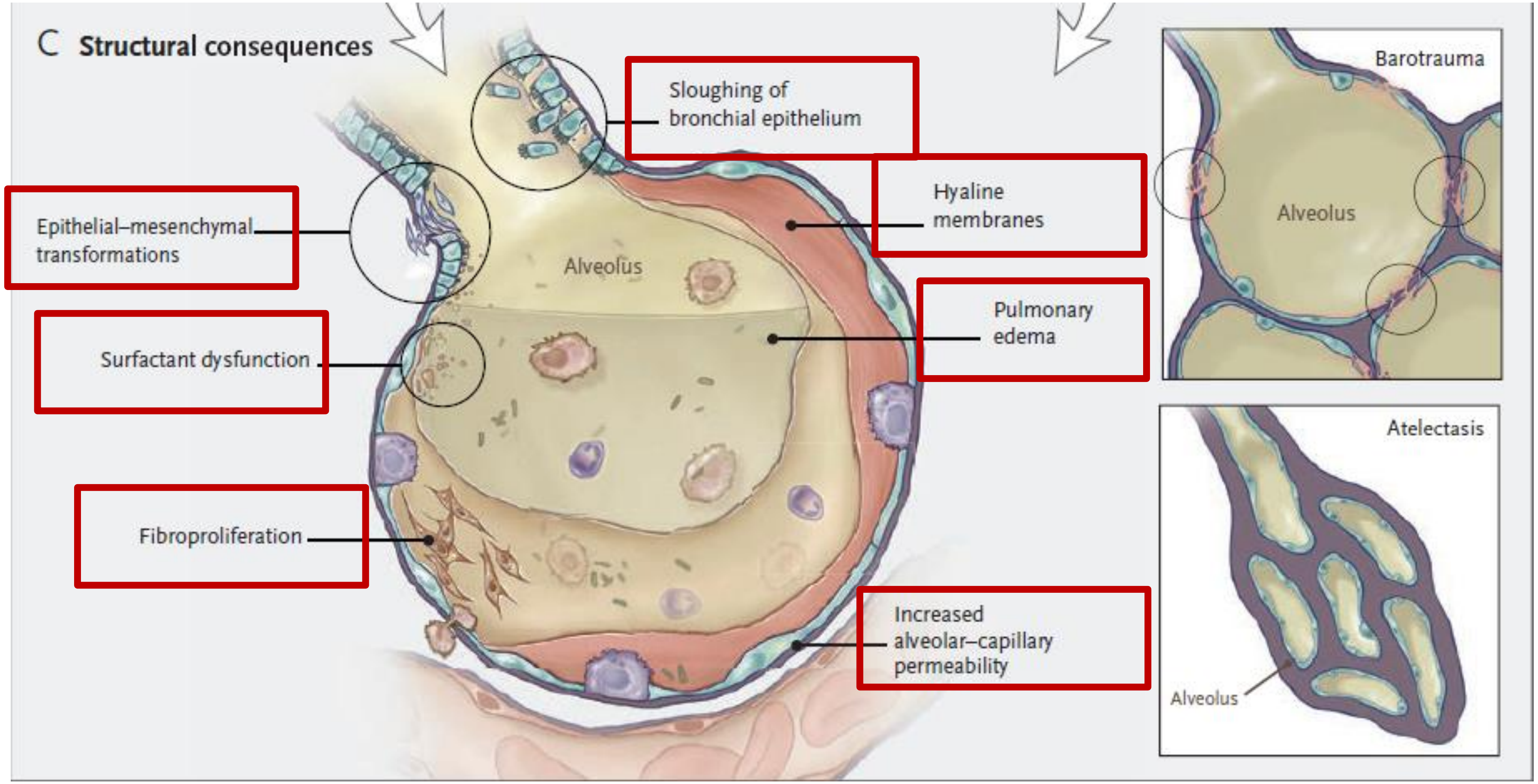
- Damage due to high $O_2$ concentration
- Parenchymal and airway injury
- Absorptive atelectasis
- Accentuation of hypercapnia
- Extra-pulmonary toxicity

# Consequences of lung injury

- Structural consequences
- Biological alterations
- Physiological abnormalities
- Systemic effects

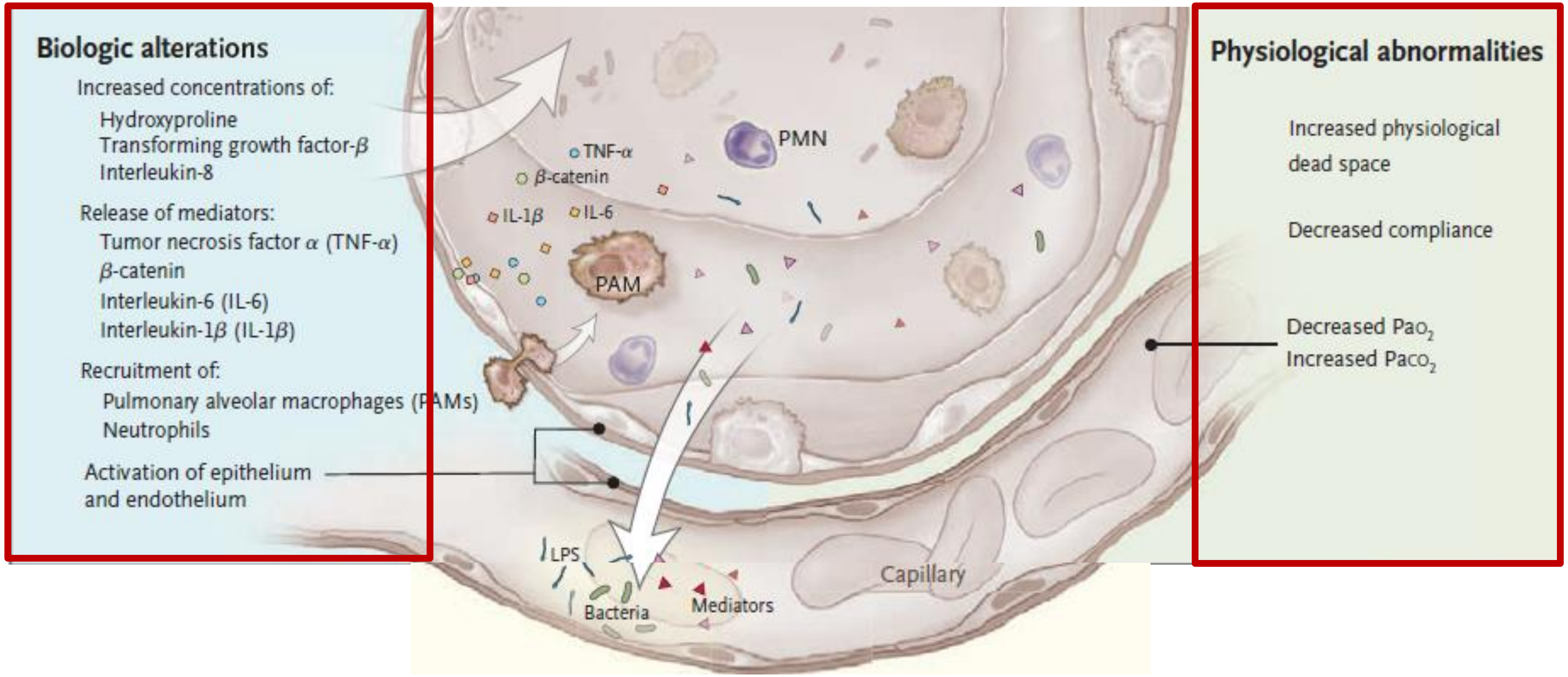

Slutsky AS, Ranieri M. Ventilator-induced lung injury. New Engl J Med 2013; 369-2126-36

# Structural consequences



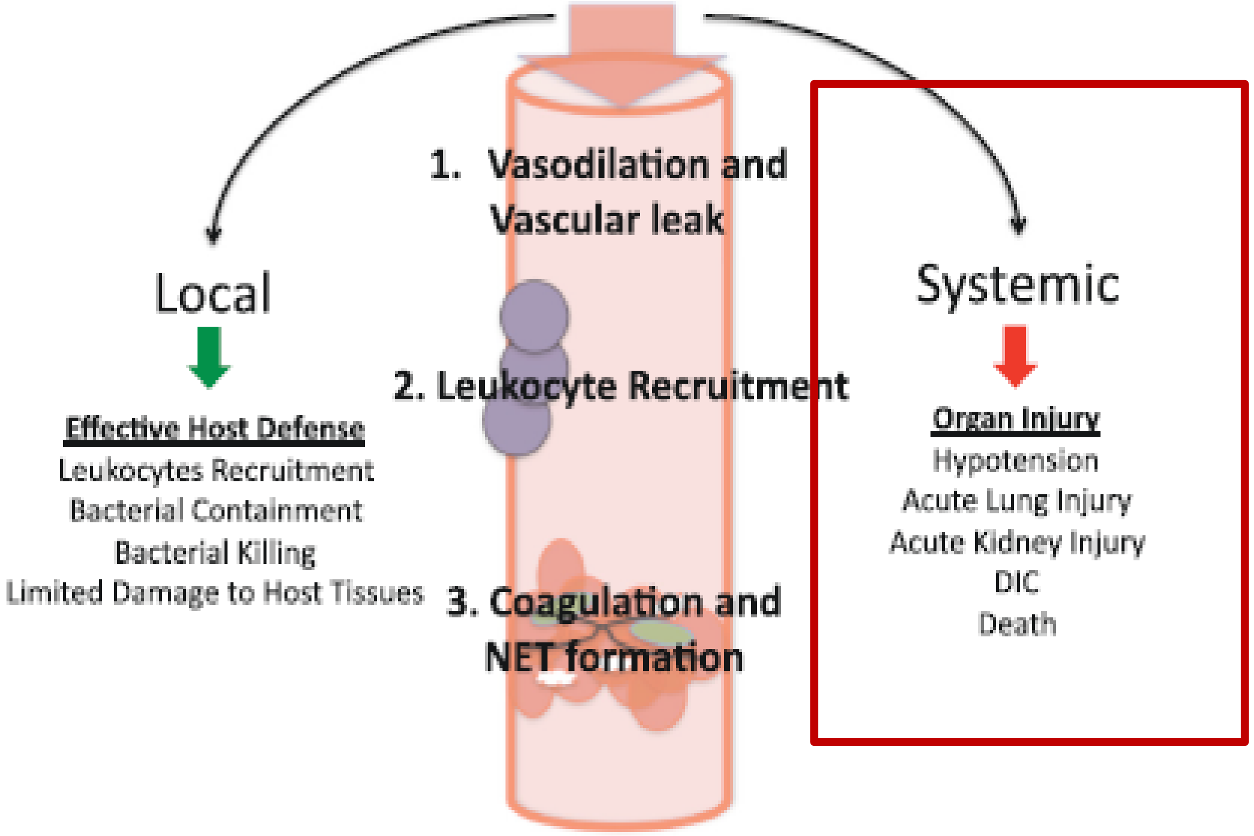

Slutsky AS, Ranieri M. Ventilator-induced lung injury. New Engl J Med 2013; 369-2126-36

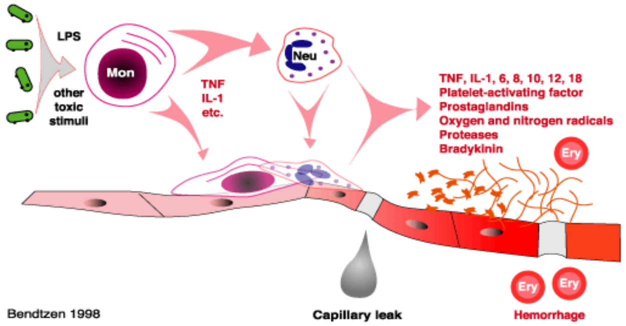
# Biologic and physiological



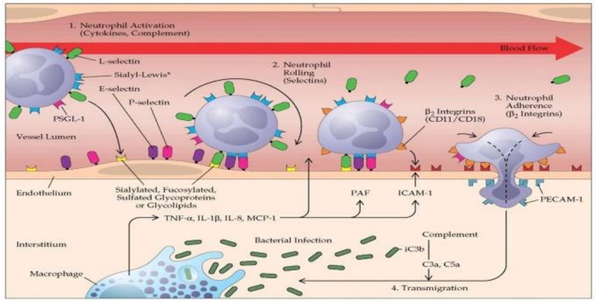

Slutsky AS, Ranieri M. Ventilator-induced lung injury. New Engl J Med 2013; 369-2126-36

# Systemic effects

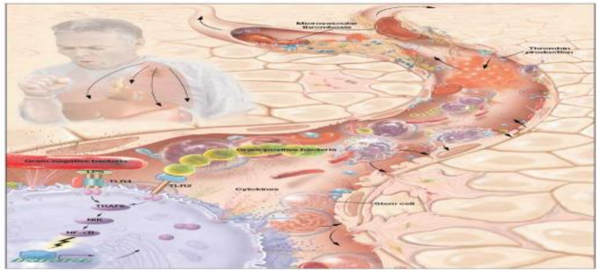



Cytokines




Leukocyte activation



Coagulation cascade

# Preventing VILI



- What is important to prevent VILI
- Is the mode of ventilation crucial?
- Is the ventilatory strategy important

# Good ventilatory mode meets



- Physiological goals
    - Achieving and maintaining adequate gas exchange
- Patient related goals
    - Ensuring patient comfort (synchrony)
    - Reducing work of breathing (match rapidly patient demands)
- Outcome goals
    - Minimize risk of lung injury
    - Improve patient outcomes

# The evidence for modes



- Conventional ventilatory modes (PCV vs. VCV)

- Specialized modes of ventilation
    - Inverse ratio ventilation
    - Airway pressure release ventilation
    - High frequency oscillation

# Pressure vs. volume

RESCARE17
6-8 October 2017
IMA HALL -KOCHI

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Volume-controlled ventilation | Pressure-controlled ventilation | | | | |
| **Mortality in hospital** | **636 per 1000** | **528 per 1000** (426 to 649) | **RR 0.83** (0.67 to 1.02) | 1089 (3 studies)[a] | ⊕⊕⊕○ **Moderate**[b,c] | |
| **Mortality in ICU** | 376 per 1000 | [illegible] (267 to [illegible]) | [illegible] | 1062 (2 studies) | [illegible] | |
| **Mortality on follow-up** Follow-up: 28 days | **323 per 1000** | **284 per 1000** (236 to 342) | **RR 0.88** (0.73 to 1.06) | 983 (1 study)[f] | ⊕⊕⊕○ **Moderate**[b,c] | |
| **Duration of mechanical ventilation** | See comment | See comment | Not estimable | 983 (1 study)[f] | See comment | Skewed data presented as median (10 days) and interquartile ranges (6 days to 16 and 17 days) did not differ |
| **Barotrauma** | **94 per 1000** | **117 per 1000** (82 to 166) | **RR 1.24** (0.87 to 1.77) | 1062 (2 studies)[d] | ⊕⊕○○ **Low**[g,h] | |

**Only 3 RCTs reporting clinical outcome**

**No difference in outcomes**

Chacko B, et al. Pressure-controlled vs. volume controlled ventilation for acute respiratory distress syndrome due to acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev 2015;

# Pressure controlled inverse ratio



## Pressure-Controlled vs Volume-Controlled Ventilation in Acute Respiratory Failure
### A Physiology-Based Narrative and Systematic Review

Nuttapol Rittayamai, MD; Christina M. Katsios, MD; François Beloncle, MD; Jan O. Friedrich, MD, PhD; Jordi Mancebo, MD; and Laurent Brochard, MD

RESULTS: Thirty-four studies met inclusion criteria, many being at high risk of bias. Comparisons of PC-CMV/PC-IRV and VC-CMV did not show any difference for compliance or gas exchange, even when looking at PC-IRV. Calculating the oxygenation index suggested a poorer effect for PC-IRV. There was no difference between modes in terms of hemodynamics, work of breathing, or clinical outcomes.

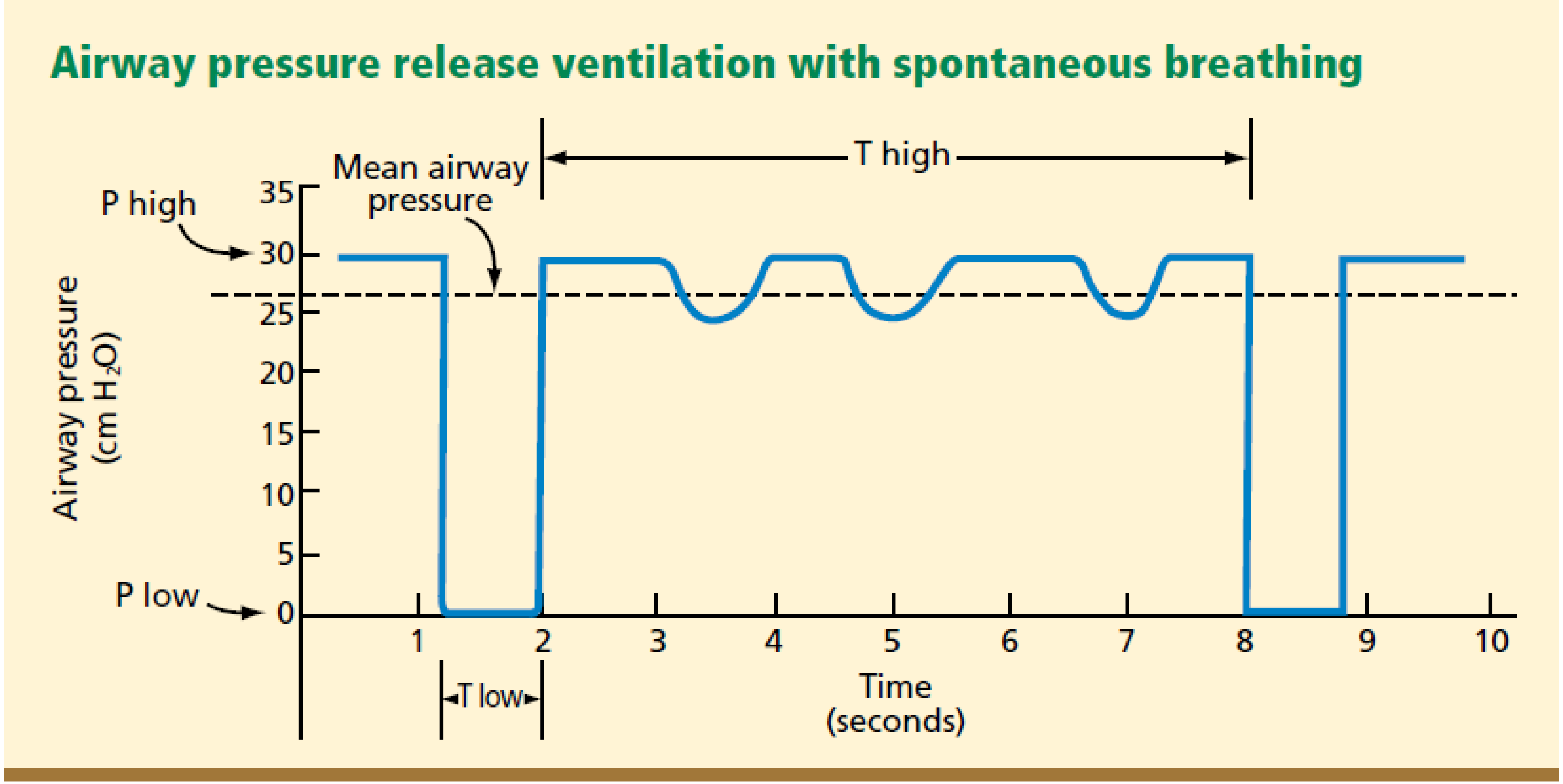
CHEST

CHEST 2015; 148(2):340-355

Rittayami N et al. Pressure-controlled vs. volume controlled ventilation in acute respiratory failure. Chest 2015; 148: 340-55

# Airway pressure release (APRV)






Modrykamien A, et al. Airway pressure release ventilation: an alternative mode of mechanical ventilation in acute respiratory distress syndrome. Ceveland Clinic J Med 2011; 78: 101-10

# Airway pressure release (APRV)



## Advantages and disadvantages of each of the components of airway pressure release ventilation

| COMPONENT | ADVANTAGES | DISADVANTAGES |
|---|---|---|
| High mean pressure | Lung recruitment, leading to better oxygenation<br>Reduction of left ventricular transmural pressure and therefore reduction of left ventricular afterload | Worsening of air leaks (bronchopleural fistula)<br>Increase of right ventricular afterload, worsening of pulmonary hypertension<br>Reduction of right ventricular venous return: may worsen intracranial hyper-tension, may worsen cardiac output in hypovolemia |
| Spontaneous breathing | Ventilation of dependent areas<br>Better venous return (increase in cardiac output)<br>Higher glomerular filtration rate<br>Better small-bowel perfusion<br>Lower sedation requirements | Increase of transpulmonary pressure might lead to volume-induced lung injury<br>Increase in venous return might worsen right ventricular dysfunction<br>Maintains work of breathing |

Modrykamien A, et al. Airway pressure release ventilation: an alternative mode of mechanical ventilation in acute respiratory distress syndrome. Ceveland Clinic J Med 2011; 78: 101-10

# Airway pressure release (APRV)



## Randomized trials of airway pressure release ventilation (APRV)

| TRIAL | NO. OF PATIENTS | MODES COMPARED | FINDINGS |
|---|---|---|---|
| Sydow et al (1994)[37] | 18 | APRV vs volume controlled inverse ratio ventilation | Lower peak pressure and better oxygenation with APRV |
| Putensen et al (2001)[33] | 3[illegible] | APRV vs pressure-controlled ventilation | Better hemodynamics, fewer intensive care unit days, better oxygenation, less sedation, and lower pressures with APRV |
| Varpula et al (2003)[34] | 33 | APRV vs pressure-controlled synchronized intermittent mandatory ventilation (both groups positioned prone for 6 h once or twice a day) | Better oxygenation in APRV group after second pronation |
| Varpula et al (2004)[35] | 58 | APRV vs synchronized intermittent mandatory ventilation | Lower inspiratory pressure with APRV |

**Improvement in physiological parameters**

**No change in clinical outcome**

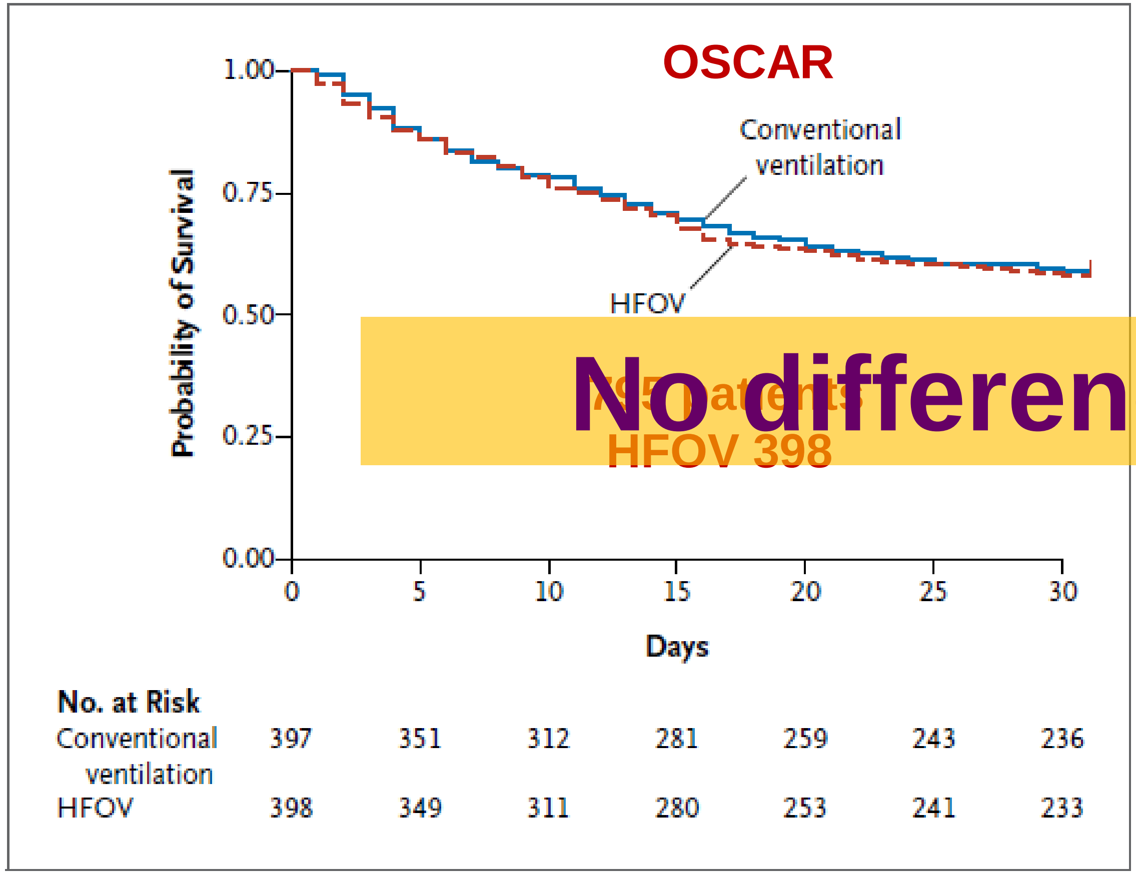
Modrykamien A, et al. Airway pressure release ventilation: an alternative mode of mechanical ventilation in acute respiratory distress syndrome. Ceveland Clinic J Med 2011; 78: 101-10

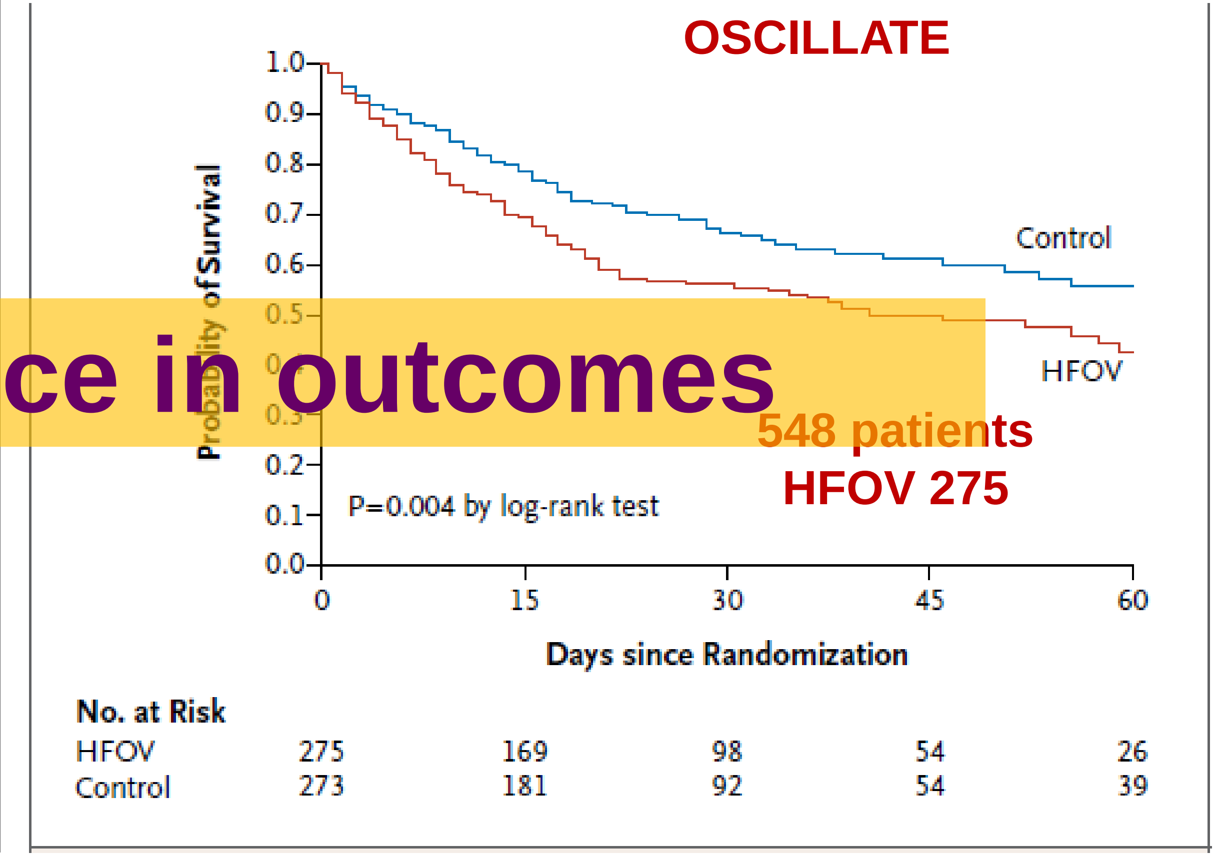
# HFOV



- Considered the “ultimate” lung protective ventilatory mode
- Uses very small tidal volumes (1-2 ml/kg)
- At high respiratory rates (3-15 breaths/sec)
- Two trials OSCILLATE and OSCAR (NEJM 2013)

# HFOV




**No difference in outcomes**

Young D, et al. High frequency oscillation for acute respiratory distress syndrome.. N Engl J Med 2013;

Ferguson ND et al. High frequency oscillation fin early acute respiratory distress syndrome.. N Engl J Med 2013;

# The strategy – targeting what?



- Volutrauma (over-distension)
- Barotrauma (trans-alveolar pressures)
- Atelectrauma (shearing force)
- Biotrauma (cytokines)


EVIDENCE is DISAPPOINTING

# Targeting volume?



- ARDSNet trial 6 ml/kg superior to 12 ml/kg
- Lower volumes (4 ml) PReVENT planned in non-ARDS patients
- 3 ml/kg with ECCO2 removal improvement in VFD
- HFOV 1 ml/kg worse outcomes

# What is the optimal volume?



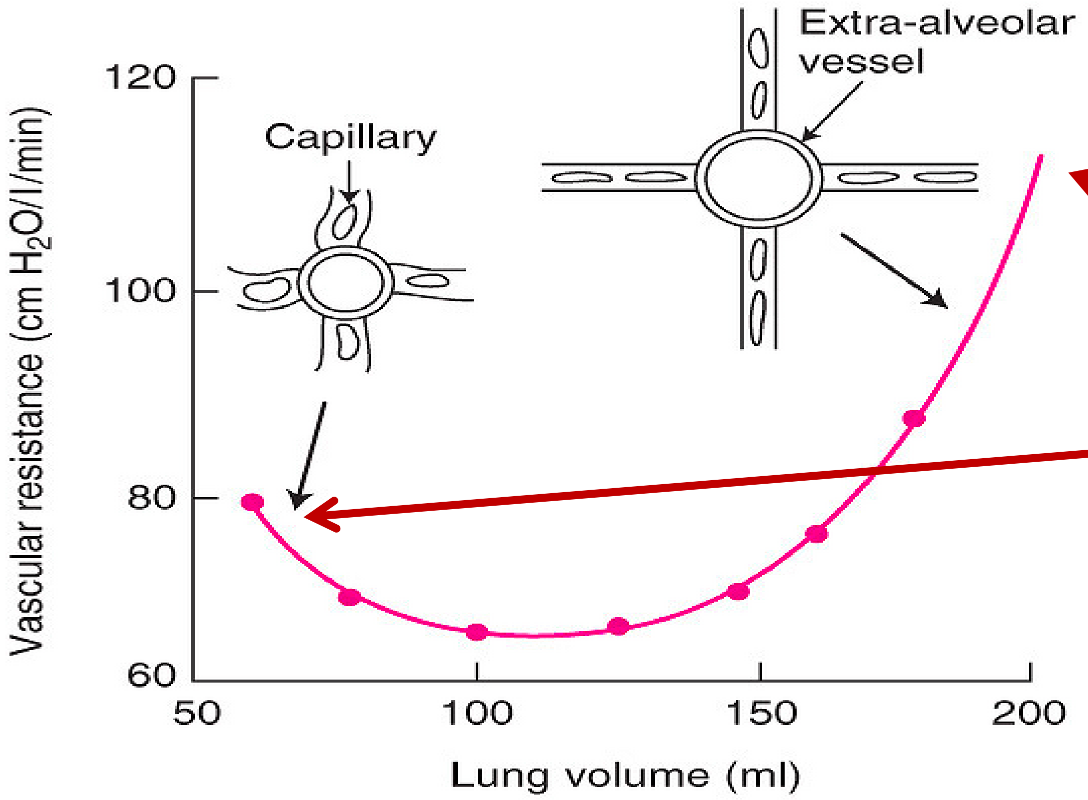



**Figure 4-6.** Effect of lung volume on pulmonary vascular resistance when the transmural pressure of the capillaries is held constant. At low lung volumes, resistance is high because the extra-alveolar vessels become narrow. At high volumes, the capillaries are stretched, and their caliber is reduced. (Data from an animal lobe

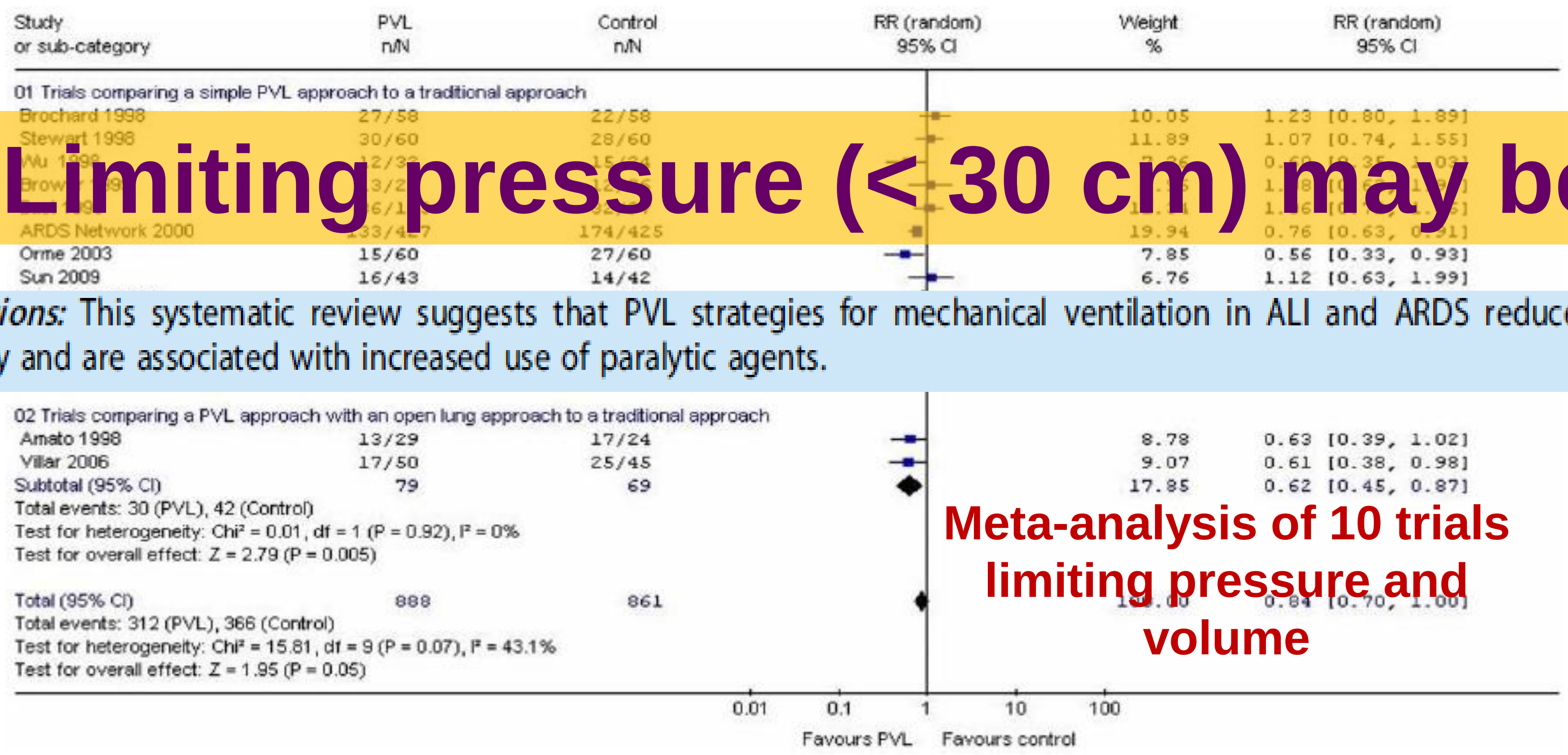
**What is the optimal volume?**

**Unclear**
**Too much is bad**
**Too little is also bad**

West Physiology

# Targeting pressure?

**Traditionally target Pplat< 30 cm; higher mortality in one HFOV study attributed to high mean airway pressure with hemodynamic instability**




**Limiting pressure (< 30 cm) may be good**

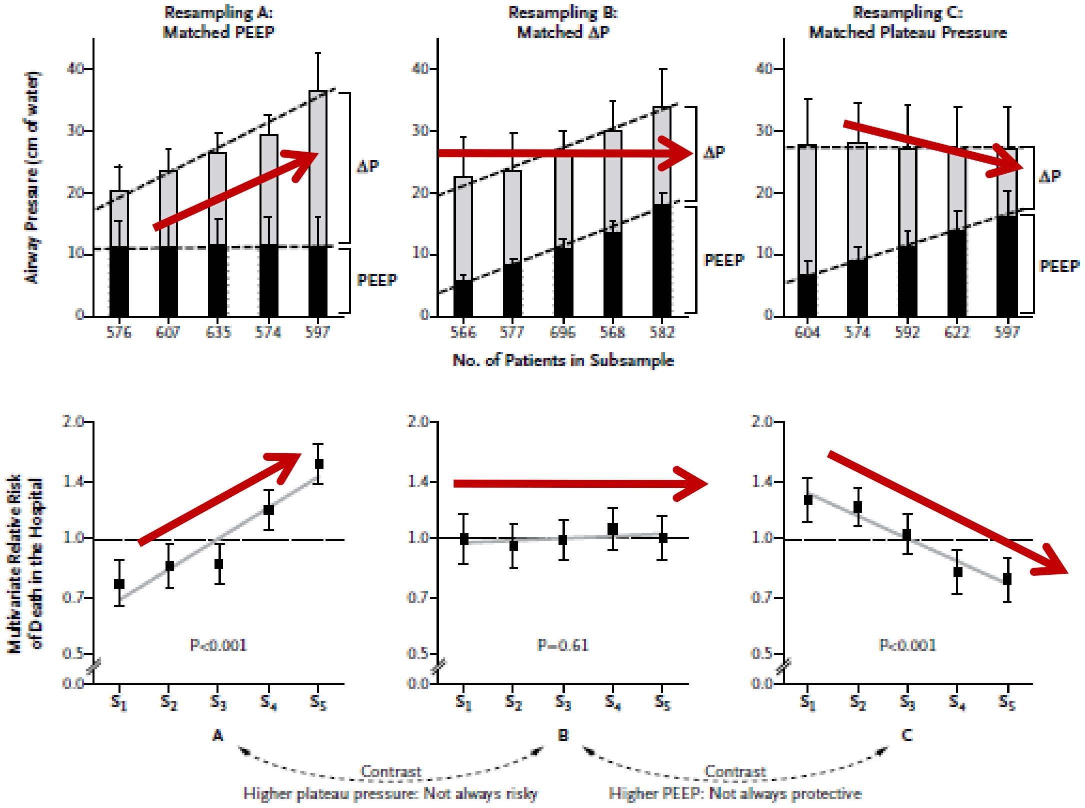
*Conclusions:* This systematic review suggests that PVL strategies for mechanical ventilation in ALI and ARDS reduce mortality and are associated with increased use of paralytic agents.

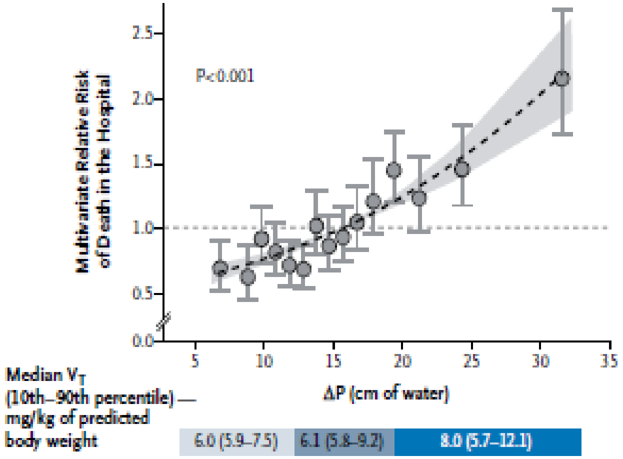
**Meta-analysis of 10 trials limiting pressure and volume**

Burns KEA, et al. Pressure and volume limited ventilation for the ventilatory management of patients with acute lung injury. A systematic review and meta-analysis. PLoS One 2011: 6: e14623

# Specific pressure or driving pressure






Amato M, et al. Driving pressure and survival in the acute respiratory distress syndrome. N Engl J Med 2015; 372: 747-55

# Targeting atelectasis



| Characteristic | ALVEOLI,[8] 2004 | LOVS,[9] 2008 | EXPRESS,[10] 2008 |
|---|---|---|---|
| | Trial | | |
| 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] |
| [illegible] | [illegible] | [illegible] | [illegible] |
| 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 ≤4[illegible] cm $H_2O$, recruitment maneuvers | PEEP as high as possible without increasing the maximum inspiratory plateau pressure >2[illegible] 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-[illegible] 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 | | |

**Conclusions** Treatment with higher vs lower levels of PEEP was not associated with improved hospital survival. However, higher levels were associated with improved survival among the subgroup of patients with ARDS.

**PEEP above lower inflection point?**

Briel M, et al. Higher versus lower positive end expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome. Systematic review and meta-analysis. JAMA 2010; 303; 865-93

# Conclusions

- Lung injury due to ventilation not uncommon
- VALI and VILI are two dimensions of injury
- Mechanisms – Volutrauma, barotrauma, atelectrauma, biotrauma
- Type of mode does not appear to influence outcome
- Limiting volume and pressure, optimal PEEP important to prevent

# Thank You