Recent advances in the ventilatory strategies for acute respiratory distress syndrome

台中榮總 重症醫學部
詹明澄

EDITORIAL

Happy 50th birthday ARDS!

Arthur S. Slutsky[1,2*], Jesús Villar[1,3,4] and Antonio Pesenti[5,6]

Intensive Care Medicine 2016 March

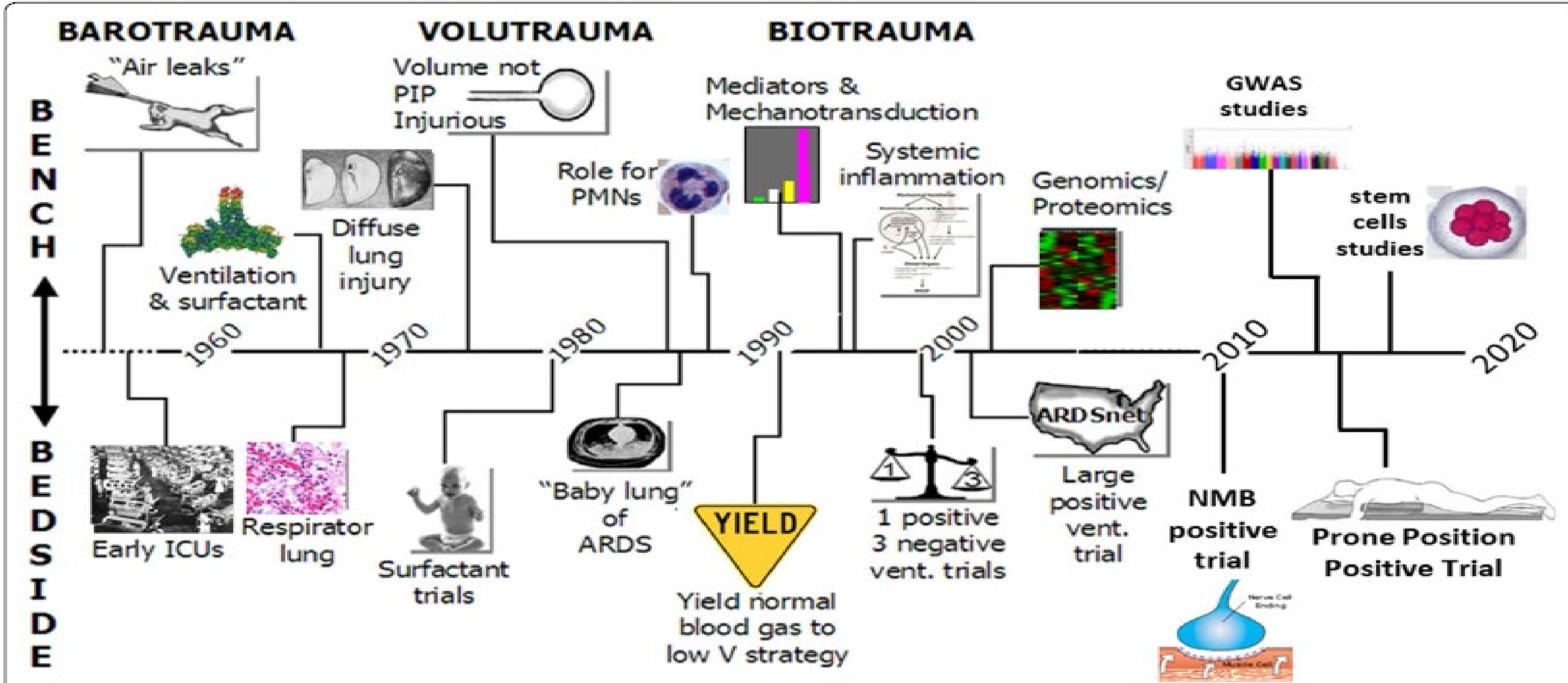

Fig. 1 Major advances related to the acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI): from the bench to the bedside. *GWAS* genome-wide association studies, *ICU* intensive care unit, *NMB* neuromuscular blocking agents, *PIP* peak inspiratory pressure, *PMN* polymorphonuclear cells, *V* volume, *vent.* ventilation. (Modified from [21])

The Lancet · Saturday 12 August 1967

ACUTE RESPIRATORY DISTRESS IN ADULTS

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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.

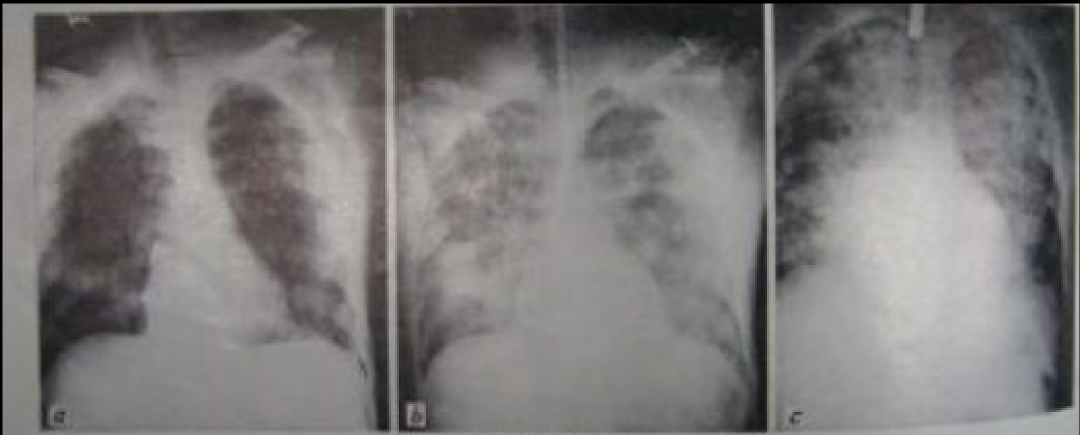


Fig. 1—Case 1 (multiple trauma): chest X-rays.
(a) 3 hours after injury. (b) 12 hours after injury. (c) 18 hours after injury.

Lancet 1967; 2: 319-323

The New England Journal

Review Artic

Medical Progress

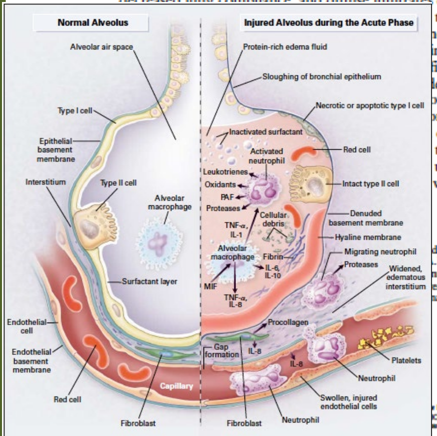
The Acute Respiratory Distress Syndrome

Lorraine B. Ware, M.D., and Michael A. Matthay, M.D.

THE acute respiratory distress syndrome is a common, devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. Since the last review of this syndrome appeared in the *Journal*,[1] more uniform definitions have been devised and important advances have occurred in the understanding of the epidemiology, natural history, and pathogenesis of the disease, leading to the design and testing of new treatment strategies. This article provides an overview of the definitions, clinical features, and epidemiology of the acute respiratory distress syndrome and discusses advances in the areas of pathogenesis, resolution, and treatment.

HISTORICAL PERSPECTIVE AND DEFINITIONS

The first description of acute respiratory distress syndrome appeared in 1967, when Ashbaugh and colleagues described 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates ev-



The NEW ENGL

Acute Respira

B. Taylor Thompson, M.D., Rachel

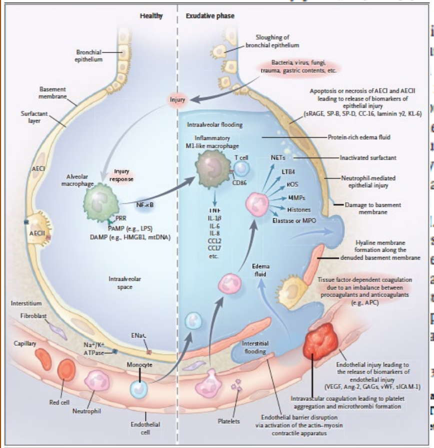
From the Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, and Harvard Medical School — both in Boston (B.T.T.); Centre for Inflammation and Tissue Repair, the Division of Medicine, University College London, London (R.C.C.); and the Divisions of Nephrology and Critical Care Medicine, University of California San Francisco, San Francisco (K.D.L.). Address reprint requests to Dr. Thompson at the Division of Pulmonary and Critical Care, Department of Medicine, Massachusetts General Hospital, Bulfinch Bldg., Suite 148, 55 Fruit St., Boston, MA 02114, or at thompson.taylor@mgh.harvard.edu.

This article was last updated on August 11, 2017, at NEJM.org.

N Engl J Med 2017;377:562-72.
DOI: 10.1056/NEJMra1608077

FIFTY YEARS AGO, ASHBAUGH ... tachypnea, refractory hypox... ter infection or trauma.[1] Pr...

DEFINITION AN



The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

Ventilator-Induced Lung Injury

Arthur S. Slutsky, M.D., and V. Marco Ranieri, M.D.

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This article was updated on April 24, 2014, at NEJM.org.

N Engl J Med 2013;369:2126-36.
DOI: 10.1056/NEJMra1208707

THE PURPOSE OF MECHANICAL VENTILATION IS TO REST THE RESPIRATORY muscles while providing adequate gas exchange. Ventilatory support proved to be indispensable during the 1952 polio epidemic in Copenhagen, decreasing mortality among patients with paralytic polio from more than 80% to approximately 40%.[1] Despite the clear benefits of this therapy, many patients eventually die after the initiation of mechanical ventilation, even though their arterial blood gases may have normalized.

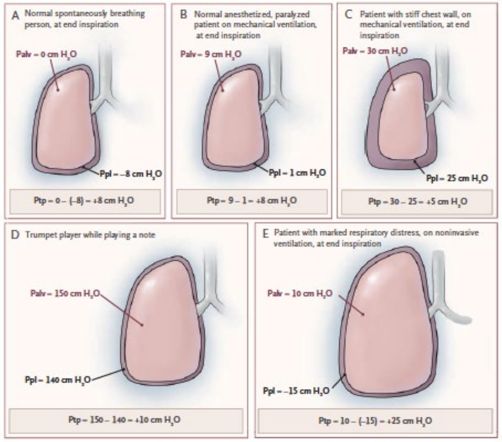
This mortality has been ascribed to multiple factors, including complications of ventilation such as barotrauma (i.e., gross air leaks), oxygen toxicity, and hemodynamic compromise.[2,3] During the polio epidemic, investigators noted that mechanical ventilation could cause structural damage to the lung.[4] In 1967, the term "respirator lung" was coined to describe the diffuse alveolar infiltrates and hyaline membranes that were found on postmortem examination of patients who had undergone mechanical ventilation.[5] More recently, there has been a renewed focus on the worsening injury that mechanical ventilation can cause in previously damaged lungs and the damage it can initiate in normal lungs. This damage is characterized pathologically by inflammatory-cell infiltrates, hyaline membranes, increased vascular permeability, and pulmonary edema. The constellation of pulmonary consequences of mechanical ventilation has been termed ventilator-induced lung injury.

The concept of ventilator-induced lung injury is not new. In 1744, John Fothergill discussed a case of a patient who was "dead in appearance" after exposure to coal fumes and who was successfully treated by mouth-to-mouth resuscitation.[6] Fothergill noted that mouth-to-mouth resuscitation was preferable to using bellows because ...thout injury, as great a force as those of an... ellows cannot always be determin'd." Fother... t mechanical forces generated by bellows (i.e.,

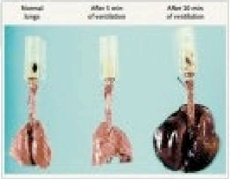
... this century that the clinical importance of ...ts was confirmed by a study showing that a ...mize such injury decreased mortality among ...istress syndrome (ARDS).[7] Given the clinical ...g injury, this article will review mechanisms ... and physiological consequences, and clinical ...its effects.

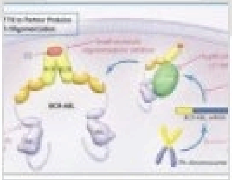
...LOGICAL FEATURES

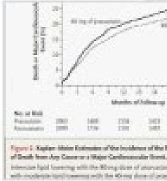
... approximately 500 million breaths. For each ...late the lungs comprises the pressure to over... (a measure of the pressure gradient required



1812 PICK: AREAS OF MEDICINE SORT BY: MOST RELEVANT 1990 s 2012







1998

1999

2000

2001

2002

2003

2004

Definition of ALI/ARDS

- Acute onset
- Bilateral infiltrates on CXR
- PCWP ≤ 18cmH_2O; or no left side heart failure
- Hypoxemia
  - If PaO_2/FiO_2 ≤ 200 Acute respiratory distress syndrome (ARDS)
  - If PaO_2/FiO_2 ≤ 300 Acute lung injury (ALI)

AECC 1994

Berlin Definition

Table 3. The Berlin Definition of Acute Respiratory Distress Syndrome

	Acute Respiratory Distress Syndrome
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (eg, echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg PaO_2/FIO_2 300 mm Hg with PEEP or CPAP 5 cm H_2O[c]
Moderate	100 mm Hg PaO_2/FIO_2 200 mm Hg with PEEP 5 cm H_2O
Severe	PaO_2/FIO_2 100 mm Hg with PEEP 5 cm H_2O

JAMA. 2012;307(23):5669

Epidemiology-Do we underestimate?

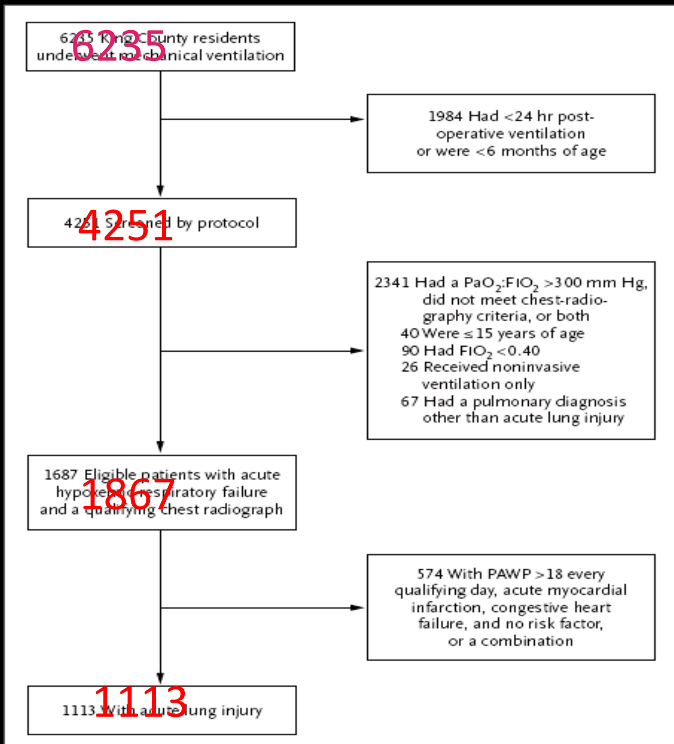


Table 1. Incidence of Acute Lung Injury and ARDS and Mortality from These Conditions.*

Variable	Acute Lung Injury	ARDS
Cases — no.	1,113	828
Crude incidence — no. per 100,000 person-yr	78.9	58.7
Age-adjusted incidence — no. per 100,000 person-yr†	86.2	64.0
Mortality (95% CI) — %	38.5 (34.9–42.2)	41.1 (36.7–45.4)
Estimated annual cases — no.†	190,600	141,500
Estimated annual deaths — no.†	74,500	59,000
Estimated annual hospital days — no.†	3,622,000	2,746,000
Estimated annual days in ICU — no.†	2,154,000	1,642,000

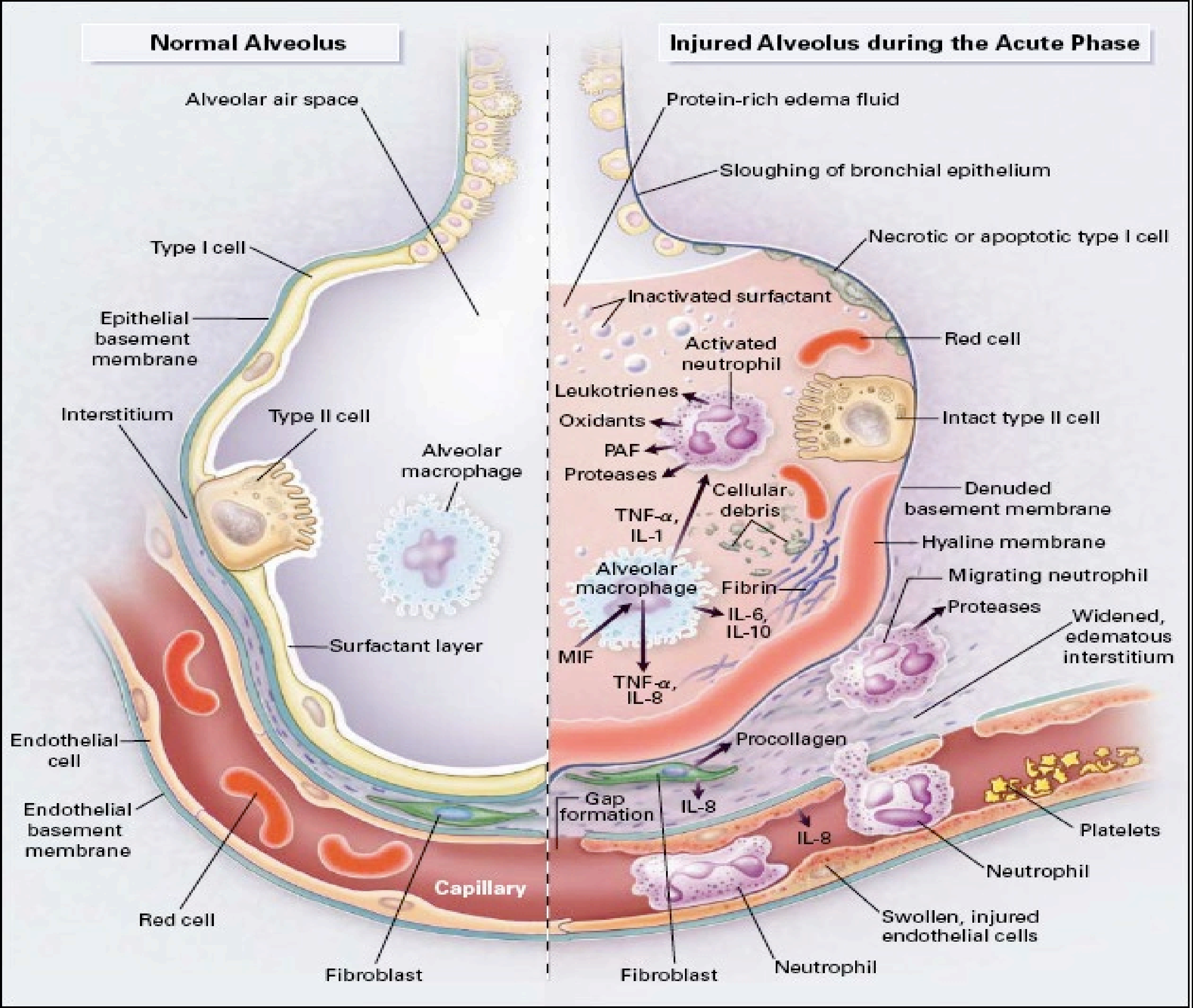
N Engl J Med 2005;353:1685-93.

Lung Safe Study

Global Epidemiology of ARDS

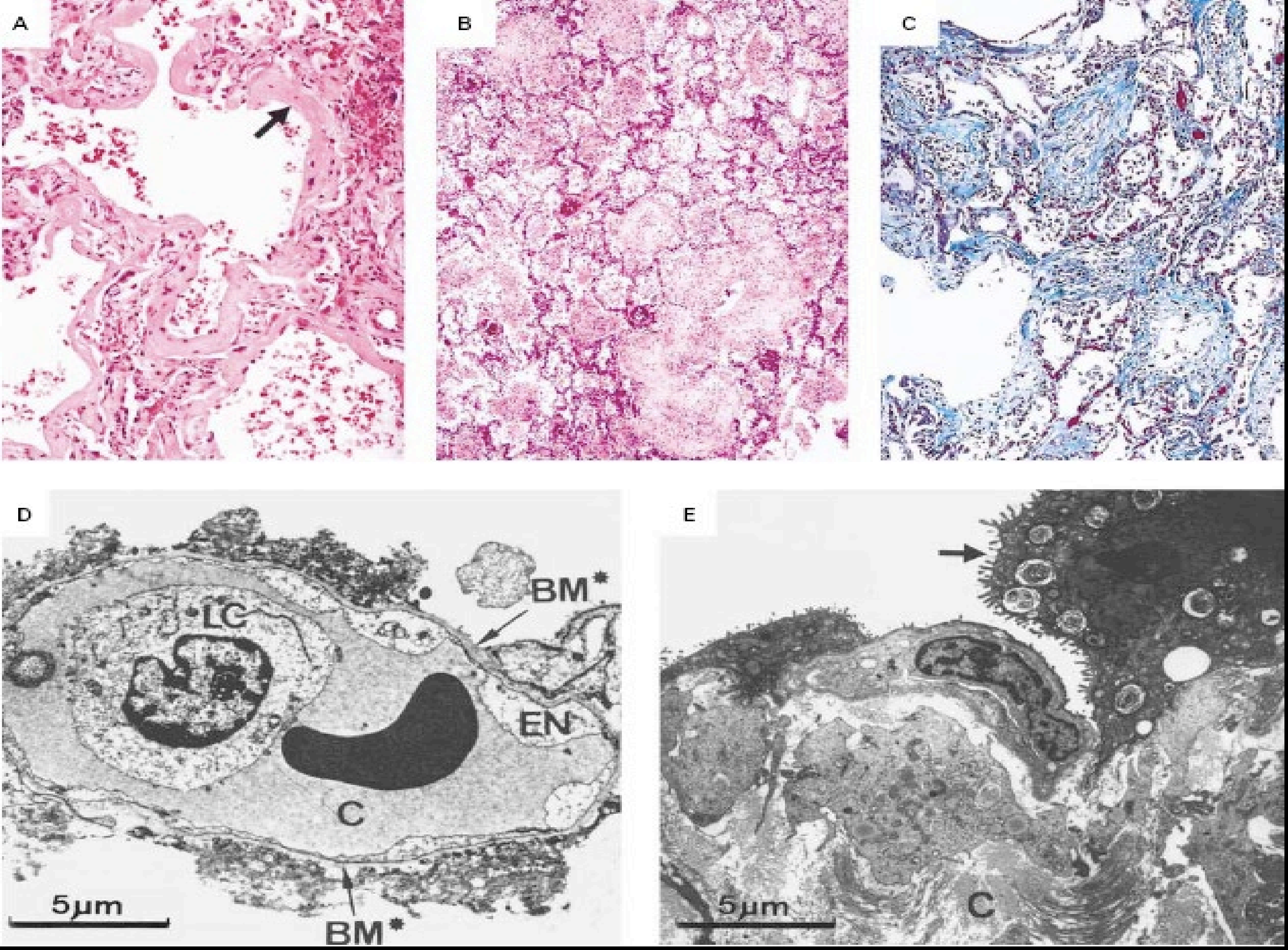
- international, multicenter, prospective cohort study in winter 2014
  - 459 ICUs from 50 countries
- 10.4% (3022/29144) fulfilled ARDS criteria.
- Underrecognized
  - Clinician recognition of ARDS only 60%
- Undertreated
  - Less than 2/3 Vt < 8 of mL/kg.
  - P_{plat} measured in 40.1%, whereas 82.6% PEEP < 12 cm H_2O.
  - Prone positioning was used in 16.3% of severe ARDS.
- High mortality
  - Hospital mortality, mild 34.9%, moderate 40.3%, severe 46.1%.

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

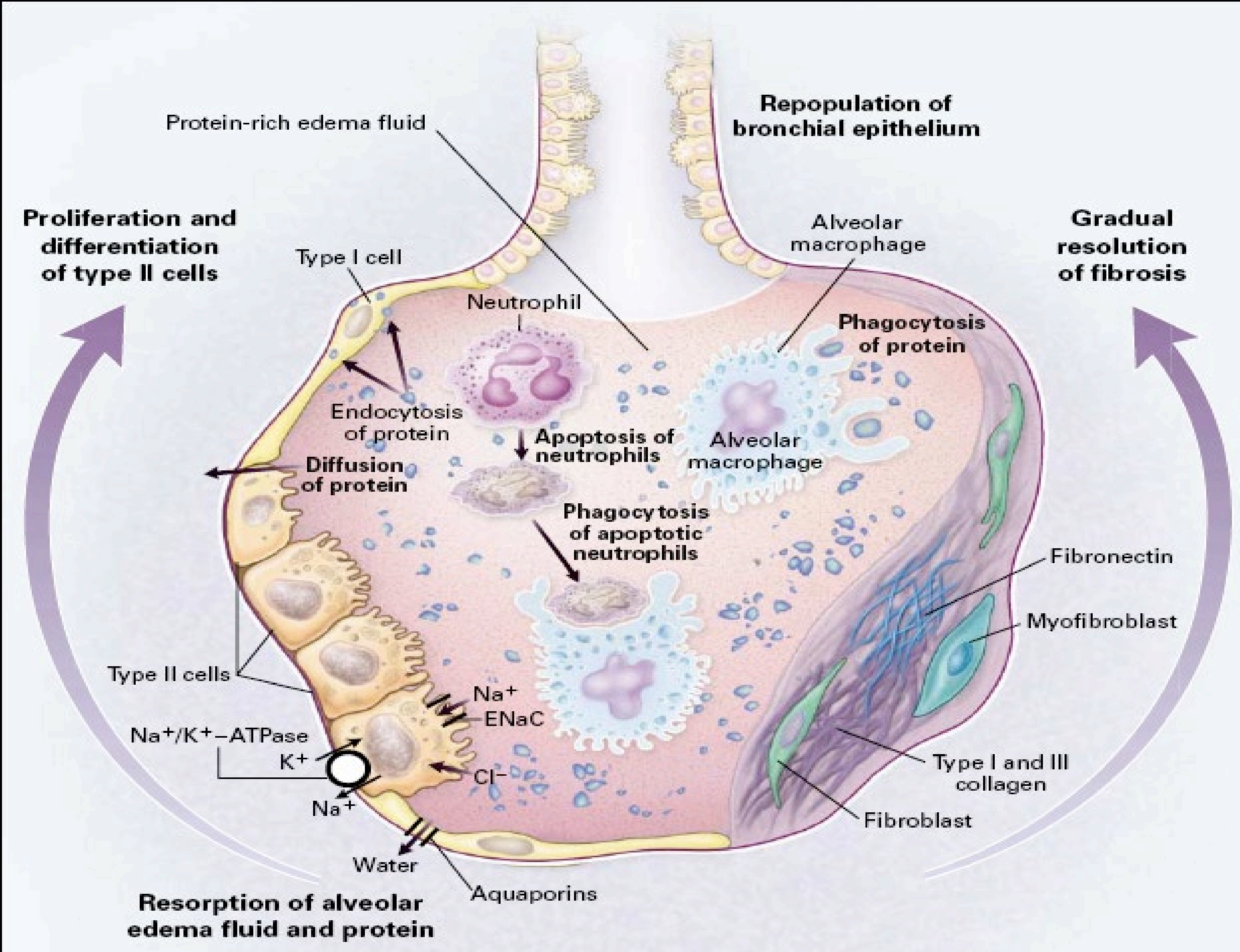


Pathogenesis of ALI/ARDS

NEJM 2000



NEJM 2000


Protein-rich edema fluid
Repopulation of bronchial epithelium
Proliferation and differentiation of type II cells
Type I cell
Alveolar macrophage
Gradual resolution of fibrosis
Neutrophil
Phagocytosis of protein
Endocytosis of protein
Apoptosis of neutrophils
Alveolar macrophage
Diffusion of protein
Phagocytosis of apoptotic neutrophils
Fibronectin
Myofibroblast
Type II cells
Na+
ENaC
Na+/K+–ATPase
K+
Cl−
Na+
Type I and III collagen
Fibroblast
Water
Aquaporins
Resorption of alveolar edema fluid and protein

NEJM 2000

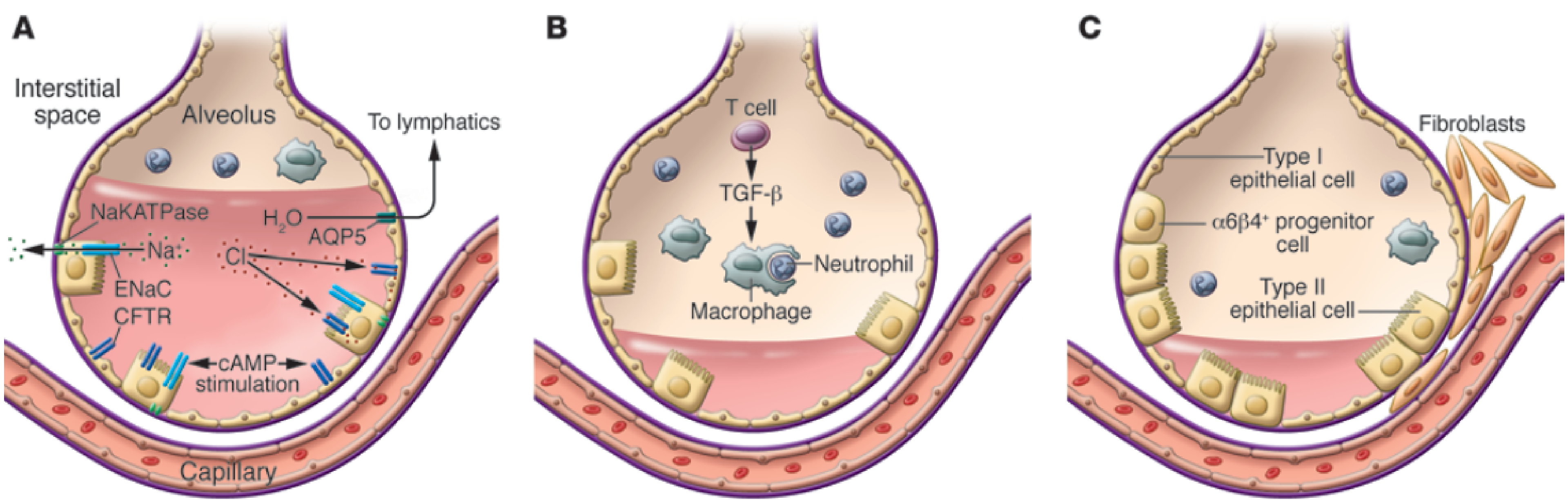


Figure 4

Resolution of ALI requires removal of alveolar edema fluid, removal of the acute inflammatory cells, and repair of the injured alveolar epithelium. (**A**) Alveolar edema fluid reabsorption is driven by vectorial transport of sodium and chloride from the airspaces to the lung interstitium, creating a mini–osmotic gradient. Sodium is transported across apical sodium channels (including epithelial sodium channel [ENaC]) and then extruded basolaterally by sodium-potassium ATPase (NaKATPase). Chloride is transported by transcellular or paracellular pathways. In the presence of endogenous or exogenous cAMP stimulation, the rate of alveolar fluid transport increases substantially, accomplished by increased expression and activity of ENaC, NaKATPase, and opening of the CFTR. For net fluid clearance to occur, however, there needs to be a reasonably intact alveolar epithelial barrier (see **C**). AQP5, aquaporin 5. (**B**) The resolution of inflammation in ALI and ARDS requires the removal of neutrophils from the distal airspace of the lung. Neutrophils are normally taken up by alveolar macrophages, a process termed *efferocytosis*. The rate of neutrophil clearance can be accelerated by regulatory T lymphocytes, in part by release of TGF-β. (**C**) Restoration of the alveolar epithelial barrier initially occurs by reepithelialization of the epithelial surface by alveolar type II cells. Although it was previously thought that this occurred via proliferation of resident type II cells, new work suggests there may be niches of progenitor cells that also contribute. An $\alpha 6\beta 4^+$ progenitor cell has been identified in the mouse lung that is responsible for restoration of the alveolar epithelial barrier after bleomycin-induced lung injury (88). Thus, repair may occur by endogenous stem cell proliferation, not just by epithelial cell migration and proliferation of existing differentiated cells.

Common Causes of ARDS

Direct Lung Injury

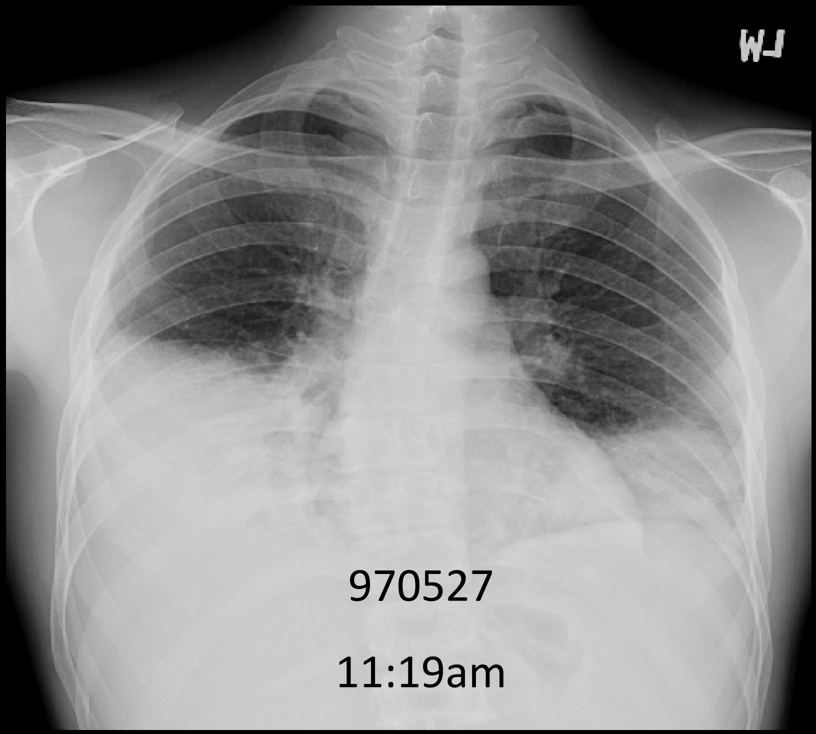
- Pneumonia
- Aspiration of gastric content
- Pulmonary contussion
- Fat embolism
- Near-drowning
- Inhalation injury
- Reperfusion injury after transplantation, pulmonary lobectomy

Indirect Lung Injury

- Sepsis
- Severe trauma with shock and multiple transfusion
- Cardiopulmonary bypass
- Drug overdose
- Acute pancreatitis
- Transfusion of blood prodcuts

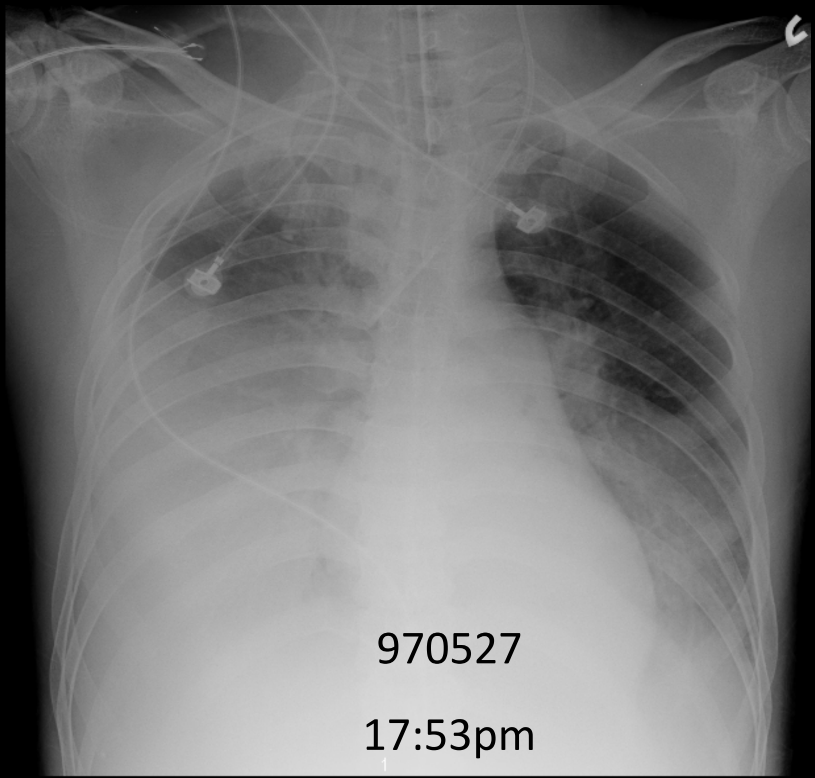
Brief History

- Mr. Y, 28 y/o
- Productive cough, purulent sputum for 4 days
- 5/27 OPD 11:20am
  - Respiratory distress
  - SaO_2 88%, O_2 canula 6l/min
- 11:56 ER
  - BP 91/56mmHg, HR 117/min, RR 35/min, BT 36℃
  - Rhonchi bilateral



Admission to ICU

- 5/27 5PM RICU
  - APACH II score 20
  - Fluid resuscitation
  - Ceftriaxone + Erythromycin
  - ARDS
    - Protective ventilatory strategy
      - Vt 360ml, PEEP 20cmH_2O, RR 26/min
    - Prone position ventilation

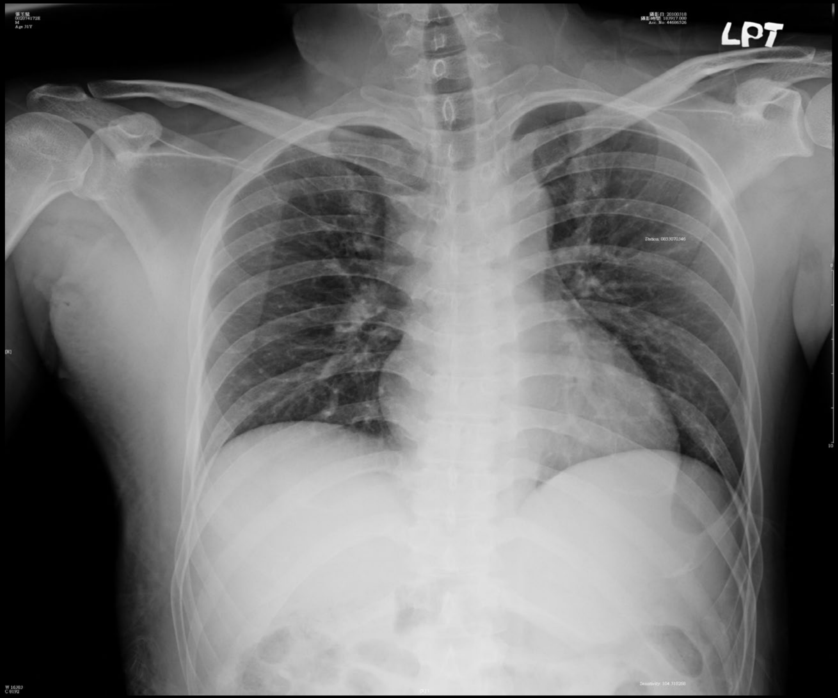


970626

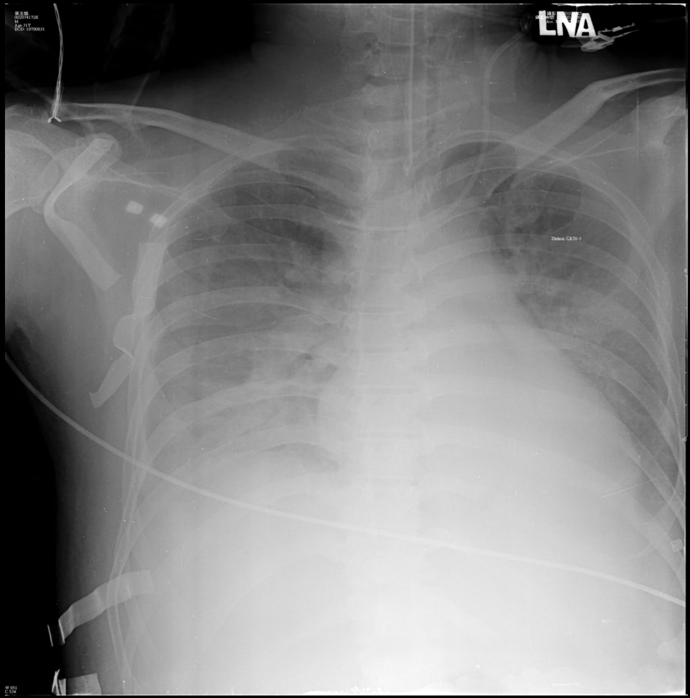
Chest X-Ray

Transfusion-related acute lung injury (TRALI)

March 18, 2010



March 25, 2010



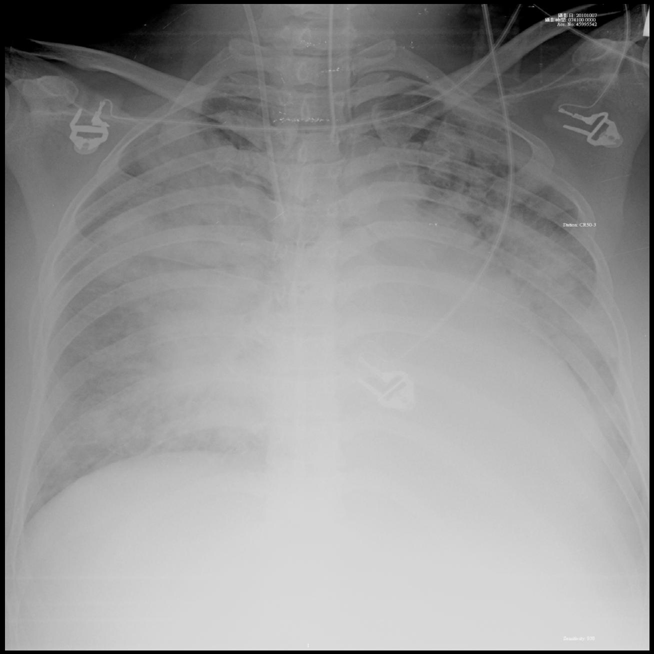
Case

- 陳ＸＸ, 1745684H, 41 y/o female
- Pregnancy 32 weeks, Triplet pregnancy by IVF, G3P0AA0, SA2
- Pre-eclampsia
  - Hypertension, Edema, Proteinuria
- Threatened preterm labor

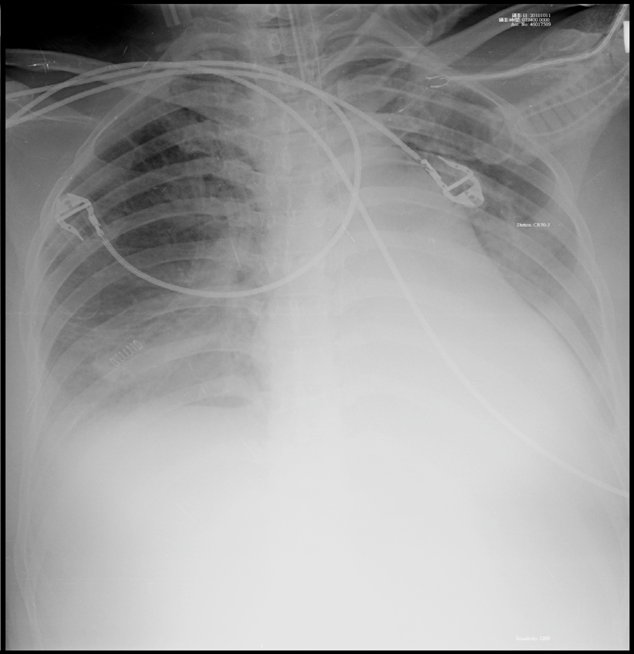
Hospital Course

- Oct 07, 2010, 5:30 am emergent CS
- Massive blood loss and transfusion
- Refractory hypoxemia and admission to RICU
  - FiO_2 100%, SpO_2 88%
  - Vt 270 ml, PEEP 22, P_{peak} 34, P_{plat} 32 cmH_2O
  - C.O. 3.55 L/min, C.I. 1.92 $L/min/m^2$, PCWP 17 cmH_2O

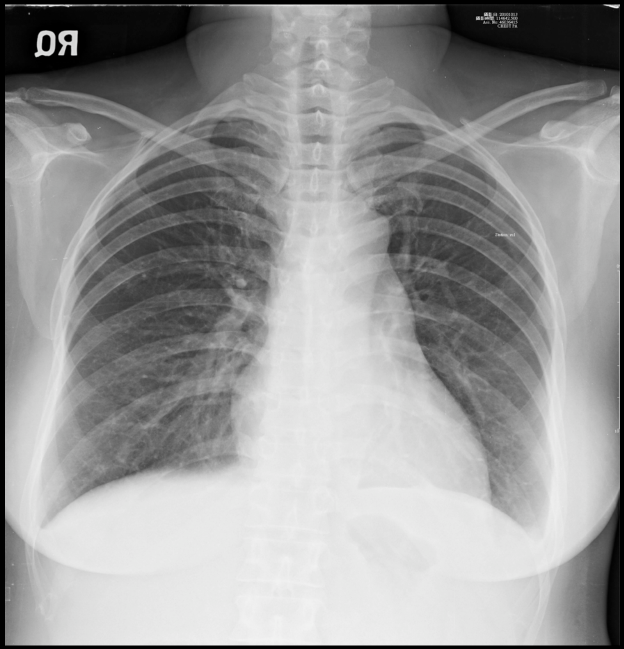
Oct 07



Oct 11

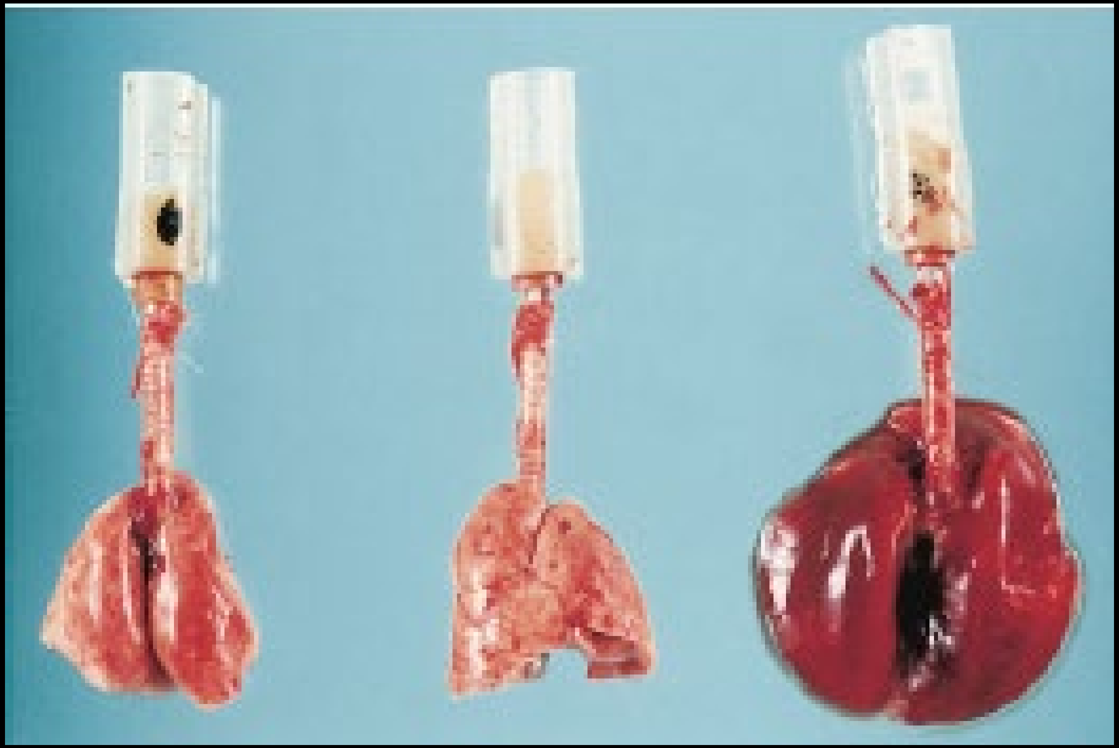


Oct 13



Barotrauma, not Just Air Leak

Normal 5 MIN 20 MIN

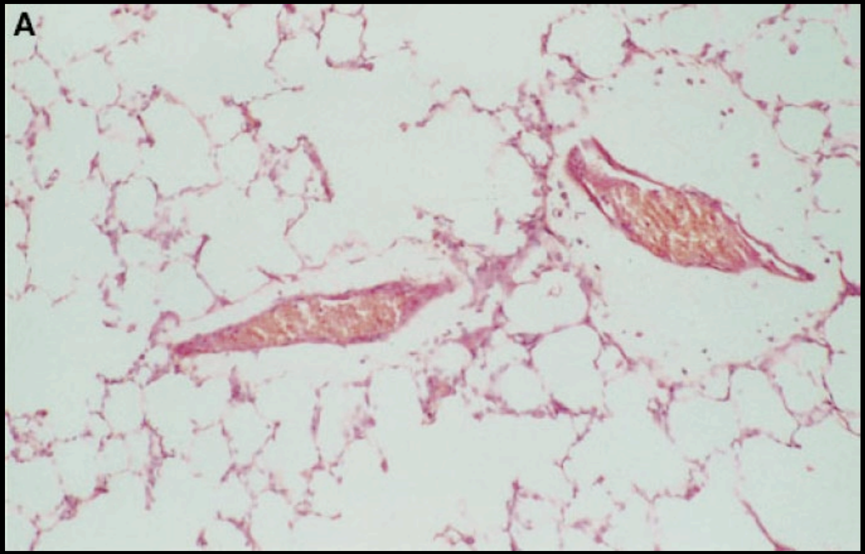


Peak Airway Pressure 45cm H_2O

VILI in Light Microscope

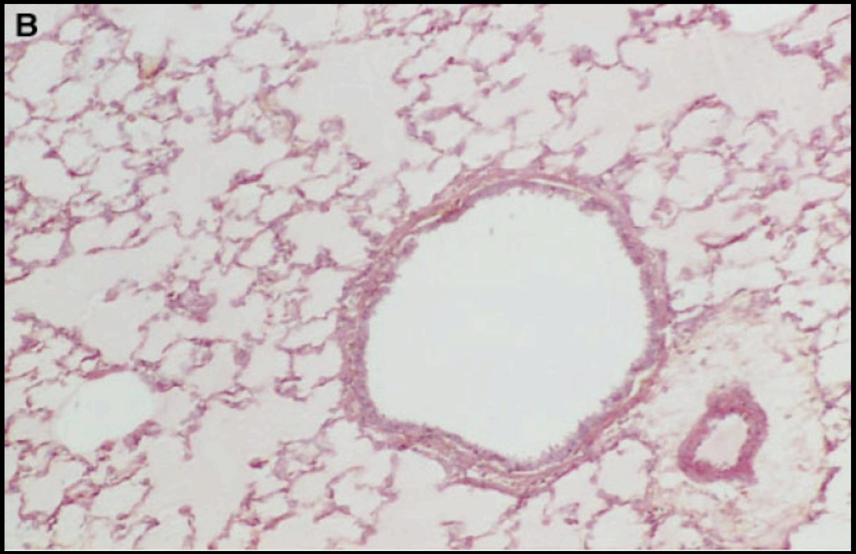
Perivascular cuffing

PC 45cmH_2O, 5ming



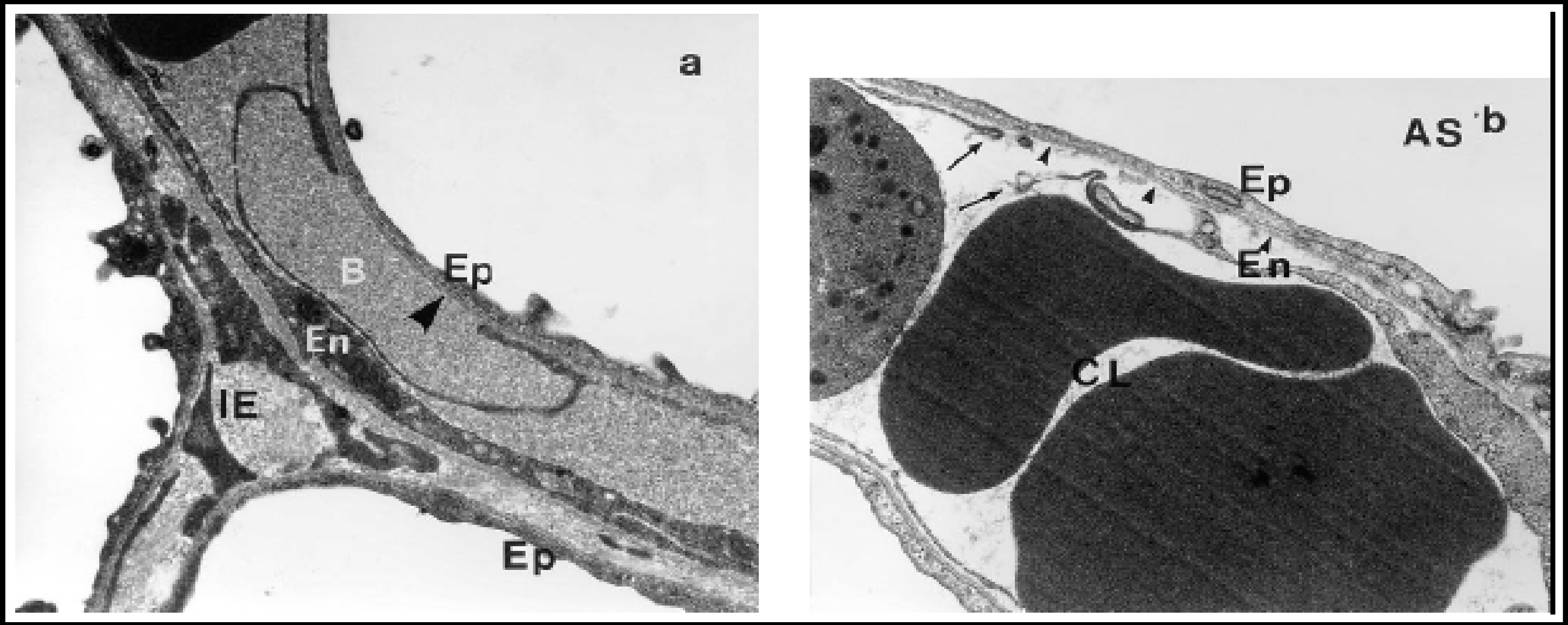
Alveolar edema

PC 45cm H_2O, 20min



AJRCCM 1998

Ultrastructural Change of Barotrauma



EP type I epithelium

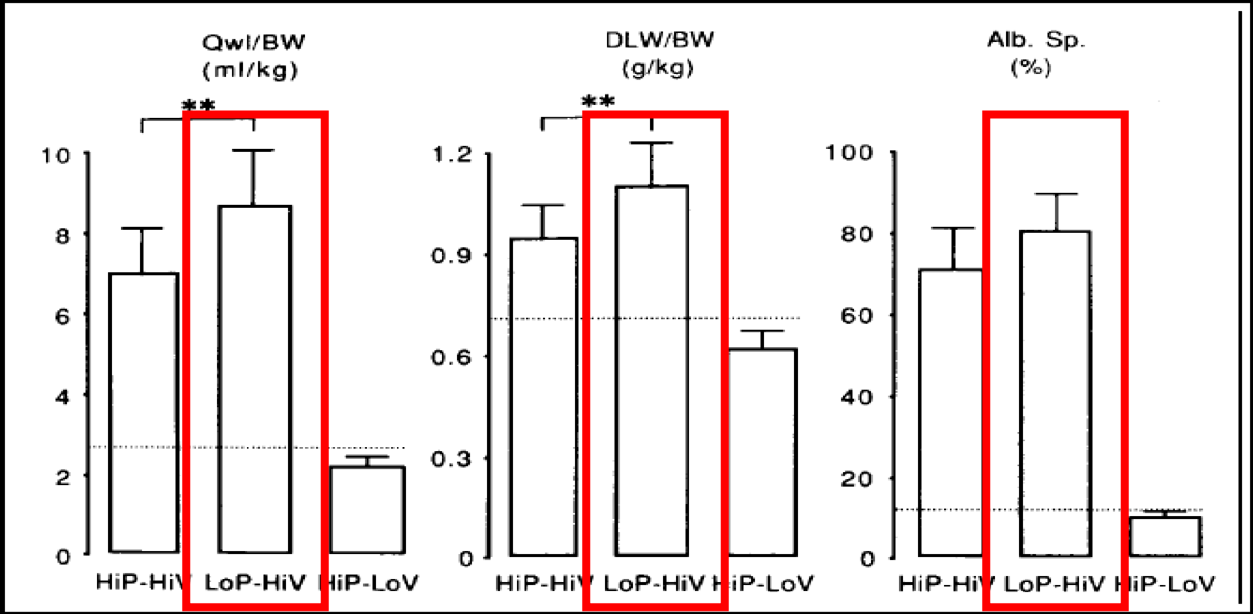
IE Interstitial edema

EN Endothelium

B Bleb

M. J. Tobin, Principles and Practice of Mechanical Ventilation, McGraw-Hill, New York. 793-811

Volutrauma



extravascular lung water content

bloodless dry lung weight

Distribution space of ^{125}I-labled albumin

HiP-Hiv **High-pressure-high-volume**

LoP-HiV **Iron lung ventilation**

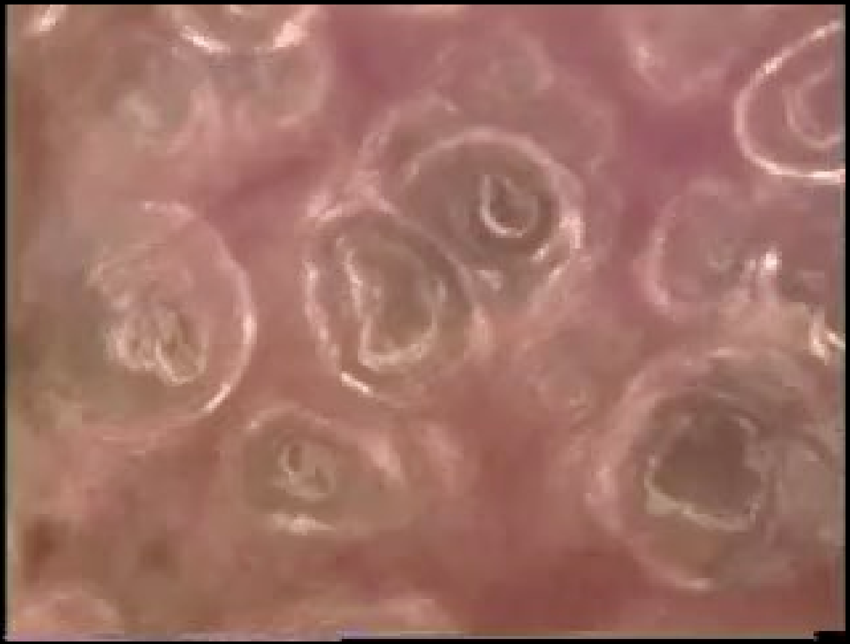
HiP-LoV **Thoracoabdominal strapping**

Deryfuss D, Am. Rev. Respir. Dis. 137: 1159-1164

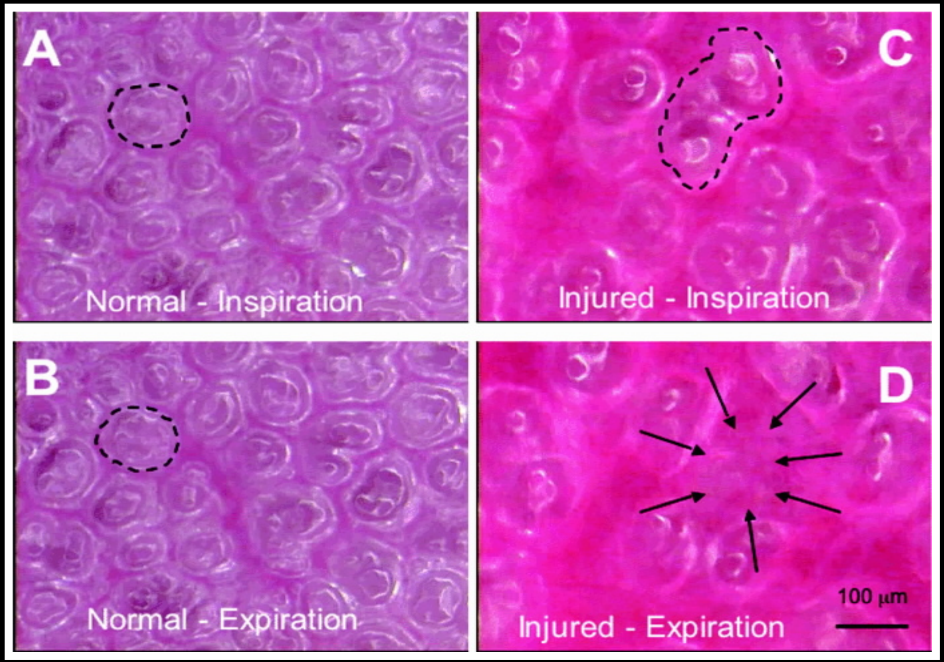
Atelectrauma

Normal alveoli

Injured alveoli



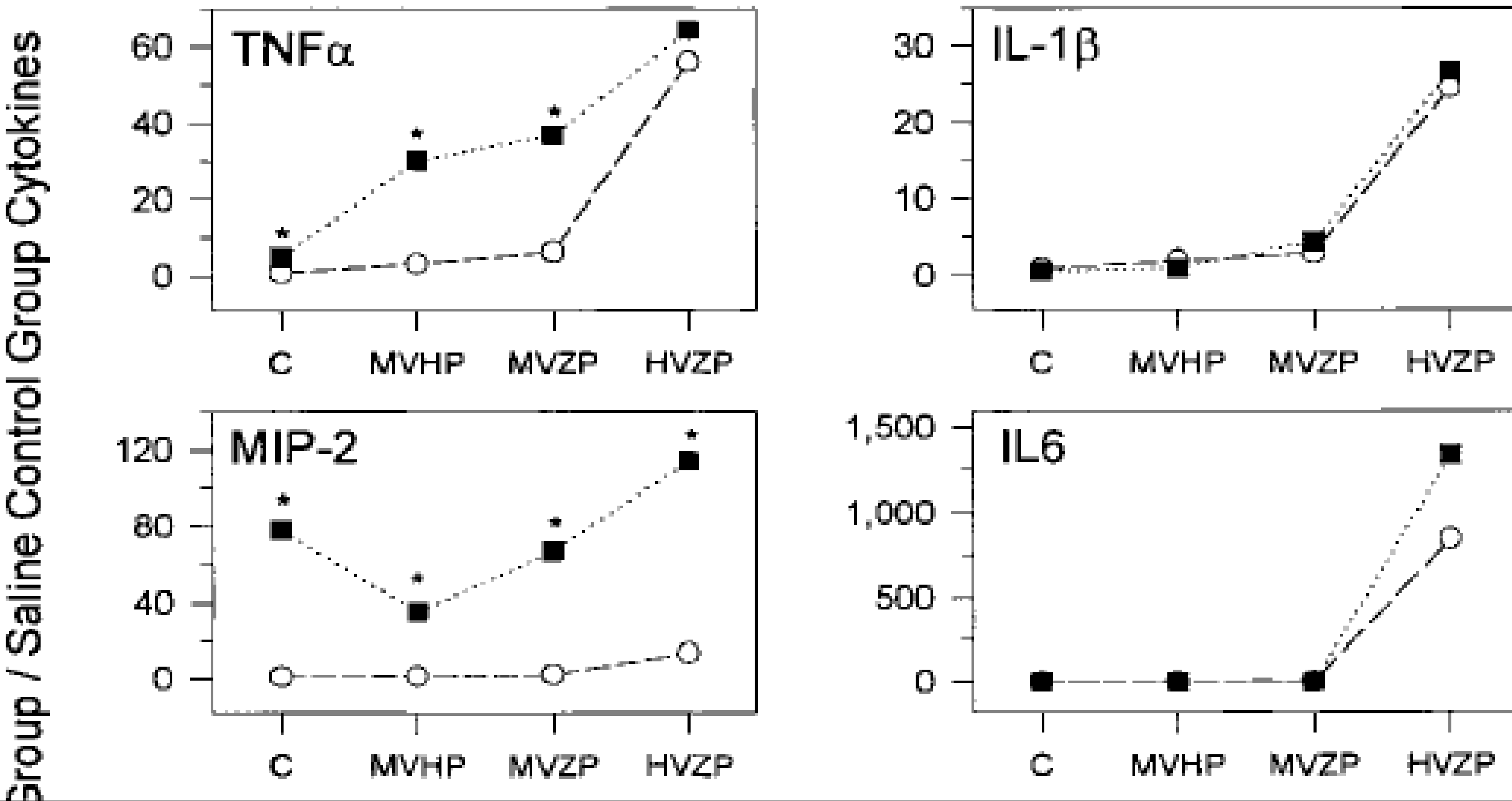
Atelectrauma



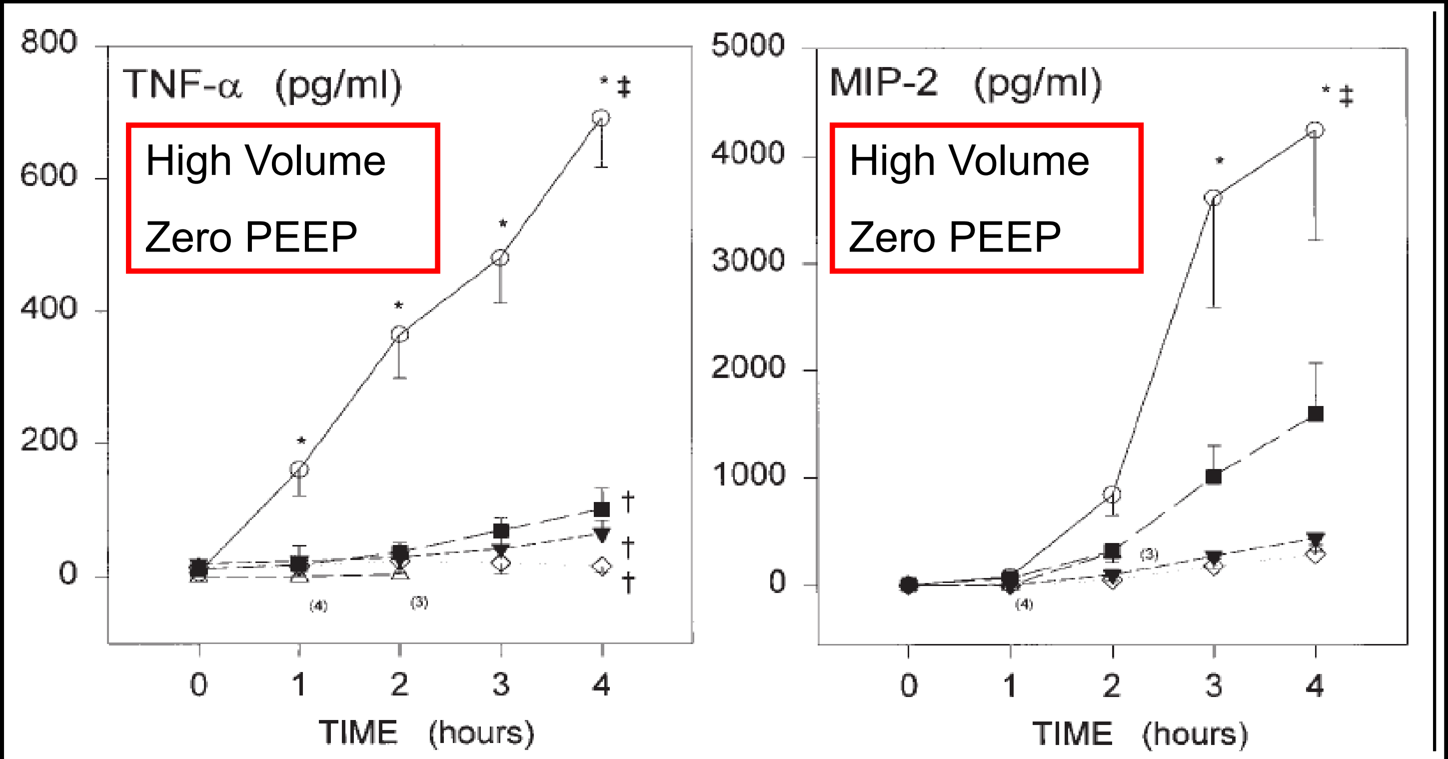
- Opening collapsed airway requires relatively high forces and thus causes epithelium disruption.
- Ventilation at low lung volumes can inhibit production of surfactant and/or lead to surfactant being squeezed out of alveoli.
- Reexpansion of atelectatic regions can be associated with marked increase in regional stress.

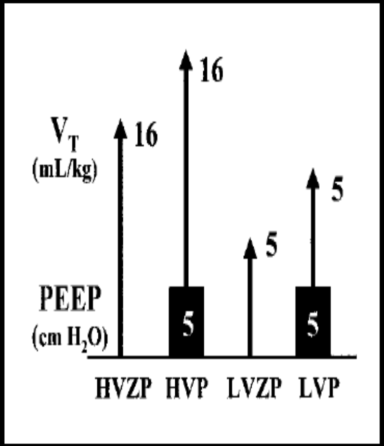
Injurious Mechanical Ventilation Trigger cytokine production

J. Clin. Invest. 1997. 99:944–952



Injurious Mechanical Ventilation Affects Local and Systemic Cytokines





AJRCCM Vol 160. pp 109-116, 1999

IL-6 and IL-8 is Associated with Morbidity and Mortality in ALI

	Alive		Dead		
	n	Median(IQR)	n	Median(IQR)	P Value
IL-6					
Baseline	505	227(94-630)	276	411(133-1471)	<0.001
Day 3	478	80(39-179)	240	208(80-635)	<0.001
IL-8					
Baseline	505	33(0-78)	275	67(24-180)	<0.001
Day 3	478	24(0-51)	240	66(25-144)	<0.001

Crit Care Med 2005; 33: 1-6

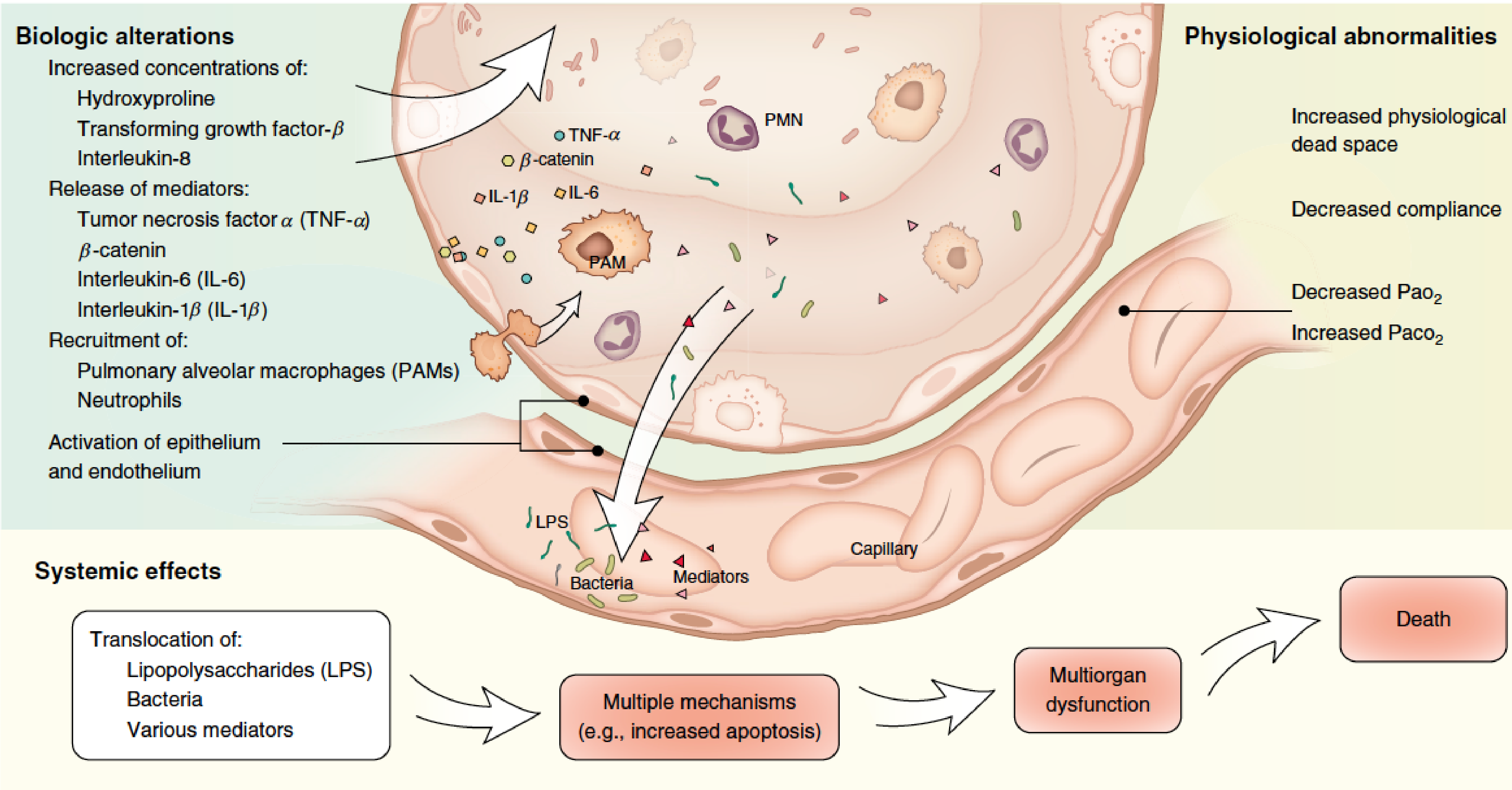
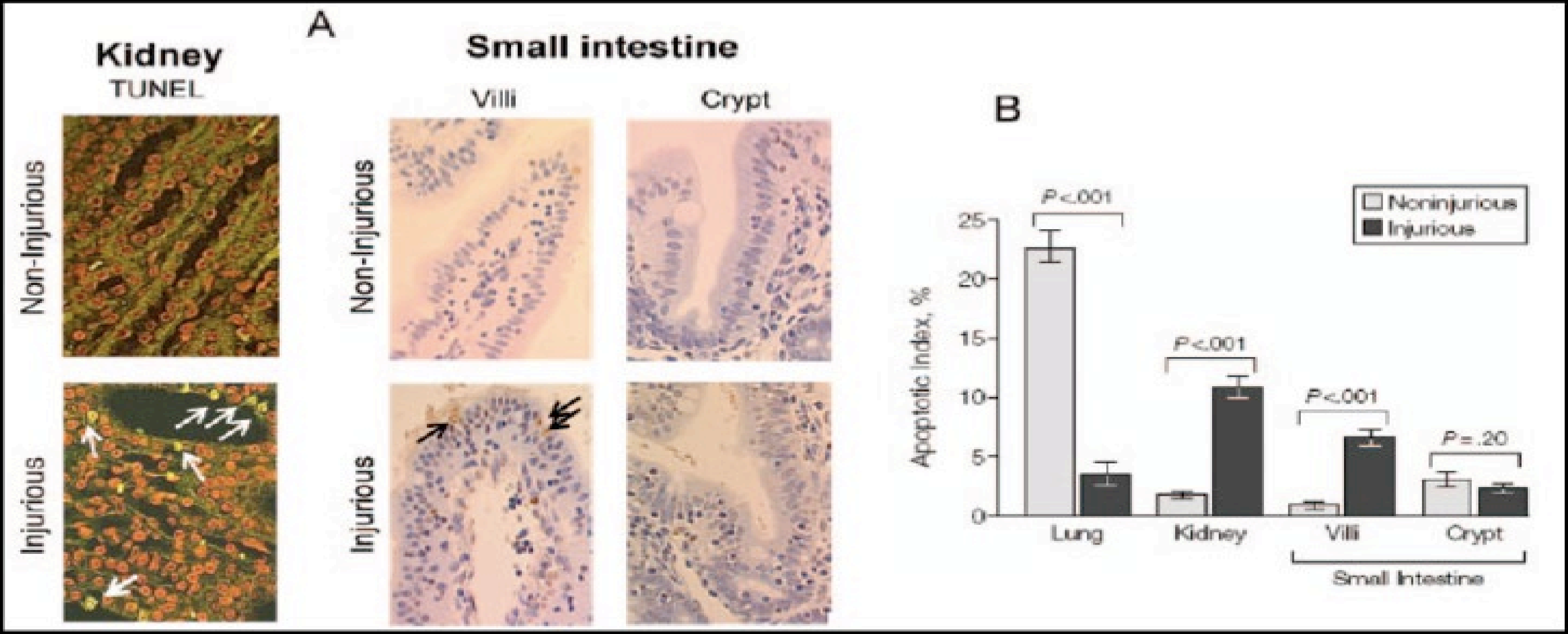


Figure 9. Alterations caused by ventilator-induced lung injury (VILI). Biologic, physiologic, and systemic effects caused by injurious ventilatory strategies. Further injury can be caused by mediators released into the lung. These mediators can recruit neutrophils into the lung or cause changes that can promote pulmonary fibrosis. VILI can also lead to increased alveolar–capillary permeability that in turn can facilitate translocation of mediators, bacteria, or lipopolysaccharides into the systemic circulation. These can then potentially lead to multiorgan dysfunction syndrome and death. PMN = polymorphonuclear leukocytes. Reprinted by permission from Reference 29.

Am J Respir Crit Care Med Vol 191, Iss 10, pp 1106–1115

Injurious Ventilation Strategy Leads to Increased Epithelial Apoptosis

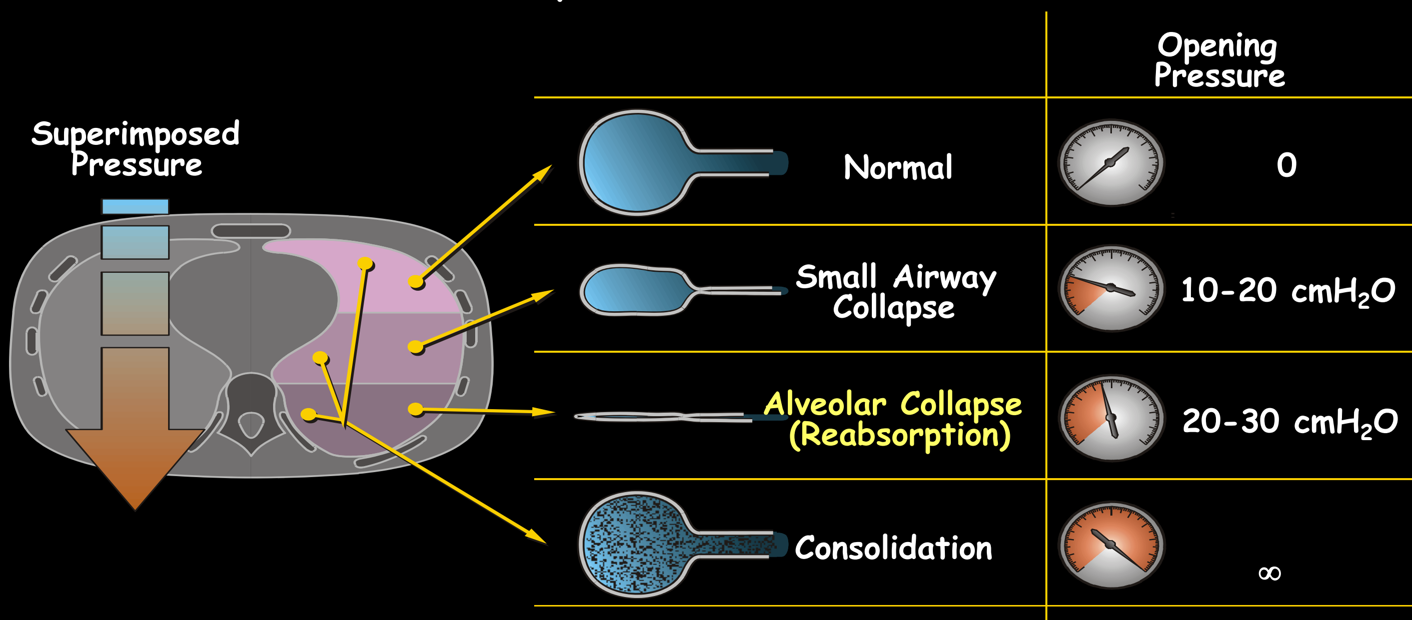


JAMA 2003;289(16):2104-2112

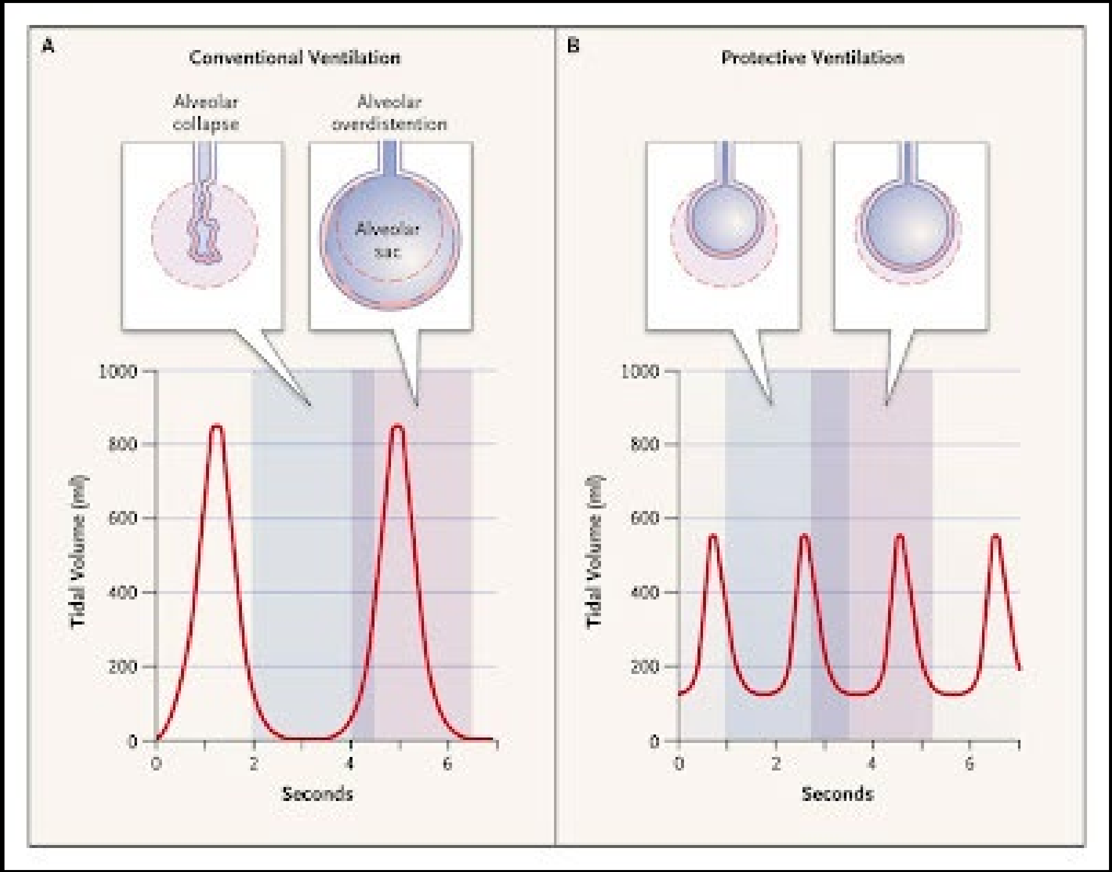
The ARDS Lung

Gattinoni JAMA 1993, Pelosi AJRCCM 1994, Gattinoni AJRCCM 2002, Gattinoni ICM 2005

Rouby Intensive Care Med 2000



Protective Ventilation



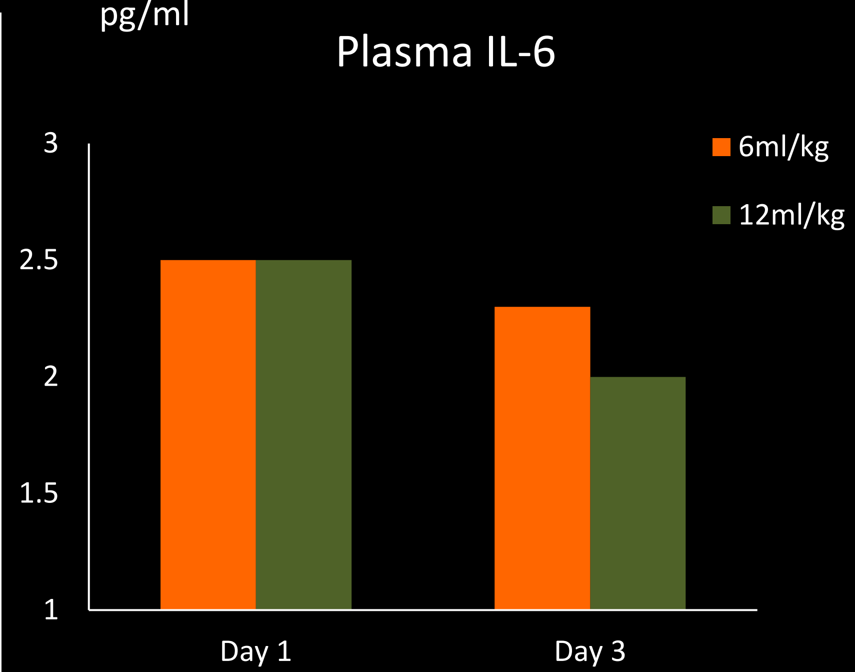
NEJM 2007

6 vs 12 ml/kg

N Engl J Med 2000;342:1301-8

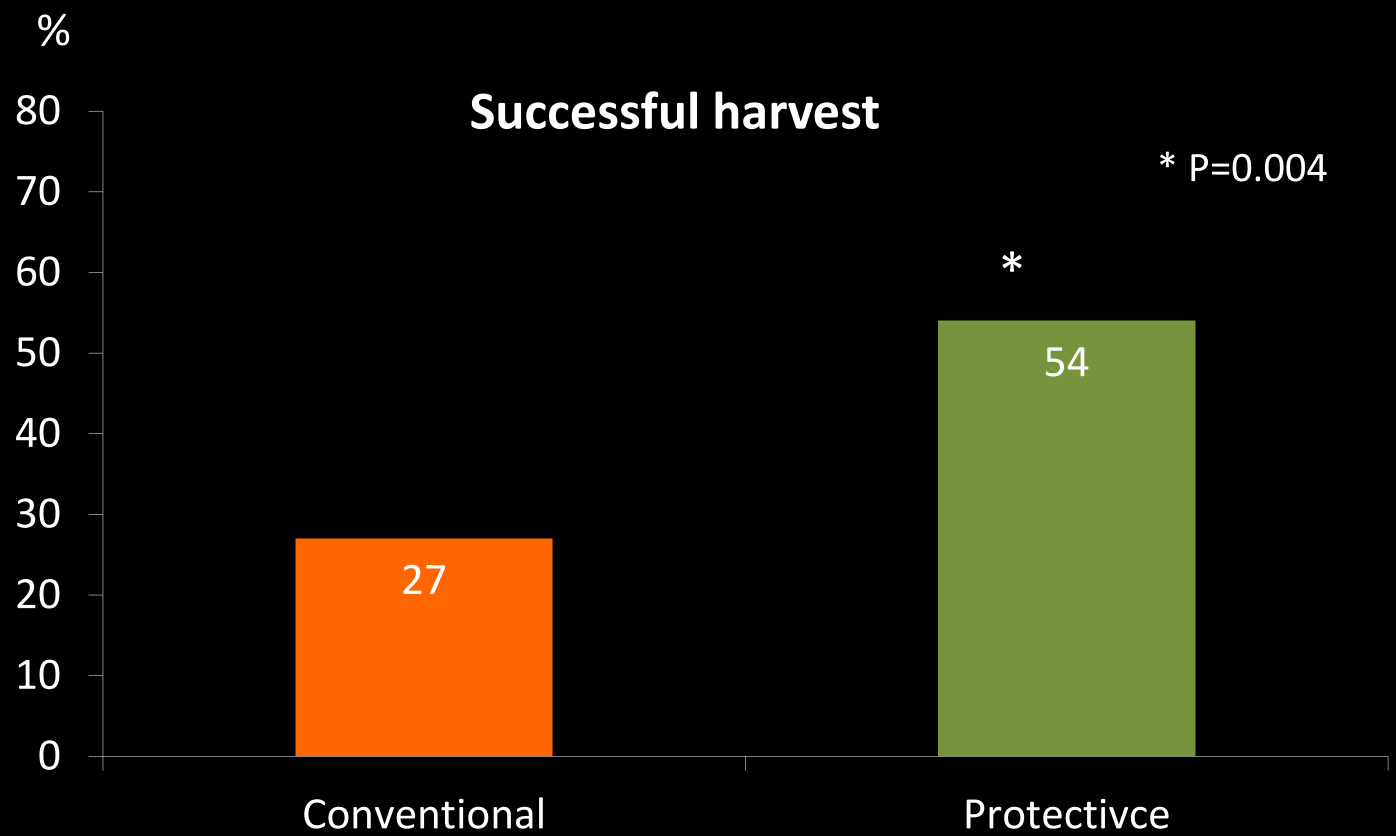
TABLE 4. MAIN OUTCOME VARIABLES.*

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



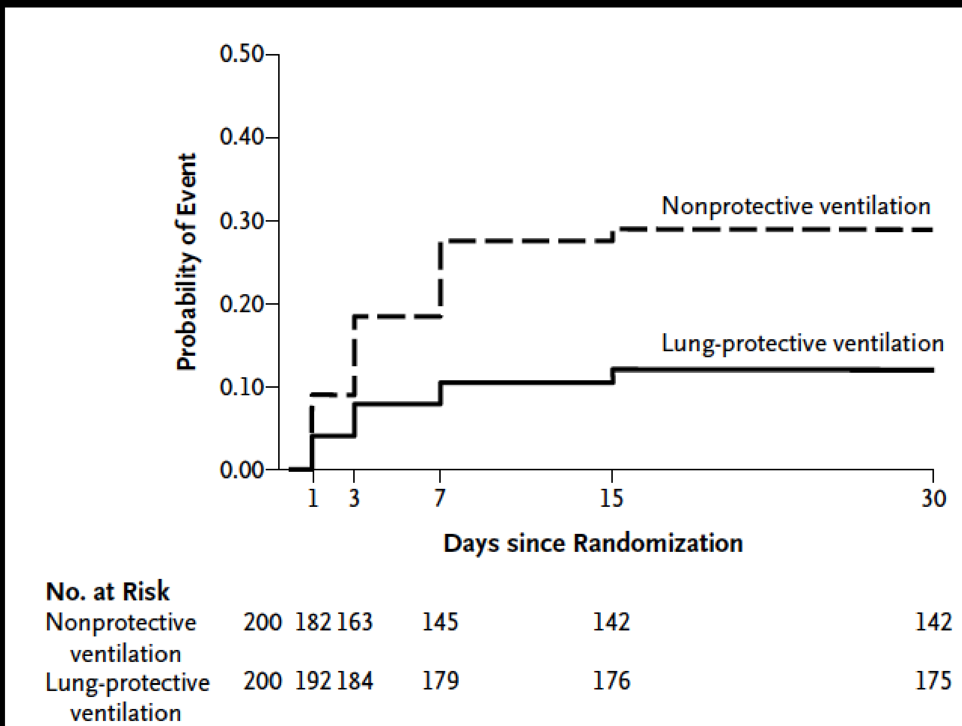
- The decrease was greater in the group treated with lower tidal volumes (P<0.001)
- The day 3 plasma interleukin-6 concentrations were also lower in this group (P=0.002).

Ventilator strategy influences organ harvest



JAMA. 2010;304(23):2620-2627

Lower intra-operative Vt for abdominal surgery



- 400 adults
  - Intermediate to high risk of pulmonary complications
  - Major abdominal surgery
  - Vt 6.4±0.8 vs 11.1±1.1
- Composite endpoint
  - Pulmonary
    - Pneumonia, need of MV
  - Extrapulmonary
    - Sepsis, death

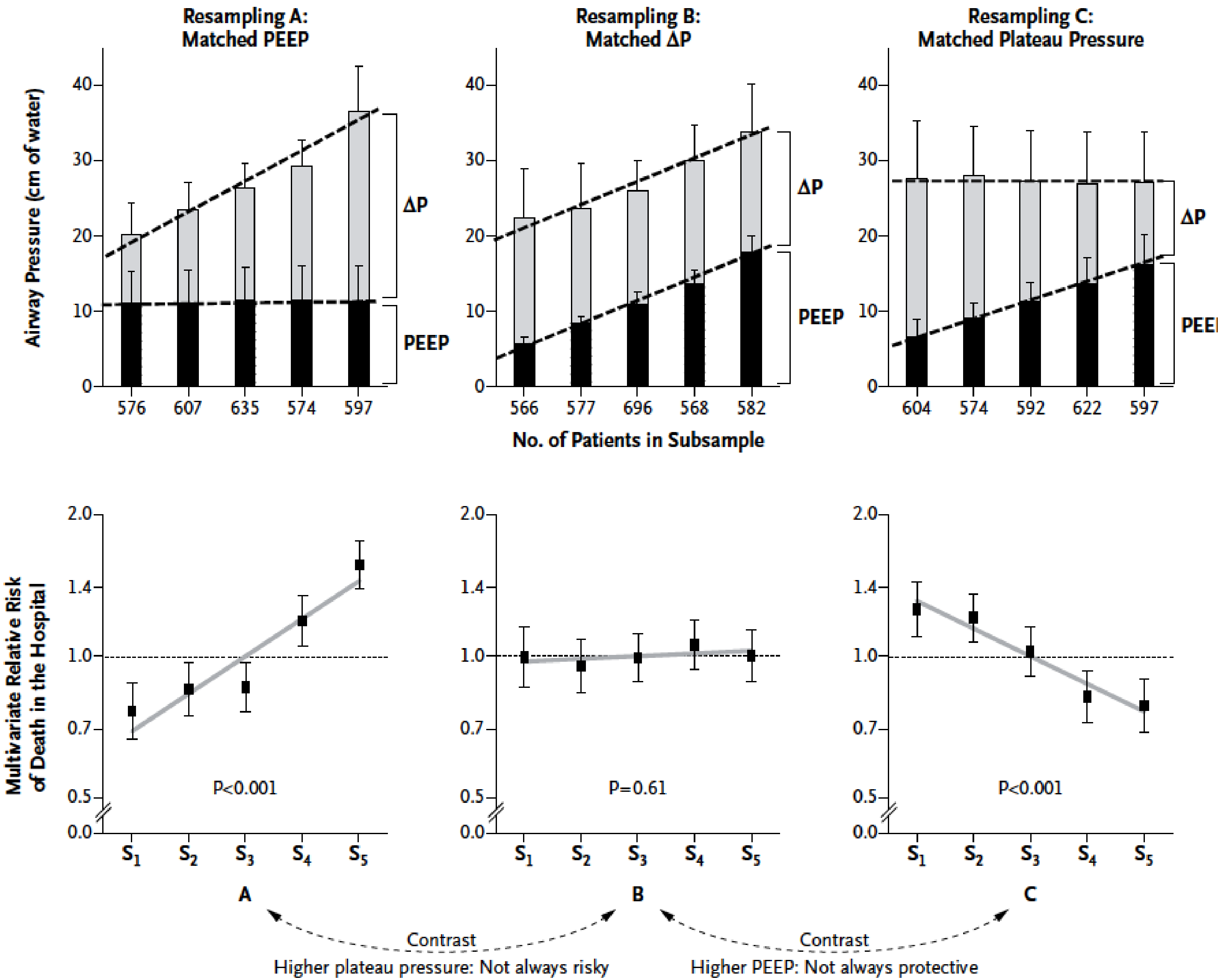
N Engl J Med 2013;369:428-37.

SPECIAL ARTICLE

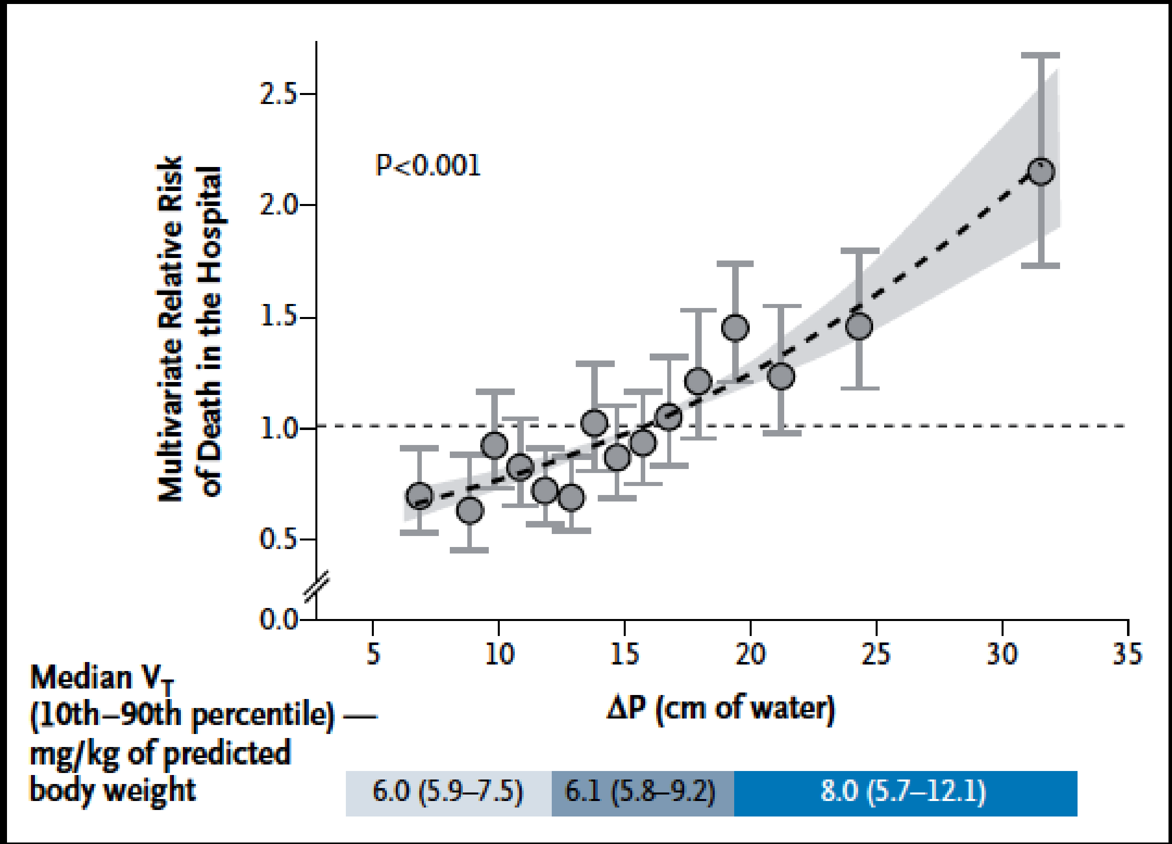
Driving Pressure and Survival in the Acute Respiratory Distress Syndrome

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

N Engl J Med 2015;372:747-55.


Resampling A: Matched PEEP
Resampling B: Matched ΔP
Resampling C: Matched Plateau Pressure
Airway Pressure (cm of water)
ΔP
PEEP
576 607 635 574 597
566 577 696 568 582
604 574 592 622 597
No. of Patients in Subsample
Multivariate Relative Risk of Death in the Hospital
P<0.001
P=0.61
P<0.001
A
B
C
Contrast
Higher plateau pressure: Not always risky
Contrast
Higher PEEP: Not always protective

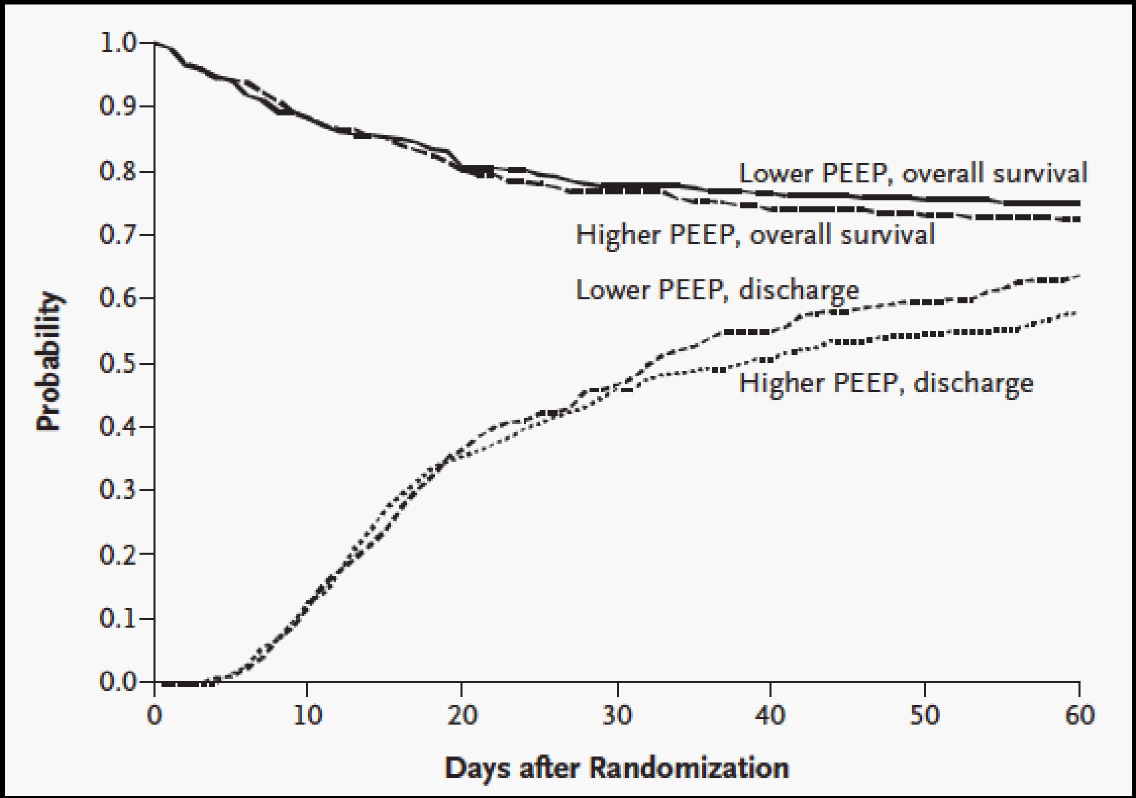
Driving pressure vs mortality



N Engl J Med 2015;372:747-55.

Higher vs Lower PEEP

The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network



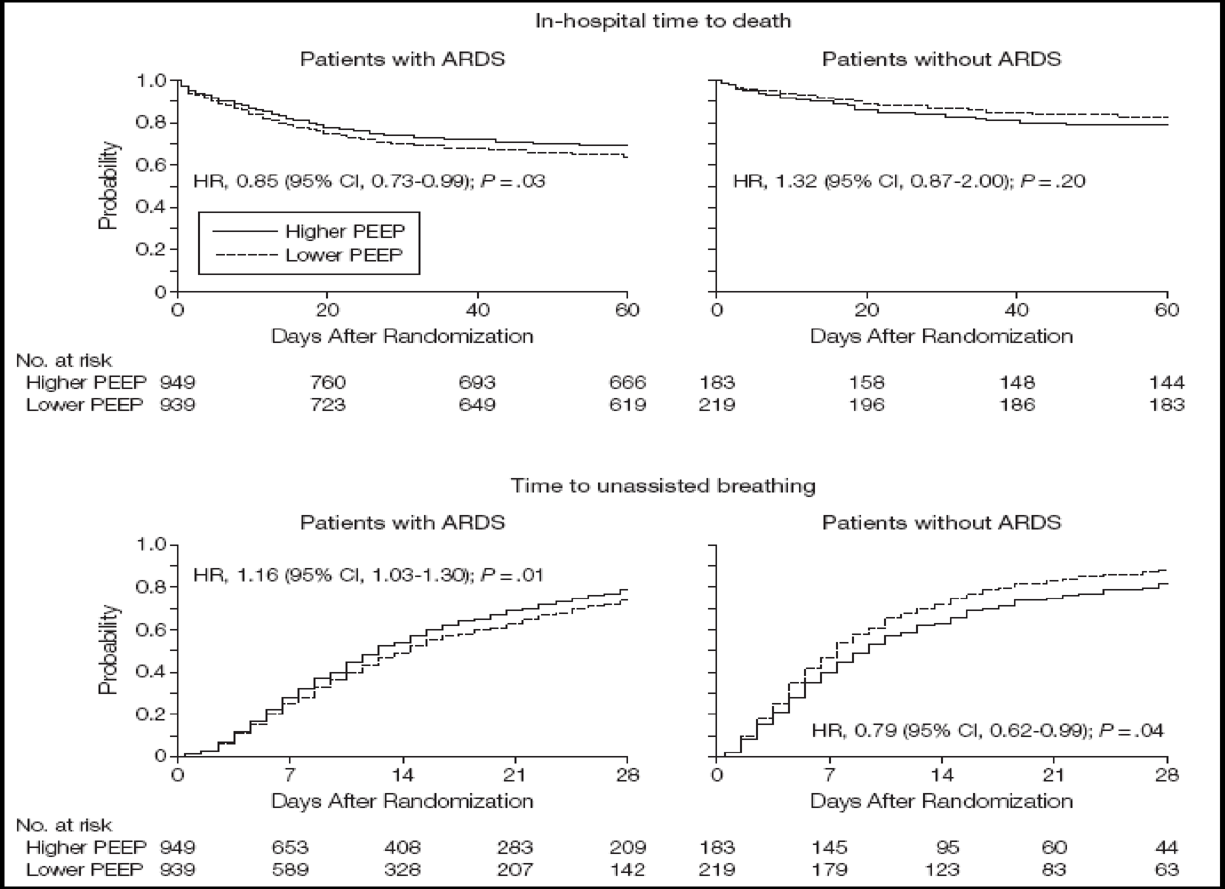
N Engl J Med 2004;351:327-36.

Table 1. Summary of Ventilator Procedures in the Lower- and Higher-PEEP Groups.*

Procedure	Value													
Ventilator mode	Volume assist/control													
Tidal-volume goal	6 ml/kg of predicted body weight													
Plateau-pressure goal	≤30 cm of water													
Ventilator rate and pH goal	6–35, adjusted to achieve arterial pH ≥7.30 if possible													
Inspiration:expiration time	1:1–1:3													
Oxygenation goal														
PaO_2	55–80 mm Hg													
SpO_2	88–95%													
Weaning	Weaning attempted by means of pressure support when level of arterial oxygenation acceptable with PEEP ≤8 cm of water and FiO_2 ≤0.40													
Allowable combinations of PEEP and FiO_2†														
Lower-PEEP group														
FiO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	5	8	8	10	10	10	12	14	14	14	16	18	18–24
Higher-PEEP group (before protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0	
PEEP	5	8	10	12	14	14	16	16	18	20	22	22	22–24	
Higher-PEEP group (after protocol changed to use higher levels of PEEP)														
FiO_2	0.3	0.3	0.4	0.4	0.5	0.5	0.5–0.8	0.8	0.9	1.0				
PEEP	12	14	14	16	16	18	20	22	22	22–24				

Higher vs Lower PEEP

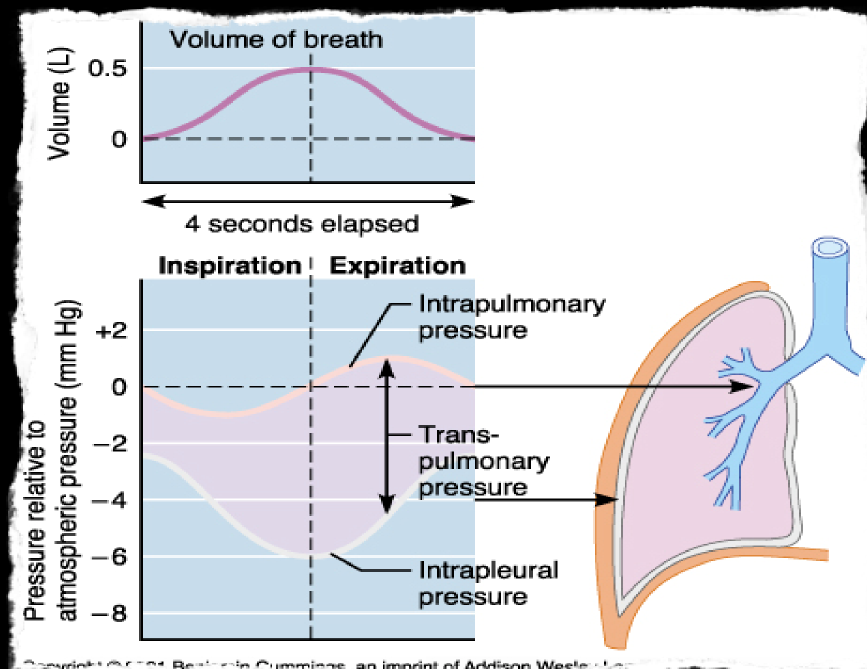
metaanalysis



JAMA. 2010;303(9):865-873

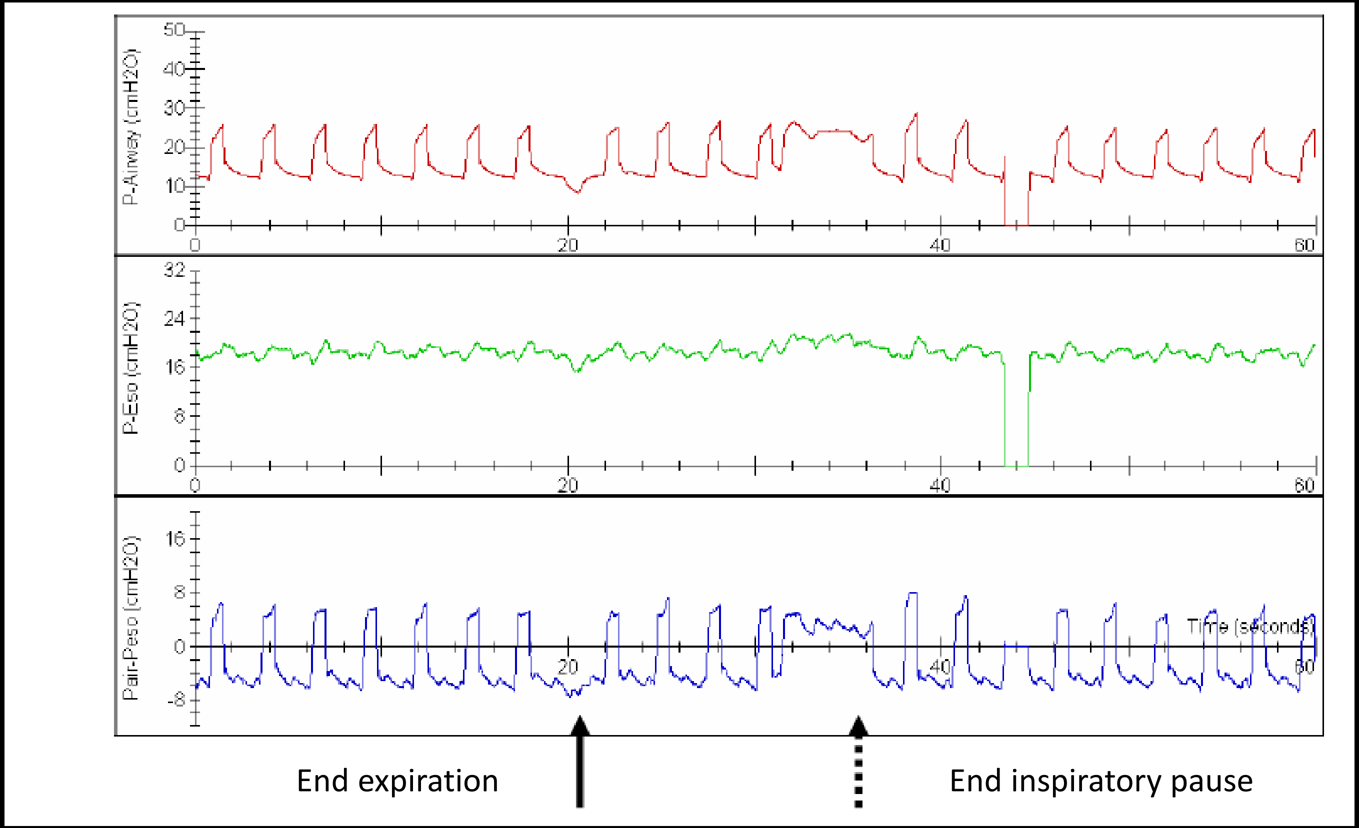
PEEP Guided by Esophageal Balloon

1. Optimal level of PEEP has been difficult to determine
2. Adjusting PEEP in according to lung and chest wall mechanics is achievable
3. Pao = flow x resistance + Vt/compliance
4. $P_{tp} = P_{aw} - P_{pleura}$ (P_{es})



Esophageal Balloon-Guide PEEP setting

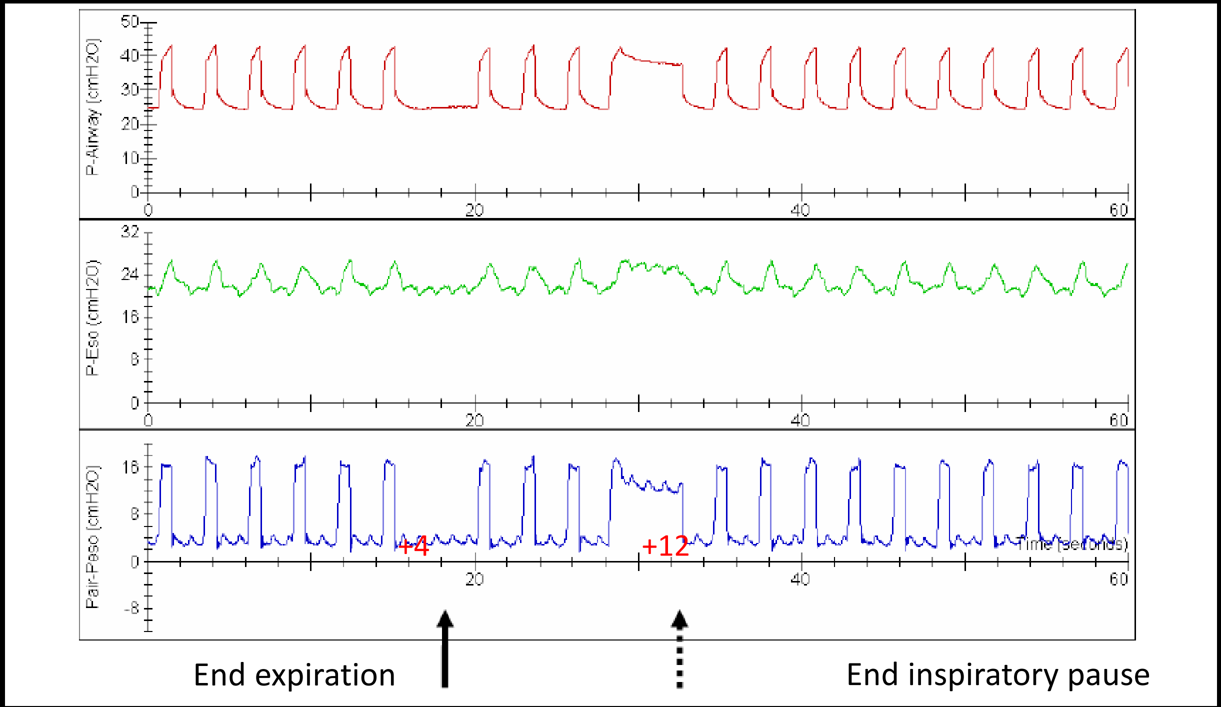
Vt 400ml, FiO2 0.6, PEEP 12, colon ca. with perforation and peritonitis



N Engl J Med 2008;359:2095-104.

Esophageal Balloon-Guide PEEP setting

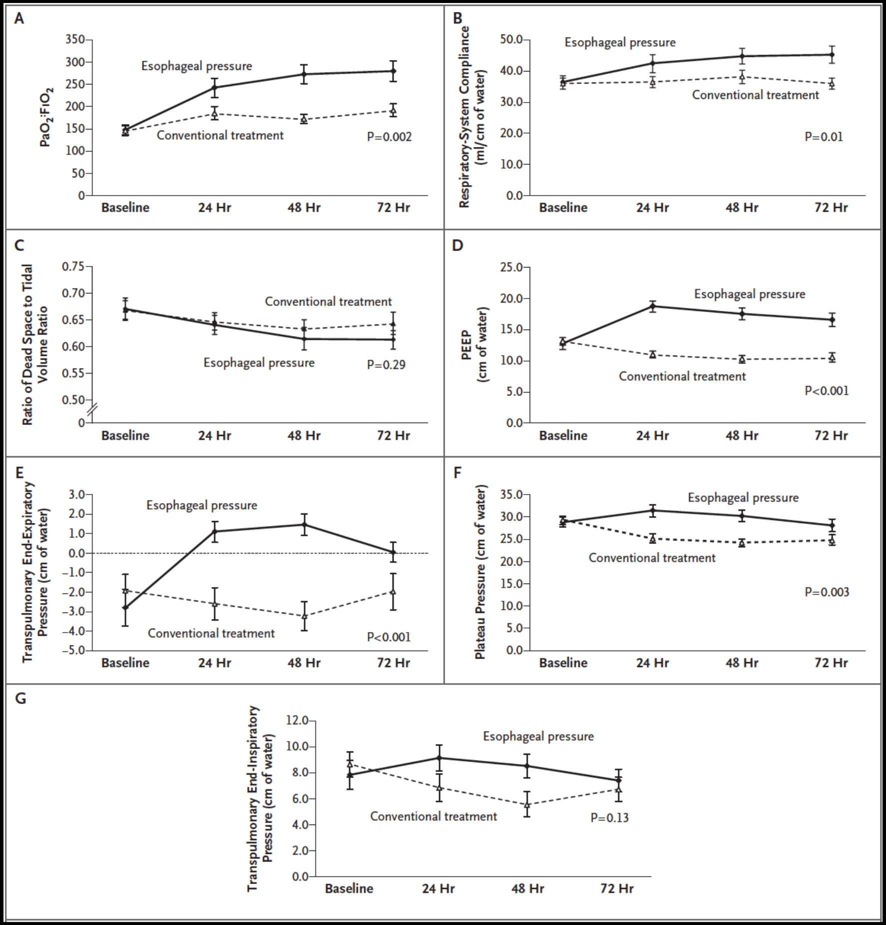
N Engl J Med 2008;359:2095-104.

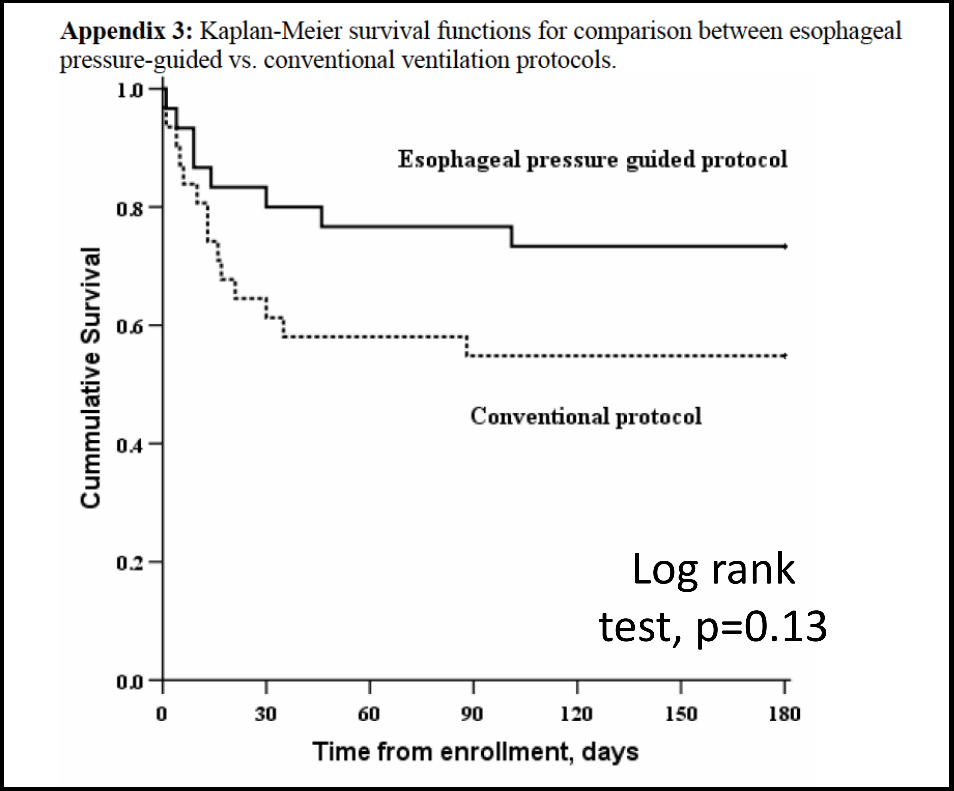


PEEP increase from 12 to 24 cm H_2O, Vt 320ml

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

Esophageal P. vs Conventional Tx





N Engl J Med 2008;359:2095-104.

Corticosteroid for persistent ARDS

- Double-blind, randomized controlled, NHLBI ARDSNet
- 180 patients with ADRS for more than 7 days, methylprednisolone vs placebo
- No differences of mortality at 60 and 180 days.
- Methylprednisolone is associated with higher ventilator and shock free days at 28 days
- Higher mortality in methylprednisolone group at least 14 days of ARDS

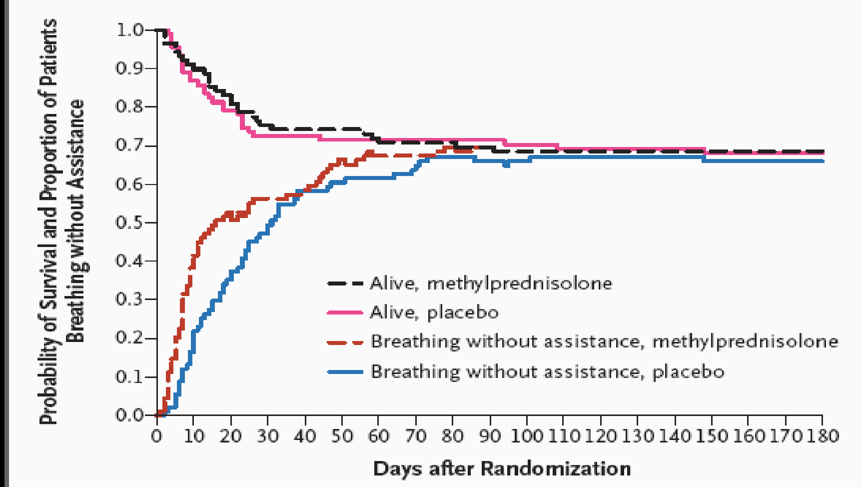


Figure 2. Probability of Survival and the Proportion of Patients with Persistent ARDS Who Became Able to Breathe without Assistance during the First 180 Days after Randomization.
At 180 days, 29 patients in the placebo group had died, 58 had been discharged home, and 4 had not been discharged home; the respective values in the methylprednisolone group were 28, 57, and 4. The status was known for all 180 patients at 180 days.

N Engl J Med 2006;354:1671-84.

Fluid management of ARDS

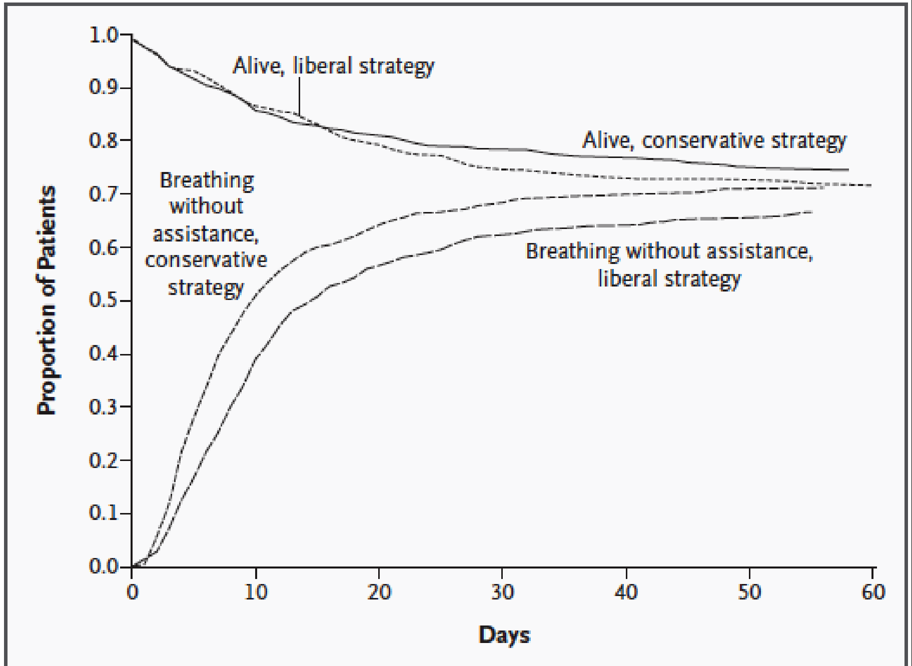
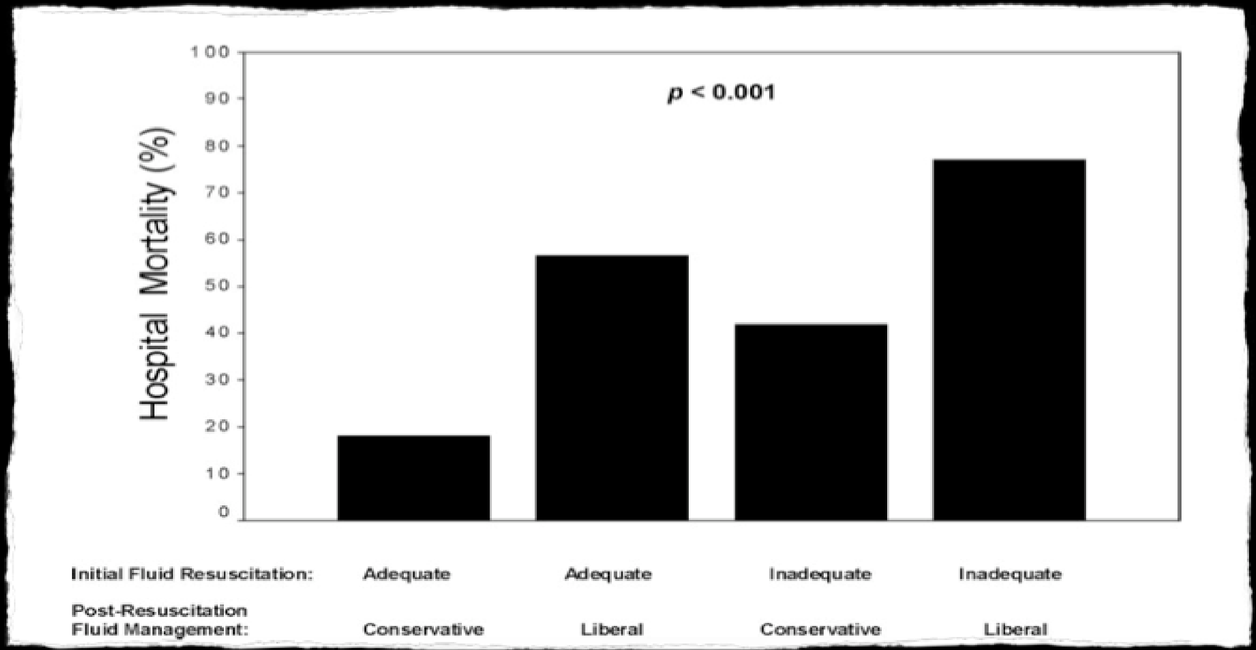


Figure 3. **Probability of Survival to Hospital Discharge and of Breathing without Assistance during the First 60 Days after Randomization.**

N Engl J Med 2006;354:2564-75.

Fluid management is important

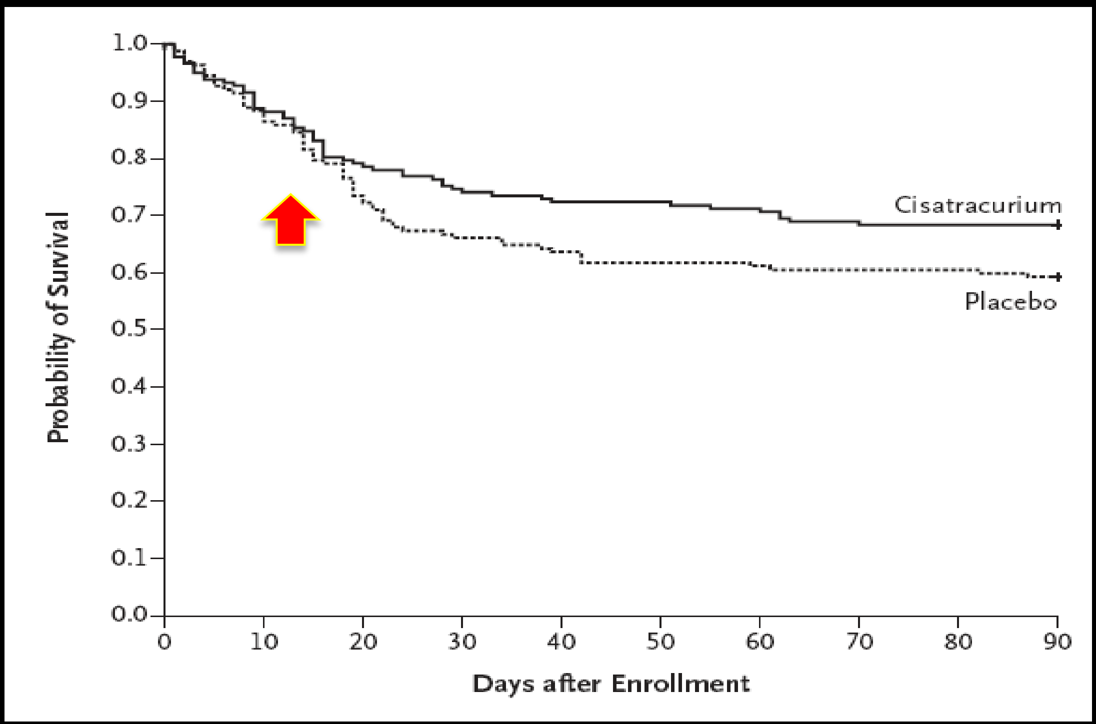


- **Adequate initial fluid resuscitation (AIFR)**
- **an initial fluid bolus of > 20 mL/kg prior to and achievement of a CVP of > 8 mm Hg within 6 h after he onset of therapy with vasopressors.**
- **Conservative late fluid management (CLFM)**
- **even-to-negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset.**

CHEST 2009; 136:102–109

Neuromuscular Blockade in Early ARDS

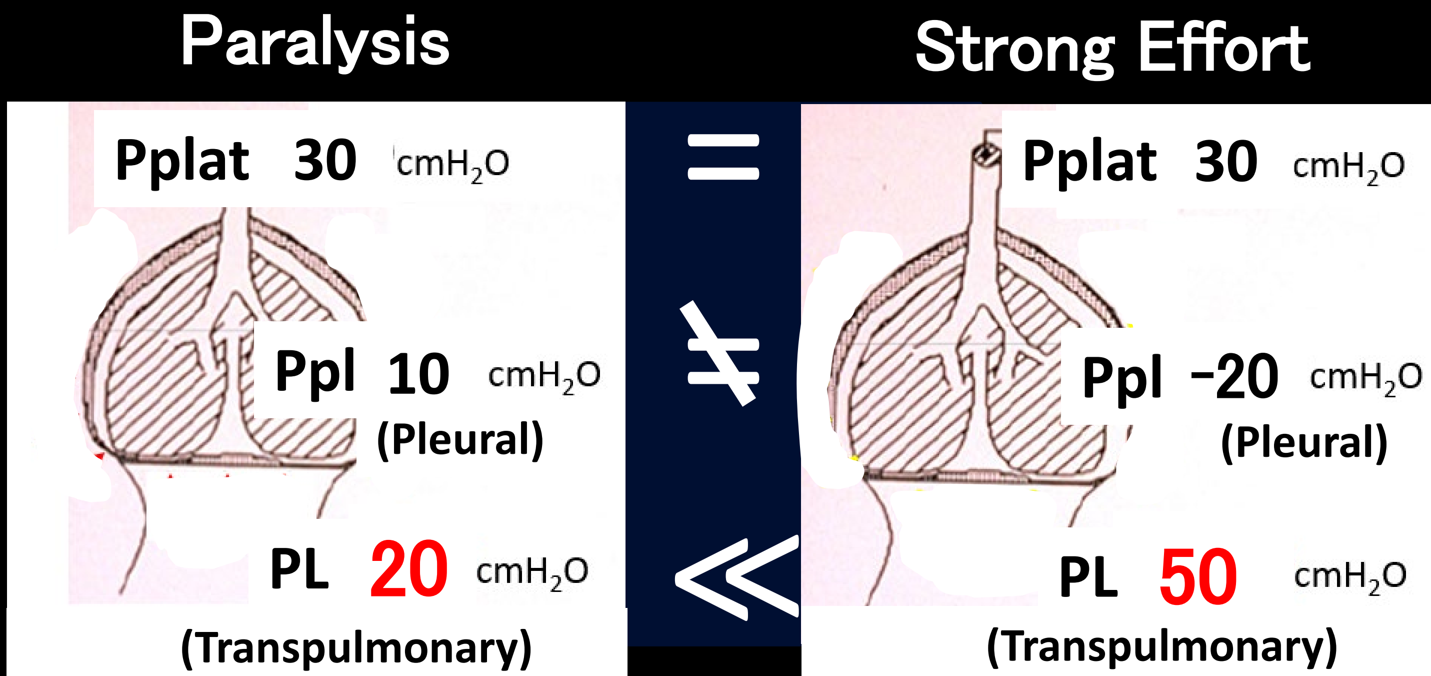
ACURASYS study



- Multi-center, double-blind, randomized controlled trial
- 340 patients with ARDS admitted to ICU within 48 hours
- Cisatracurium besylate v.s. placebl
- Hazard ratio of 90 days death in the cisatracurium v.s. placebo is 0.68 (95% CI, 0.48 to 0.98; P = 0.04),

N Engl J Med 2010;363:1107-16.

High P_L & Strong Effort

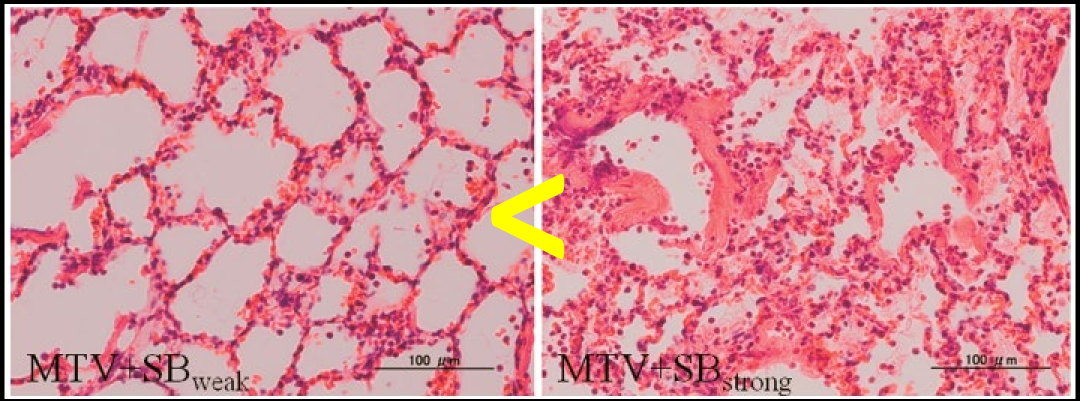


Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: High transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury*

Takeshi Yoshida, MD; Akinori Uchiyama, MD, PhD; Nariaki Matsuura, MD, PhD;
Takashi Mashimo, MD, PhD; Yuji Fujino, MD, PhD

(Crit Care Med 2012; 40:1578–1585)

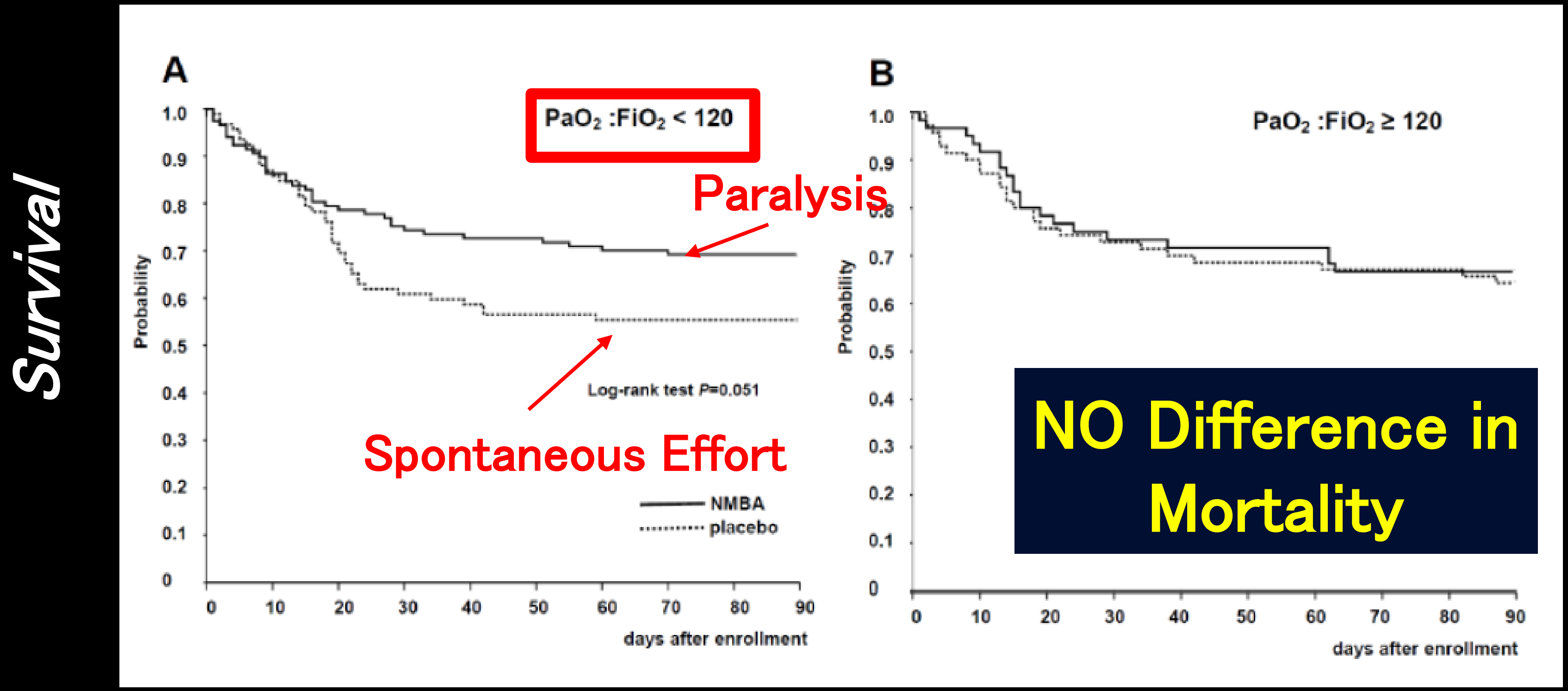
Weak Effort **Strong Effort**



Severe Lung Injury

Papazian L et al. *New Engl J Med* 2010

More Severe | *Less* Severe



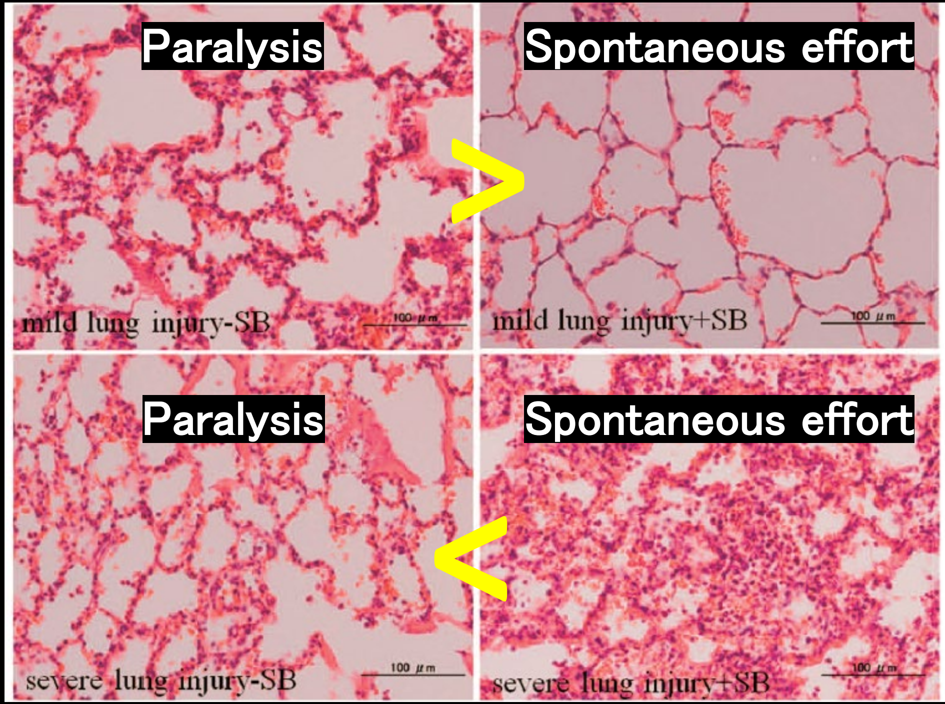
The Comparison of Spontaneous Breathing and Muscle Paralysis in Two Different Severities of Experimental Lung Injury*

Takeshi Yoshida, MD[1,2]; Akinori Uchiyama, MD, PhD[2]; Nariaki Matsuura, MD, PhD[3];
Takashi Mashimo, MD, PhD[2]; Yuji Fujino, MD, PhD[2]

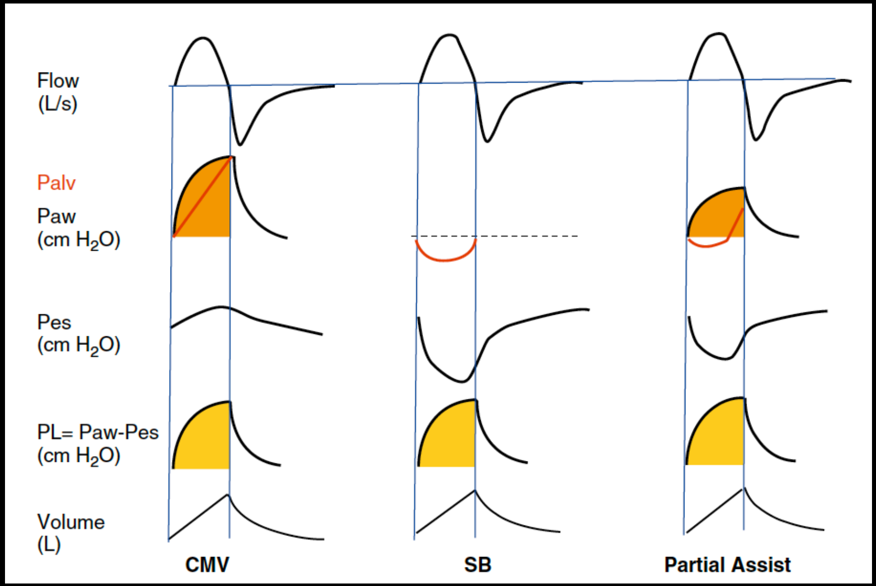
(*Crit Care Med* 2013; 41:536–545)

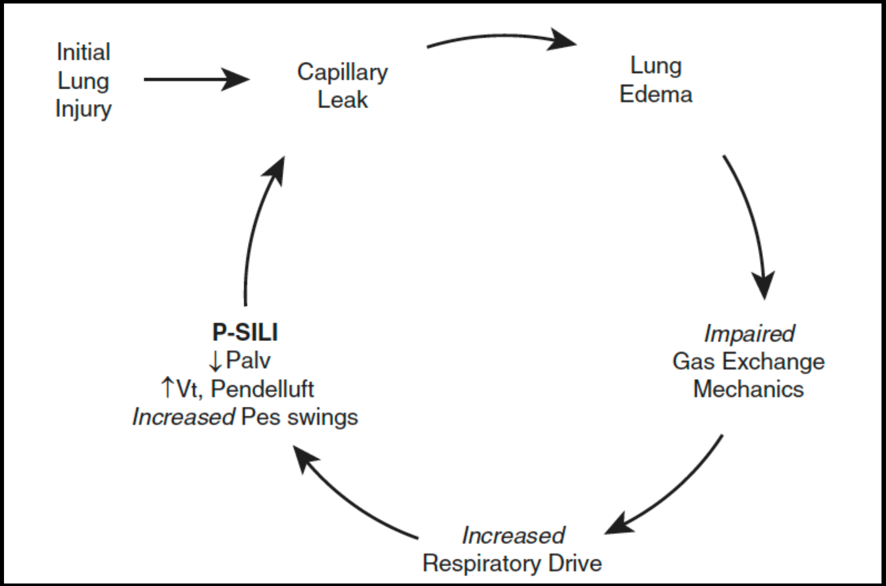
MILD
ARDS

SEVERE
ARDS



Patient self-inflicted lung injury

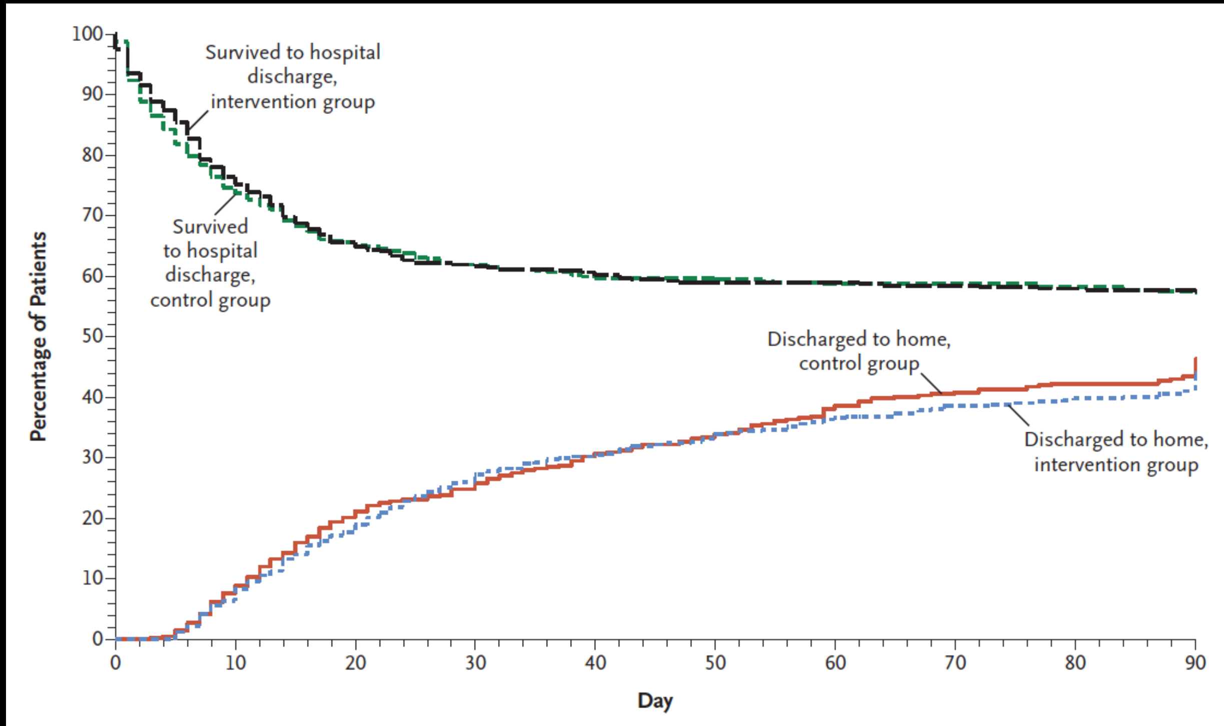




Am J Respir Crit Care Med Vol 195, Iss 4, pp 438–442

Early Neuromuscular Blockade in ARDS

ROSE trial, PETAL network



NEJM May 19, 2019

Table 1. Comparisons of the ACURASYS and ROSE Trials.*

Variable	ACURASYS Trial	ROSE Trial	Commentary
No. of centers (location)	20 ICUs (Europe)	48 hospitals (United States)	It is unlikely that different practices across the Atlantic would explain the different results of the two trials.
No. of patients (intervention group vs. control group)	340 (178 vs. 162)	1006 (501 vs. 505)	Estimates for sample-size calculations were different.
Trial design for group assignment	Double blind	Unblinded	Potential effect should be minimal.
ARDS definition	American–European consensus	Berlin criteria	It is unlikely that this difference had a major effect on the characteristics of patients enrolled in the trials.
Criteria for moderate-to-severe ARDS	Pa_{O_2}:F_{IO_2} <150 mm Hg with PEEP ≥5 cm of water	Pa_{O_2}:F_{IO_2} <150 mm Hg with PEEP ≥8 cm of water	ROSE allowed enrollment of patients with Pa_{O_2}:F_{IO_2} of 150–200 mm Hg after initial assessment but before randomization.
Median time from ARDS diagnosis to trial inclusion (IQR) — hr	16 (6–29)	8 (4–16)	Earlier inclusion time in ROSE may have resulted in enrollment of some patients who might have died before they could have been enrolled in ACURASYS.
Intervention vs. control strategies	Cisatracurium infusion plus deep sedation vs. deep sedation	Cisatracurium infusion plus deep sedation vs. light sedation	No routine neuromuscular blocking agents were allowed in the control groups.
Mechanical-ventilation approach	Lung-protective ventilation with low PEEP	Lung-protective ventilation with high PEEP	In the first 7 days, PEEP levels were higher by about 2–3 cm of water in ROSE than in ACURASYS.
Monitoring of patient–ventilator dyssynchrony	Not reported	Not reported	Ideally, future studies should assess dyssynchronies.
ICU-acquired paresis and long-term outcomes	No difference between groups	No difference between groups	Patients in the control group in ROSE had higher mean levels of activity to day 6 than patients in the intervention group.
Serious adverse events	Pneumothorax more frequent in the control group (11.7% vs. 4%)	Rates of overall barotrauma did not differ between groups	There were more acute cardiovascular events in the intervention group in ROSE than in the control group.

* Shown are comparisons between the ARDS et Curarisation Systematique (ACURASYS)[2] and Reevaluation of Systemic Early Neuromuscular Blockade (ROSE)[5] trials, which assessed the use of neuromuscular blocking agents in patients with moderate-to-severe acute respiratory distress syndrome (ARDS). ICU denotes intensive care unit, IQR interquartile range, Pa_{O_2}:F_{IO_2} the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, and PEEP positive end-expiratory pressure.

Arthur S. Slutsky et al NEJM 2019

Reverse Triggering

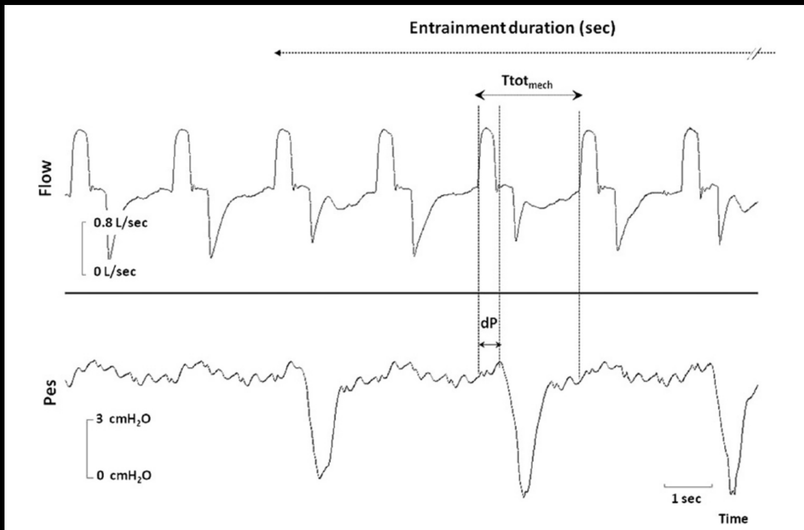
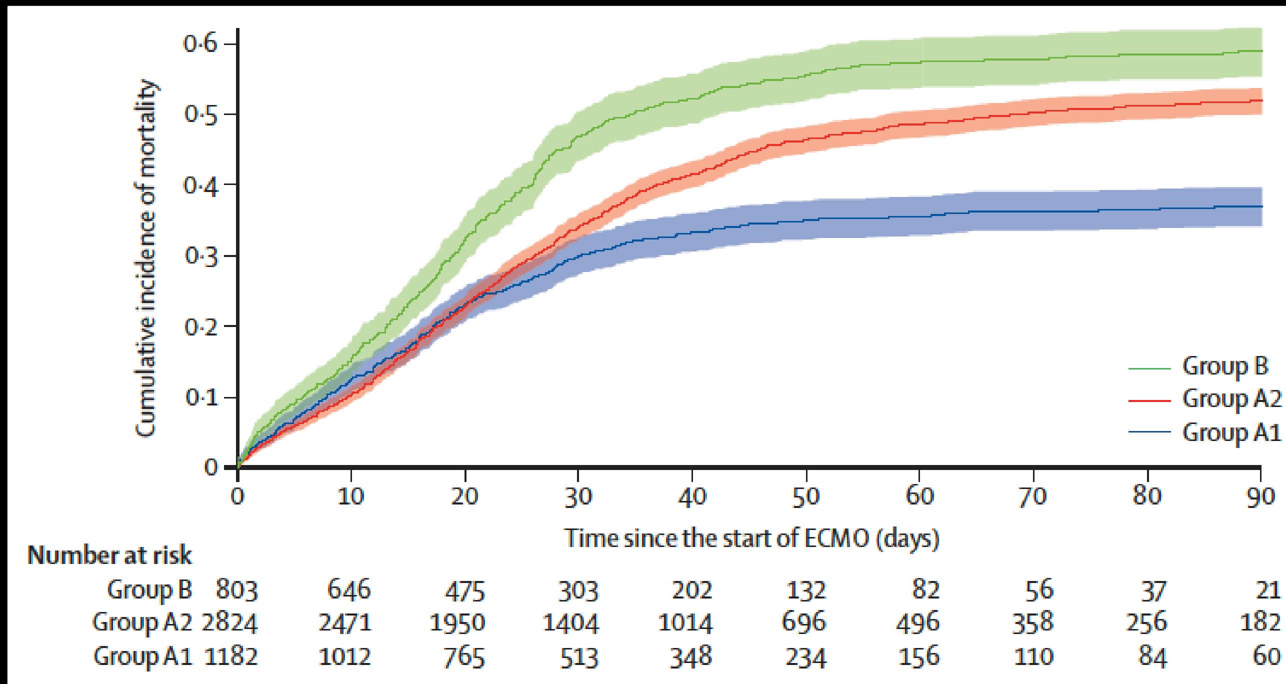


FIGURE 1. Definition of variables based on flow and Pes tracings. The entrainment duration in this patient was 32.17 s, and the entrainment ratio was 1:2 (one neural cycle every two mechanical cycles). Dotted lines denote the commencement of the mechanical and neural cycles. $Ttot_{mech}$ is the duration, in seconds, of the mechanical cycle, and dP is defined as the interval between the commencement of the mechanical and the neural inspiration. In this example, dP was 0.66 s and $Ttot_{mech}$ was 2.29 s. The phase angle (θ) was calculated as $\theta = dP/ Ttot_{mech} \times 360°$, resulting in a value of 104°. dP = phase difference; Pes = esophageal pressure; $Ttot_{mech}$ = ventilator cycle duration.

- Reverse triggering is a type of dyssynchrony that occurs when a patient effort occurs after ('is triggered by') the initiation of a ventilator (non-patient triggered) breath.
- Frequently recognized, in patients heavily sedated.
- Can be injurious, including breath stacking, pendelluft, excessive regional stress.

CHEST 2013; 143(4):927–938

ECMO for severe COVID-19 pneumonia



- ECMO on or before May 1, 2020 (group A1)
- Between May 2 and Dec 31, 2020 (group A2)
- Late-adopting centres were those that provided ECMO for COVID-19 only after May 1, 2020 (group B)

Lancet 2021; 398: 1230–38

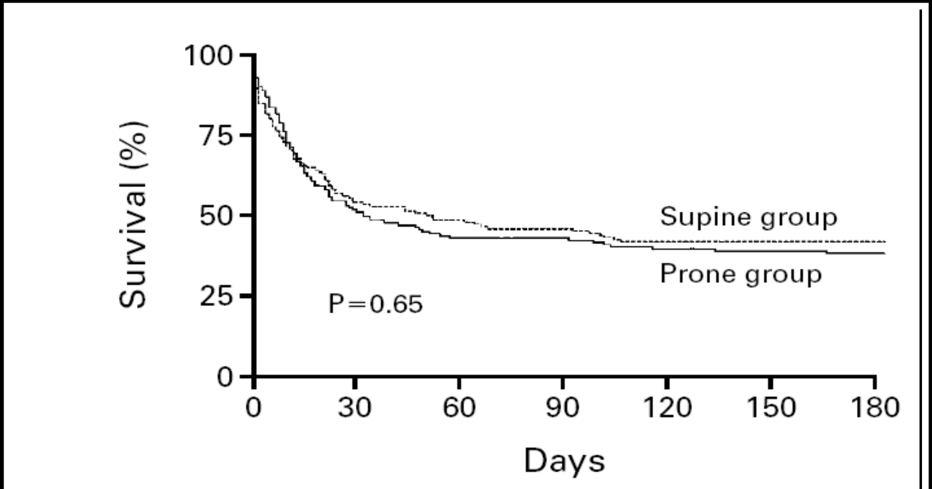

2002 06 18


2002 07 11


2002 06 11

Gattinoni's first trial

- Multi-center, randomized trial
  - December 1996 to October 1999
  - ALI and ARDS
  - 152 prone, 152 supine
  - prone position for 6 or more hours daily for 10 days

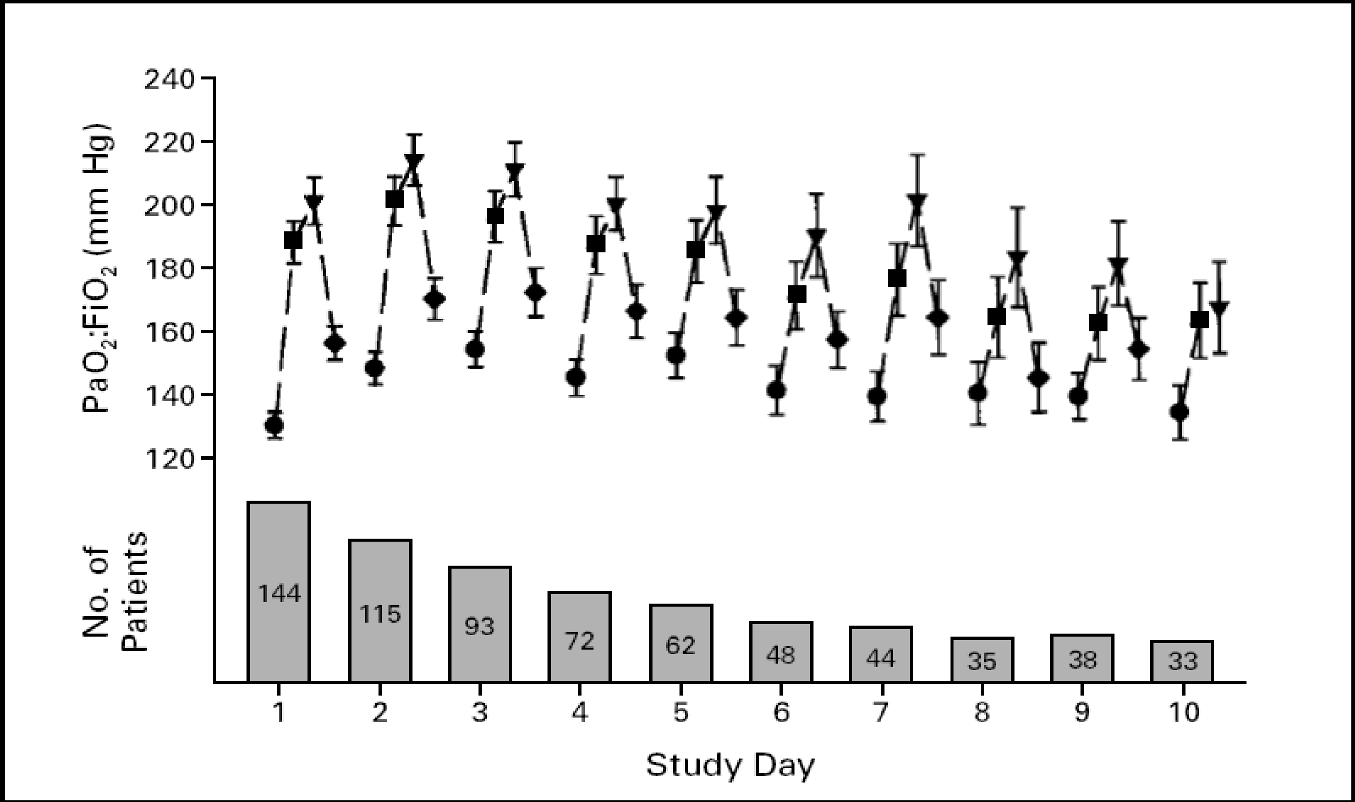


No. at Risk

Supine group	152	82	72	68	62	62	62
Prone group	152	78	63	63	58	57	56

Gattinoni L. et al N Engl J Med 2001;345:568-73

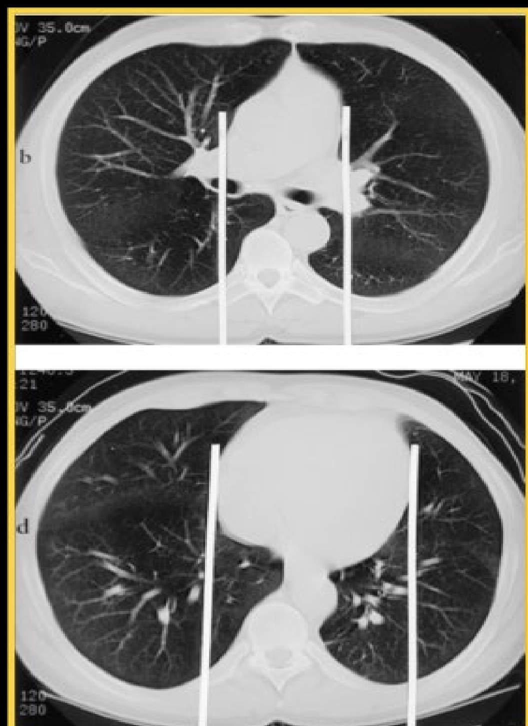
PPV Improves Oxygenation



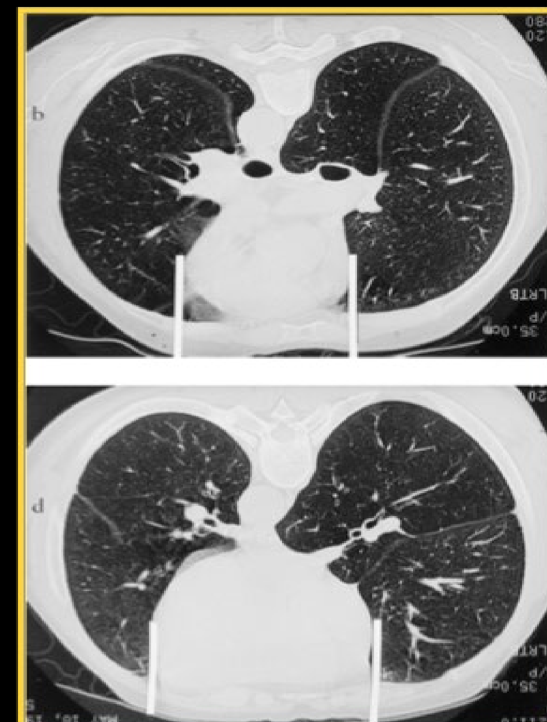
Gattinoni L. et al N Engl J Med 2001;345:568-73

Less Compression of Lungs by the Heart in Prone Position

Supine

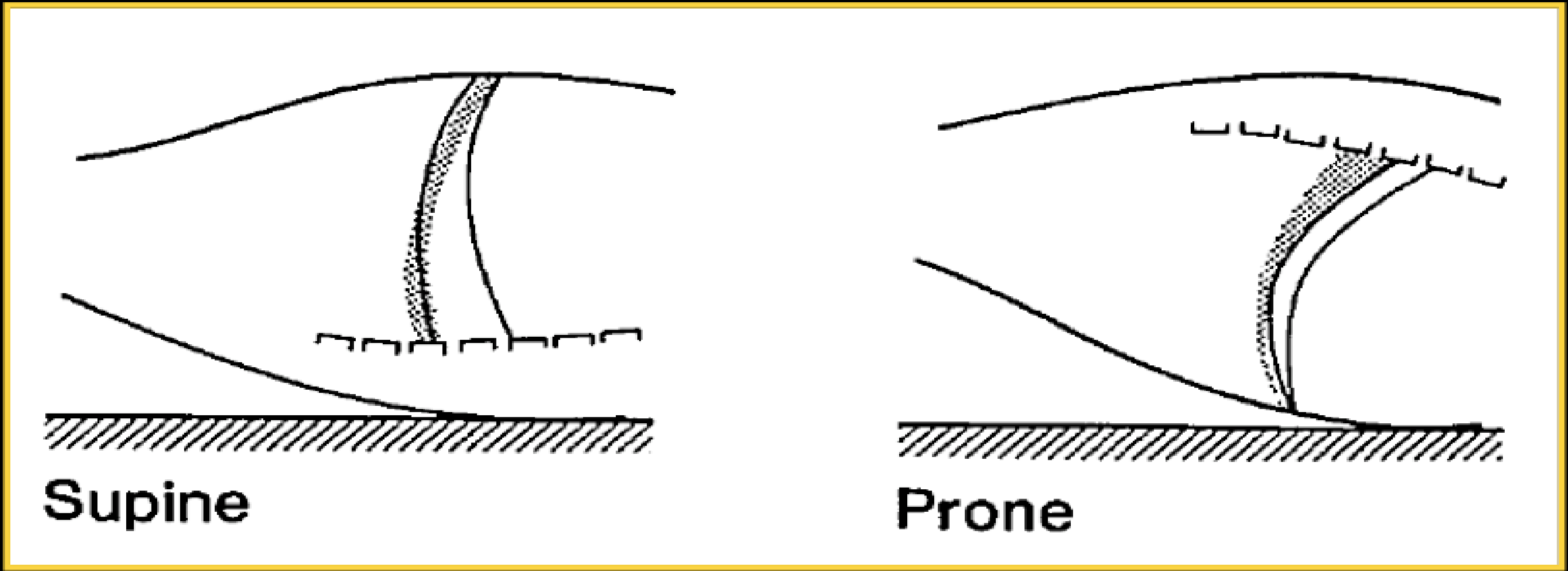


Prone

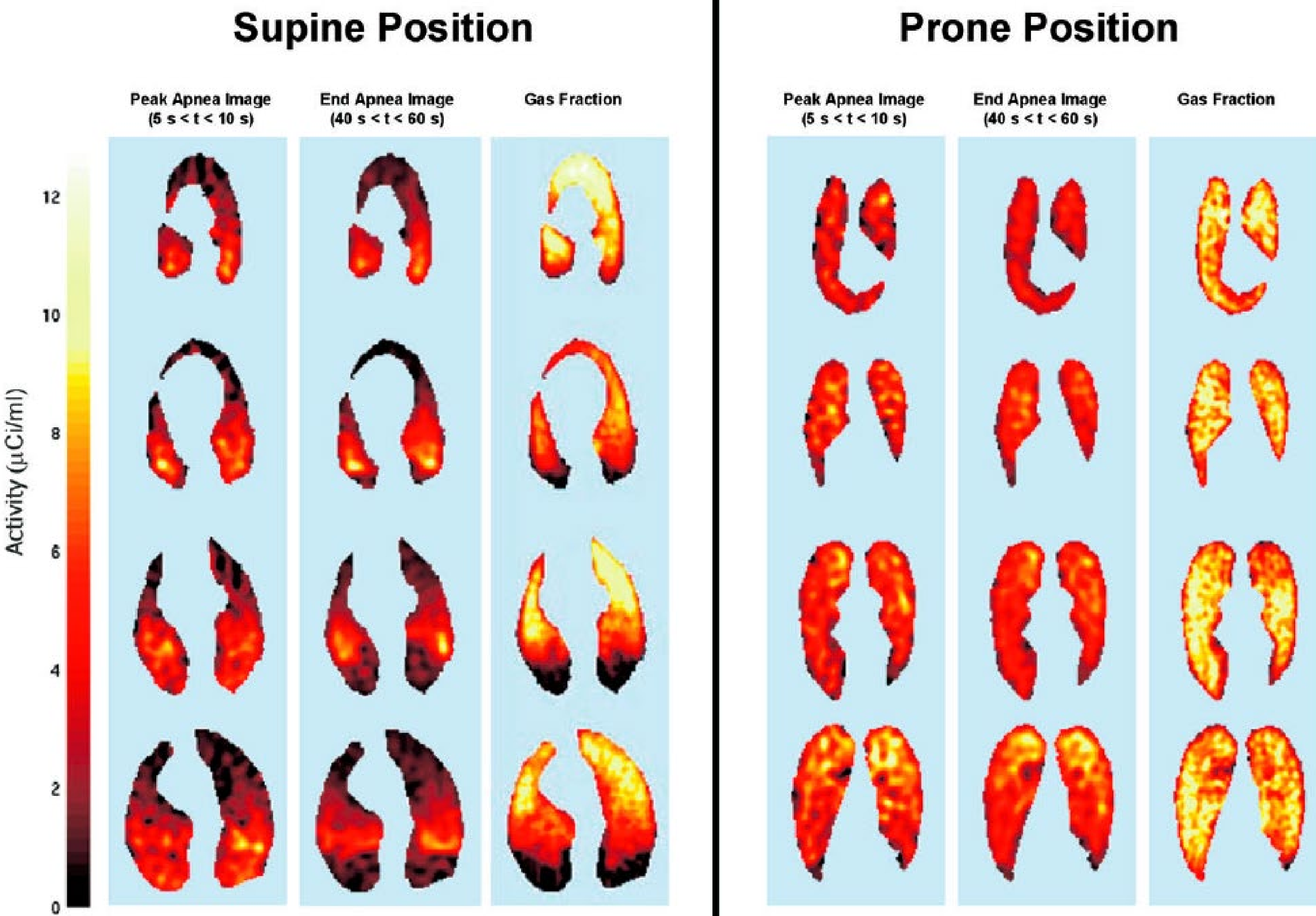


Am J Respir Crit Care Med Vol 161. pp 1660–1665, 2000

Diaphragm Excursion Between Supine and Prone



Anesthesiology 70:891-898; 1989



Am J Respir Crit Care Med Vol 172. pp 480–487, 2005

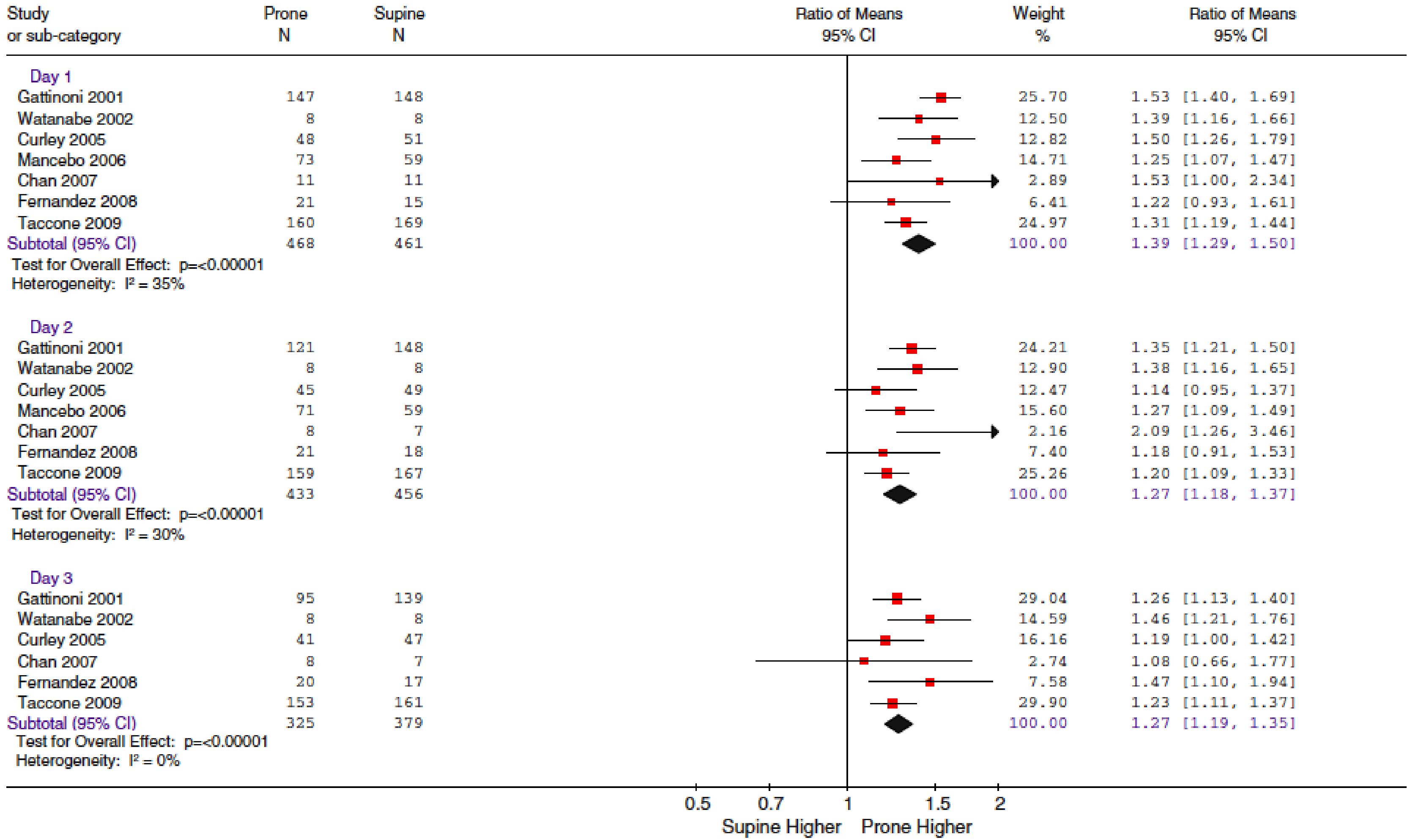
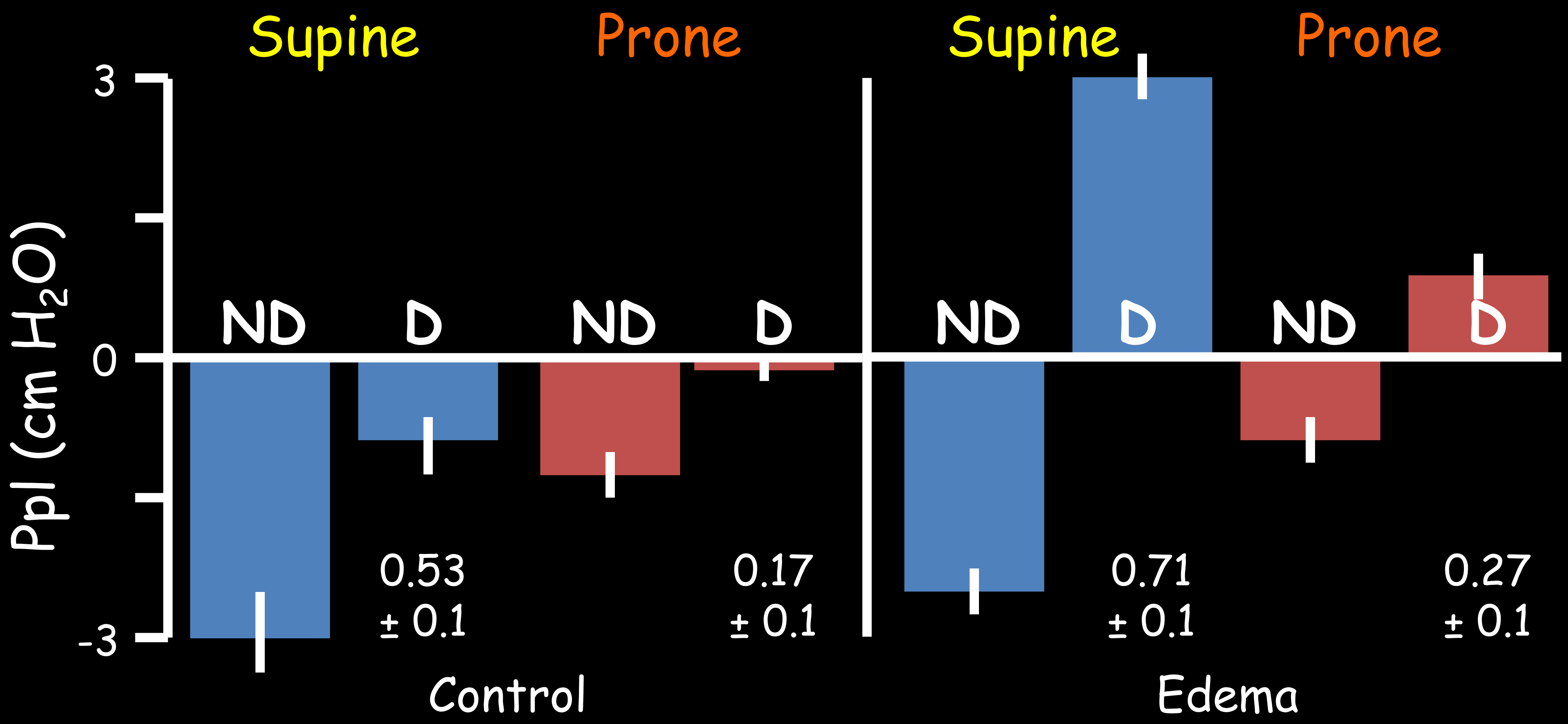


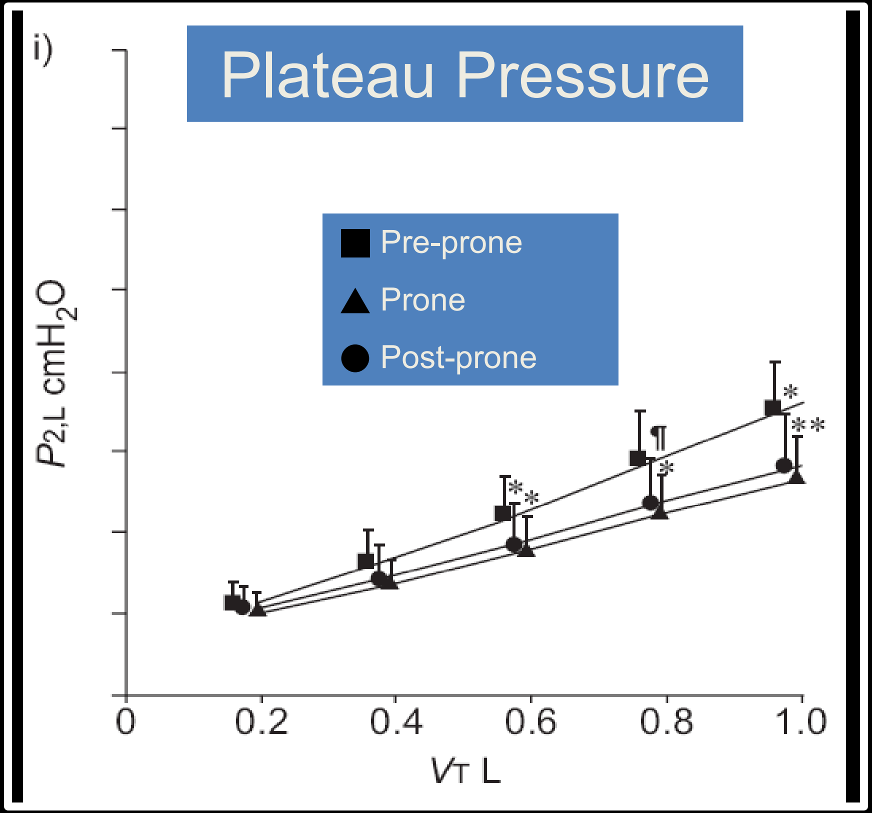
Fig. 4 Effect of prone ventilation on PaO_2 (partial pressure of arterial oxygen)/FiO_2 (inspired fraction of oxygen) on postrandomization calendar days 1–3. Ratio of means = mean PaO_2/FiO_2 in the prone group (in the prone position)/mean PaO_2/FiO_2 in the supine group (at the closest available time). Weight is the contribution of each study to the overall ratio of means. *CI* confidence interval, I^2 percentage of total variation across studies due to between-study heterogeneity rather than chance

Dual Effect of Prone Position on Ppl Gradient in ALI

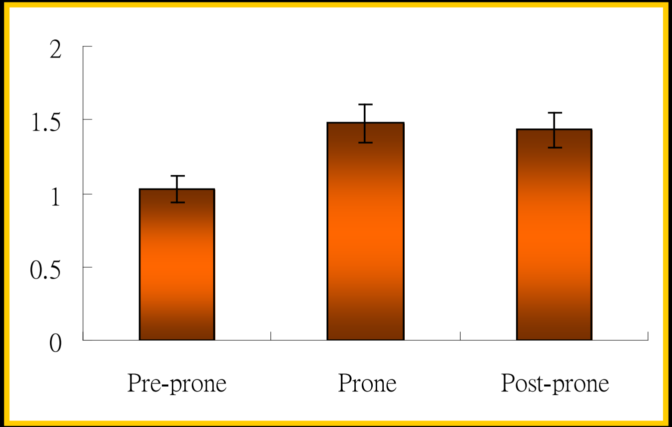


Mutoh, JAP 1992

Prone Position Reduces Lung Stress and Strain



EELV



End-Expiratory Lung Volume

Eur Respir J 2005; 25: 534–544

Big Trials of PPV

tendency of longer duration

TABLE I.—*Notable features of the largest randomised controlled clinical studies investigating the effect of prone positioning on the outcome of patients with hypoxemic acute respiratory failure.*

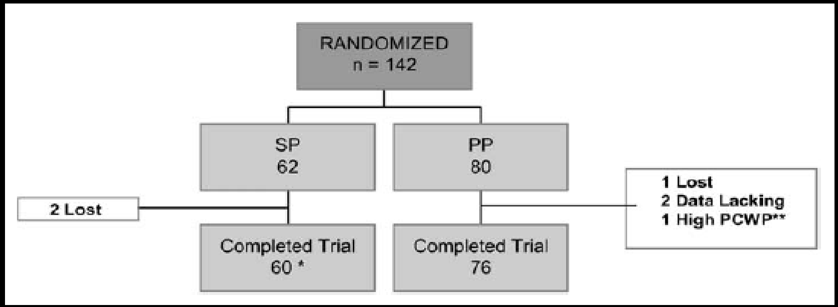
	Prone-supine II 2009[20]	Mancebo J *et al.* 2006[18]	Guérin C *et al.* 2004[16]	Prone-supine I 2001[15]
Patients (N.)	342	136	791	304
Enrollment period (years)	2004-2008	1998-2002	1998-2002	1996-1999
Enrollment rate	0.26 pts/ICU/m	0.24 pts/ICU/m	0.24 pts/ICU/m	0.28 pts/ICU/m
Enrollment criteria	ARDS with PEEP≥5 cmH_2O	ARDS with four-quadrant infiltrates at CXR	Hypoxaemic acute respiratory failure (413 ALI/ARDS pts)	ALI/ARDS with PEEP≥5 cmH_2O
Last follow-up available	At 6 months	At hospital discharge	At 3 months	At 6 months
Actual duration of prone positioning (average)	18 hours for 8.3 days	17 hours for 10.1 days	9 hours for 4.1 days	7 hours for 4.7 days

ALI: acute lung injury; ARDS: acute respiratory distress syndrome; CXR: chest X-ray; ICU: intensive care unit; m: month; PEEP: positive end-expiratory pressure; pts: patients.

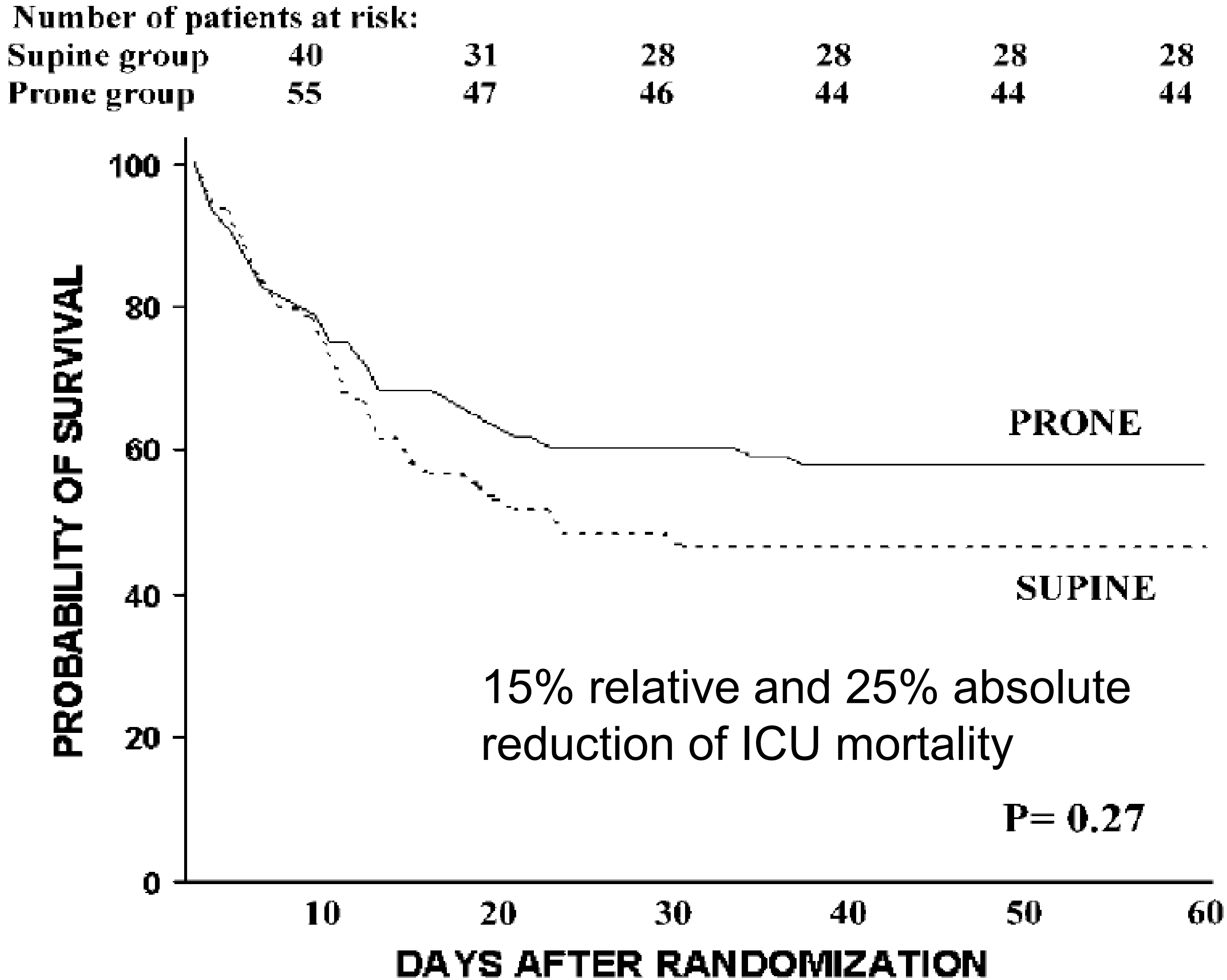
Minerva Anestesiol 2010;76:448-54)

Mancebo's trial

- Multicenter, randomized trial
  - From Dec. 1998 to Sep. 2002
  - Severe ARDS
  - 60 supine, 72 prone, total 132 patients
  - Continuous prone ventilation for 20h/day
  - Standardized guidelines for ventilator setting, weaning and sedation



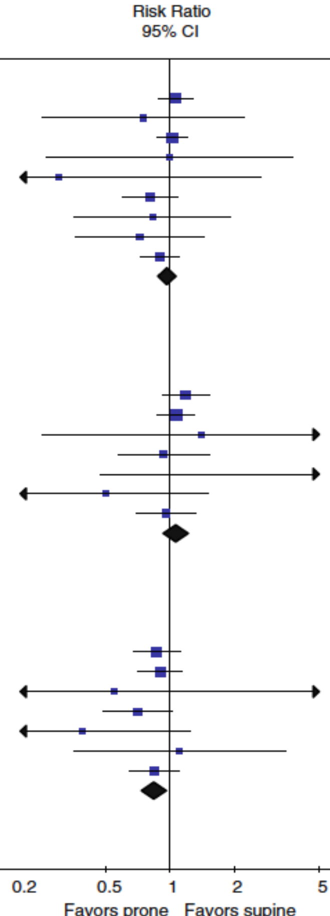
Am J Respir Crit Care Med Vol 173. pp 1233–1239, 2006



Number of patients at risk:
Supine group 40 31 28 28 28 28
Prone group 55 47 46 44 44 44
PROBABILITY OF SURVIVAL
100
80
60
40
20
0
PRONE
SUPINE
15% relative and 25% absolute reduction of ICU mortality
P= 0.27
10
20
30
40
50
60
DAYS AFTER RANDOMIZATION

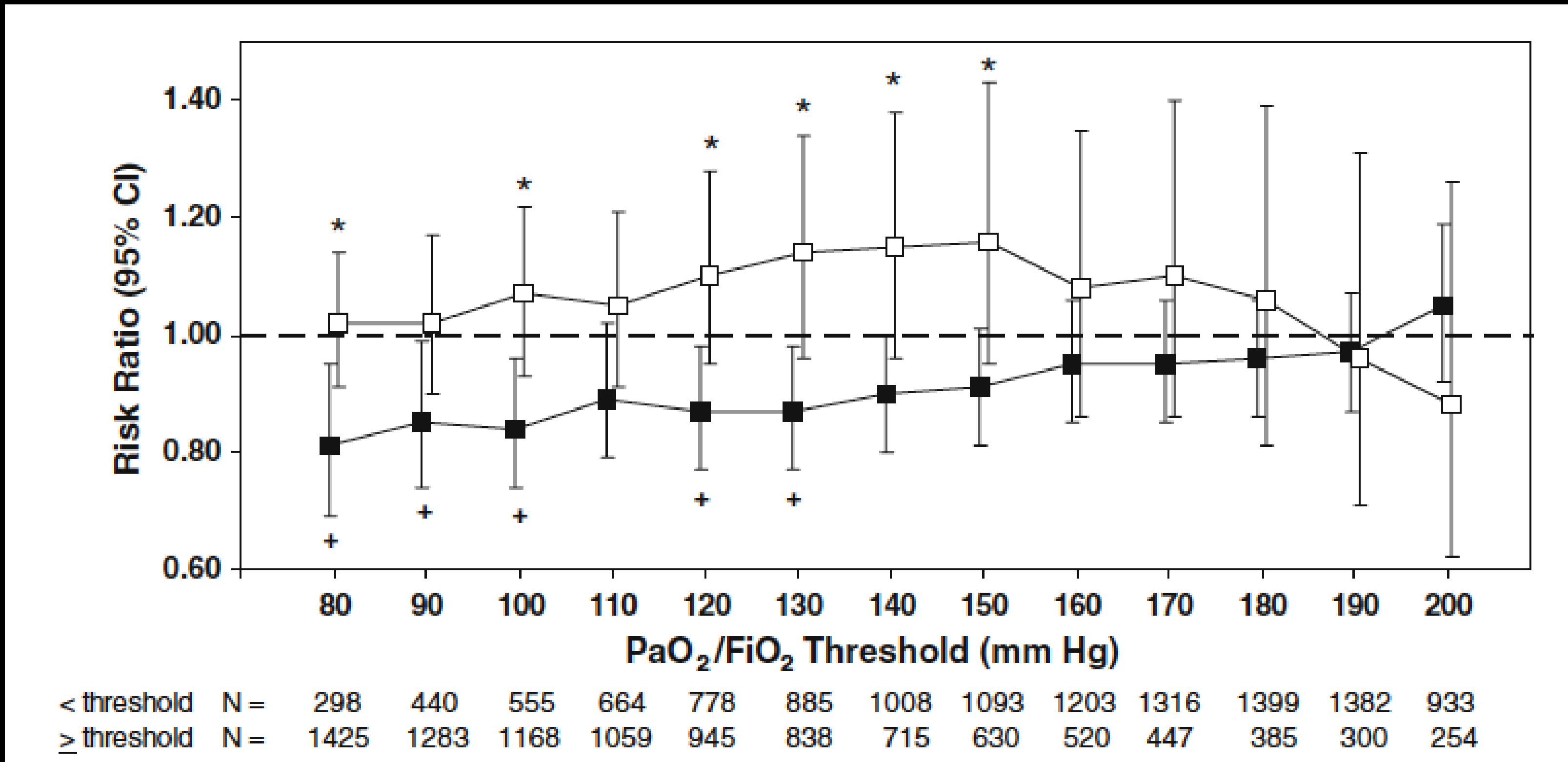
PPV reduces mortality in low PF ratio patients

Study or sub-category	Prone n/N	Supine n/N	Weight %	Risk Ratio 95% CI
All Patients				
Gattinoni 2001	92/148	87/149	27.67	1.06 [0.88, 1.28]
Beuret 2002	4/12	4/9	0.81	0.75 [0.25, 2.22]
Guerin 2004	179/413	159/377	36.18	1.03 [0.87, 1.21]
Curley 2005	4/51	4/51	0.53	1.00 [0.26, 3.78]
Voggenreiter 2005	1/21	3/19	0.20	0.30 [0.03, 2.66]
Mancebo 2006	38/76	37/60	10.47	0.81 [0.60, 1.10]
Chan 2007	5/11	6/11	1.33	0.83 [0.36, 1.94]
Fernandez 2008	8/21	10/19	1.97	0.72 [0.36, 1.45]
Taccone 2009	79/166	91/172	20.84	0.90 [0.73, 1.11]
Subtotal (95% CI)	410/919	401/867	100.00	0.97 [0.88, 1.07]
Test for Overall Effect: p=0.54				
Heterogeneity: I² = 0%				
$PaO_2/FiO_2 \geq 100$ Subgroup				
Gattinoni 2001	57/95	52/103	28.45	1.19 [0.92, 1.53]
Guerin 2004	126/323	110/302	44.31	1.07 [0.88, 1.31]
Curley 2005	3/30	2/28	0.62	1.40 [0.25, 7.77]
Mancebo 2006	16/33	16/31	7.54	0.94 [0.58, 1.53]
Chan 2007	3/4	0/4	0.25	7.00 [0.47, 103.27]
Fernandez 2008	3/12	7/14	1.46	0.50 [0.16, 1.52]
Taccone 2009	40/93	43/96	17.37	0.96 [0.70, 1.33]
Subtotal (95% CI)	248/590	230/578	100.00	1.07 [0.93, 1.22]
Test for Overall Effect: p=0.35				
Heterogeneity: I² = 0%				
$PaO_2/FiO_2 < 100$ Subgroup				
Gattinoni 2001	35/53	35/46	28.31	0.87 [0.67, 1.12]
Guerin 2004	53/90	49/75	31.56	0.90 [0.71, 1.14]
Curley 2005	1/21	2/23	0.33	0.55 [0.05, 5.61]
Mancebo 2006	22/43	21/29	13.25	0.71 [0.49, 1.02]
Chan 2007	2/6	6/7	1.31	0.39 [0.12, 1.25]
Fernandez 2008	5/9	2/4	1.38	1.11 [0.36, 3.48]
Taccone 2009	39/73	48/76	23.86	0.85 [0.64, 1.11]
Subtotal (95% CI)	157/295	163/260	100.00	0.84 [0.74, 0.96]
Test for Overall Effect: p=0.01				
Heterogeneity: I² = 0%				



Intensive Care Med (2010) 36:585–599

Mortality Benefits in Low P/F patients



Intensive Care Med (2010) 36:585–599

Lessons From Gattinoni's Study

- Short duration of prone position ventilation
  - Six hours per day
- Late application of Prone Position Ventilation
  - More than 20% patients has pressure sore at entry
- High tidal volume
  - 10.3ml/kg of predicted body weight
  - Higher tidal volume in prone group

The NEW ENGLAND JOURNAL of MEDICINE

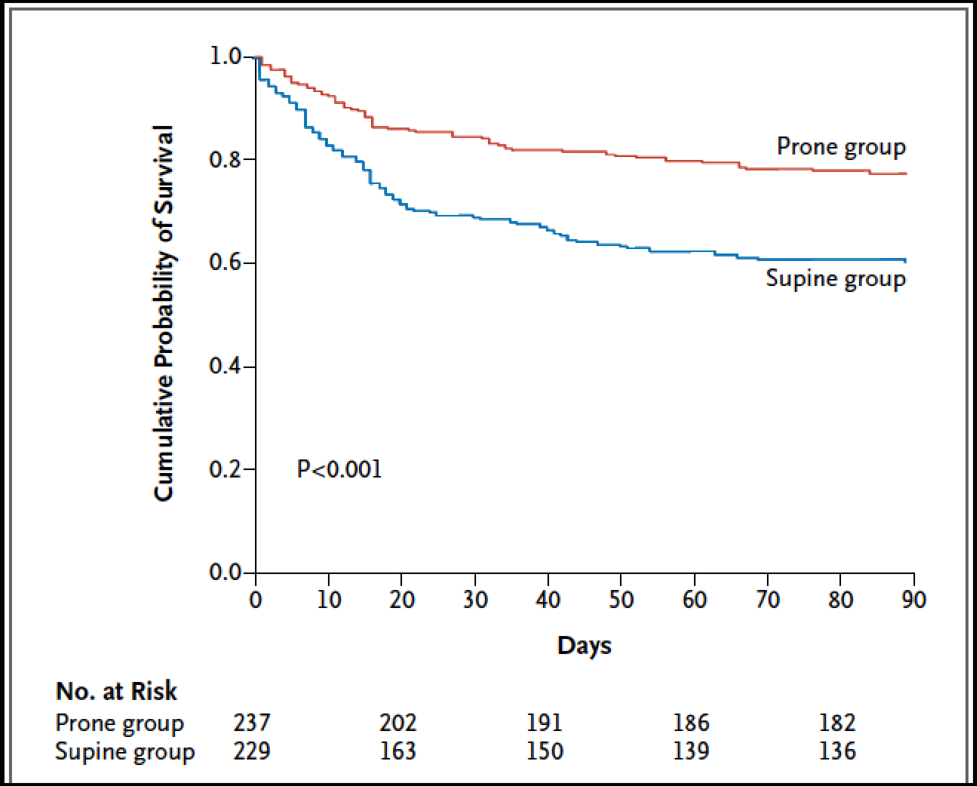
ESTABLISHED IN 1812 JUNE 6, 2013 VOL. 368 NO. 23

Prone Positioning in Severe Acute Respiratory Distress Syndrome

- Hypothesis: Prone ventilation will decrease VILI and thus decrease mortality
- Methods:
    - ARDS with P/F < 150 on FiO_2 > 0.6 & PEEP > 5 cmH_2O on Vt 6ml/kg
    - Criteria confirmed 12-24 hours later
    - Prone for more than 16 hours per day
    - Sample size: 460 patients
    - Primary outcome: 30 day mortality

Prone positioning in severe ARDS

- Multicenter, prospective, randomized, controlled trial
- 446 patients
  - 237 prone, 229 supine
- Severe ARDS
  - P/F ratio < 150
  - $FiO_2 \geq 0.6$
  - PEEP ≥ 5 cm H_2O
- ≥ 16 hours/day



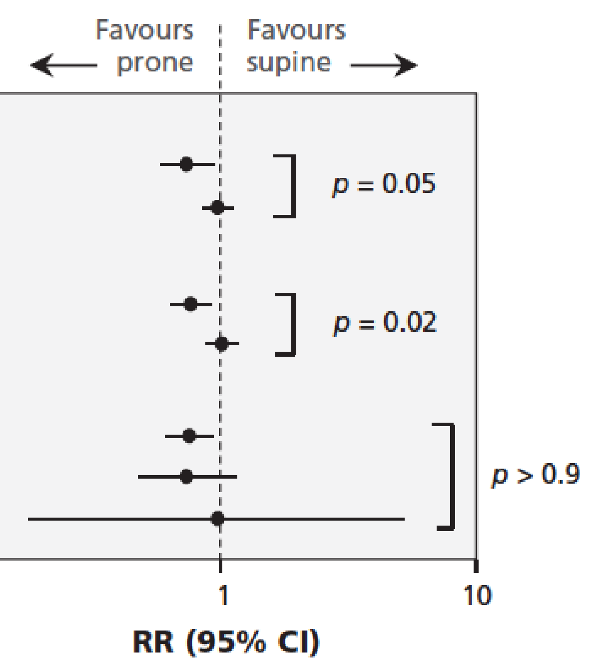
N Engl J Med 2013;368:2159-68.

CMAJ RESEARCH

CMAJ 2014. DOI:10.1503/cmaj.140081

Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis

Variable	No. of trials	Deaths, *n/N* Prone	Deaths, *n/N* Supine	RR (95% CI)	I^2 value, %
Protective lung ventilation					
Mandated	6	154/510	209/506	0.74 (CI 0.59–0.95)	29
Not mandated	4	229/458	205/395	0.98 (CI 0.86–1.12)	0
Duration of prone positioning					
≥ 16 h/d	6	191/565	243/547	0.77(CI 0.64–0.92)	21
< 16 h/d	4	192/403	171/354	1.02 (CI 0.88–1.17)	0
Level of hypoxemia*					
Severe	6	75/210	102/209	0.76 (CI 0.61–0.94)	0
Moderate	6	75/274	102/268	0.74 (CI 0.48–1.16)	42
Mild	4	3/22	3/23	0.98 (CI 0.18–5.24)	0



Prone Positioning Related Complications

Related to prone positioning (% of patients)§	
Need for increased sedation	55.2
Airway obstruction	39.3
Facial edema	29.8
Increased need for muscle relaxants	27.7
Ventilator discoordination	19.6
Transient desaturation	18.7
Hypotension	12.3
Vomiting	7.6
Arrhythmias	4.2
Loss of venous access	0.7
Displacement of a thoracotomy tube	0.5
Accidental extubation	0.5

Gattinoni L. et al N Engl J Med 2001;345:568-73

Contraindication

- Serious burns or open wounds on the face or ventral body surface
- Spinal instability
- Pelvic fracture
- Life-threatening cardiac arrhythmia
- Hypotension
- Tracheotomy tube
- Obesity, or massive ascites

ECMO volumes and indications

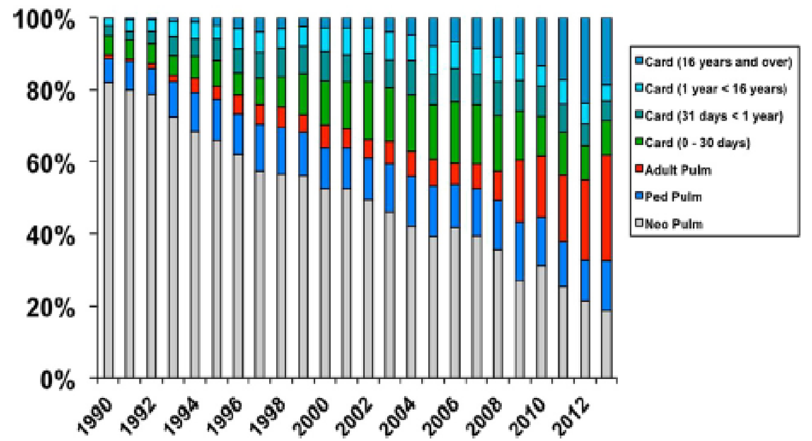


Figure 8. Cases in the Extracorporeal Life Support Organization Registry, July 2013. (From the Extracorporeal Life Support Organization Registry, reprinted with permission.)

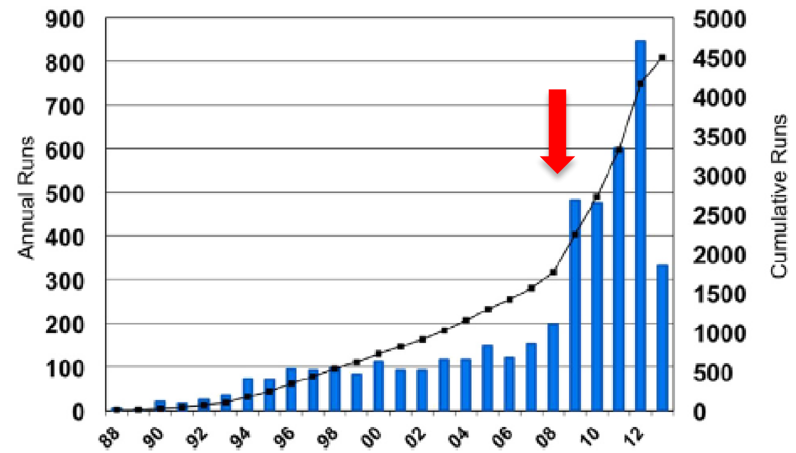


Figure 9. Adult respiratory cases, Extracorporeal Life Support Organization Registry July 2013. (From the Extracorporeal Life Support Organization Registry, reprinted with permission.)

Bartlett RH, J Am Coll Surg, 2014

“In God we trust;
All others must bring data”

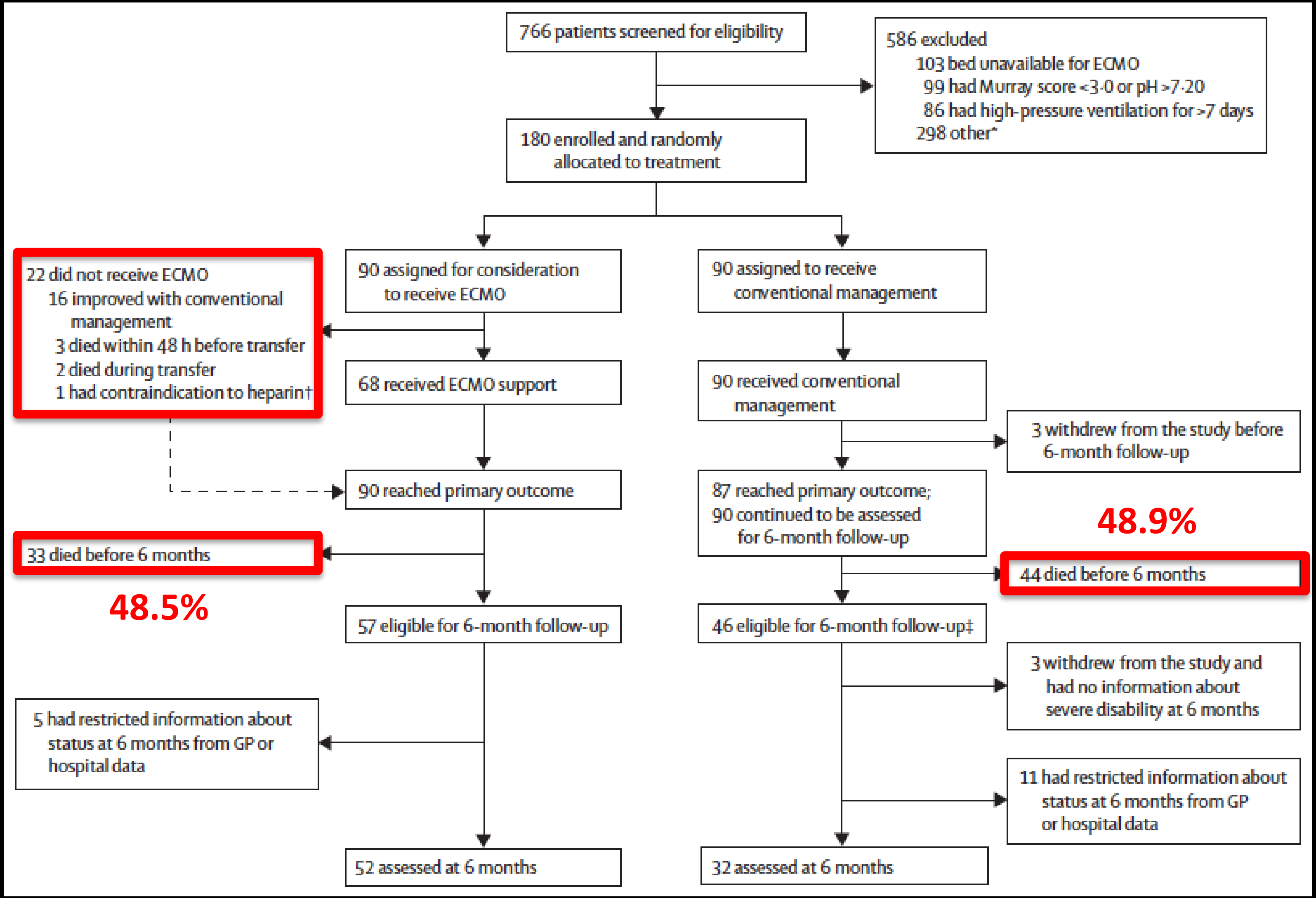
E. Edwards Deming
1900-1993

Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial

Giles J Peek, Miranda Mugford, Ravindranath Tiruvoipati, Andrew Wilson, Elizabeth Allen, Mariamma M Thalanany, Clare L Hibbert, Ann Truesdale, Felicity Clemens, Nicola Cooper, Richard K Firmin, Diana Elbourne, for the CESAR trial collaboration

- UK-based multi-center trial
- 180 patients,1:1 ratio, conventional vs ECMO
  - aged 18–65 years, severe (Murray score >3.0 or pH <7.20)
  - high pressure (>30 cm H_2O of PIP) or high FiO_2 (>0.8) ventilation for more than 7 days; intracranial bleeding; any other contraindication to limited heparinisation; or any contraindication to continuation of active treatment
- Survive to 6 months without disability
  - ECMO 63% (57/90) vs conventional 47% (41/87) (RR 0.69; 95% CI 0.05–0.97,p=0.03)

Lancet 2009; 374: 1351–63


766 patients screened for eligibility
586 excluded
103 bed unavailable for ECMO
99 had Murray score <3·0 or pH >7·20
86 had high-pressure ventilation for >7 days
298 other*
180 enrolled and randomly allocated to treatment
22 did not receive ECMO
16 improved with conventional management
3 died within 48 h before transfer
2 died during transfer
1 had contraindication to heparin†
90 assigned for consideration to receive ECMO
90 assigned to receive conventional management
68 received ECMO support
90 received conventional management
3 withdrew from the study before 6-month follow-up
90 reached primary outcome
87 reached primary outcome; 90 continued to be assessed for 6-month follow-up
48.9%
33 died before 6 months
44 died before 6 months
48.5%
57 eligible for 6-month follow-up
46 eligible for 6-month follow-up‡
3 withdrew from the study and had no information about severe disability at 6 months
5 had restricted information about status at 6 months from GP or hospital data
11 had restricted information about status at 6 months from GP or hospital data
52 assessed at 6 months
32 assessed at 6 months

ECMO for 2009 Influenza H1N1 Severe ARDS

Australia and New Zealand

JAMA. 2009;302(17):1888-1895

Table 3. Patient Outcomes[a]

Outcome Measure	2009 Influenza A(H1N1) Confirmed Infection (n = 53)	2009 Influenza A(H1N1) Suspected Infection (n = 15)	All Infections (N = 68)
Length of stay, median (IQR), d			
ICU	26 (16-35)	31 (15-38)	27 (16-37)
Hospital	35 (24-45)	40 (27-54)	39 (23-47)
Duration, median (IQR), d			
Mechanical ventilation	24 (13-31)	28 (13-34)	25 (13-34)
ECMO support	10 (7-14)	11 (10-16)	10 (7-15)
Survival at ICU discharge	38 (72)	10 (67)	48 (71)
Still in ICU	4 (8)	2 (13)	6 (9)
Survival at hospital discharge	22 (42)	10 (67)	32 (47)
Still in hospital[b]	14 (26)	2 (13)	16 (24)
Ambulant at hospital discharge[c]	21 (95)	10 (100)	31 (97)
SaO_2 on room air at hospital discharge, median (IQR), %[c]	97 (95-98)	97 (95-98)	97 (95-98)
Discharge destination			
Died	11 (21)	3 (20)	14 (21)
Home	18 (34)	4 (27)	22 (32)
Other hospital	0	1 (7)	1 (1)
Rehabilitation facility	4 (8)	5 (33)	9 (13)
Cause of death[d]			
Hemorrhage	3 (27)	1 (33)	4 (29)
Intracranial hemorrhage	4 (36)	2 (66)	6 (43)
Infection	1 (9)	0	1 (7)
Intractable respiratory failure	3 (27)	1 (33)	4 (29)

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Infection	1 (9)	0	1 (7)
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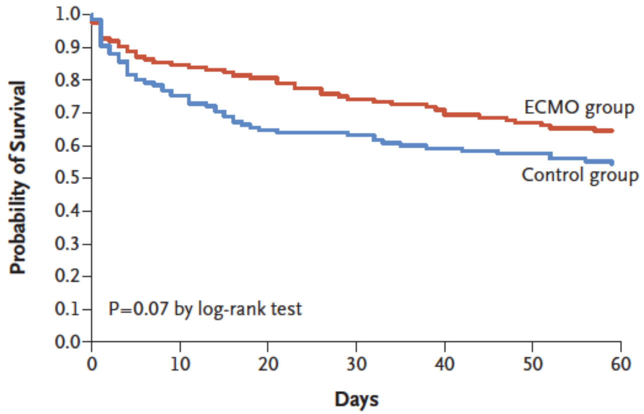
ECMO for 2009 Influenza H1N1 Severe ARDS

Australia and New Zealand

JAMA. 2009;302(17):1888-1895

Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome

A. Combes, D. Hajage, G. Capellier, A. Demoule, S. Lavoué, C. Guervilly, D. Da Silva, L. Zafrani, P. Tirot, B. Veber, E. Maury, B. Levy, Y. Cohen, C. Richard, P. Kalfon, L. Bouadma, H. Mehdaoui, G. Beduneau, G. Lebreton, L. Brochard, N.D. Ferguson, E. Fan, A.S. Slutsky, D. Brodie, and A. Mercat, for the EOLIA Trial Group, REVA, and ECMONet*



No. at Risk							
ECMO	124	105	100	92	88	83	80
Control	125	94	81	79	74	72	69

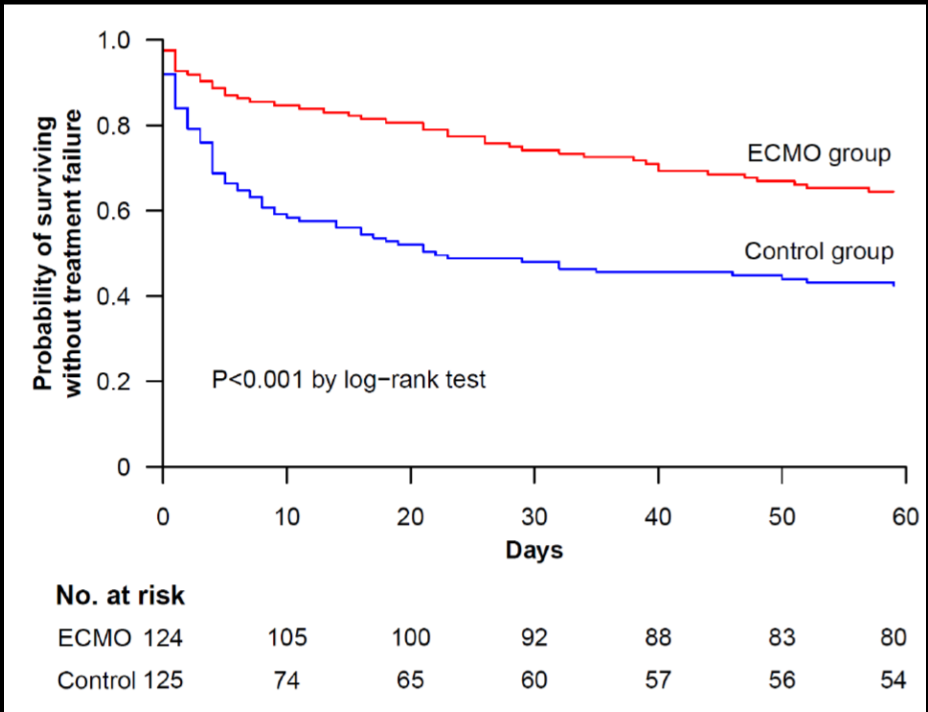
1. Very sick patients
   - P/F ratio < 80 mmHg
   - CRS < 30 cmH_2O
   - Driving pressure > 16 cmH_2O
   - SOFA > 10
2. Strict study design
   - 100% ECMO in study group
   - Optimal care in control group
     - Low tidal volume, 90% prone, 100% NM blockade

The routine use of ECMO in patients with severe ARDS is not superior to the use of ECMO as a rescue maneuver in patients whose condition has deteriorated further.

N Engl J Med 2018; 378: 1965-75.

Survival Without Treatment Failure

Crossover to ECMO or Death for the Control Group and Death for the ECMO Group



1. Ethical consideration
2. 35(28%) in the control group crossover to ECMO
3. Crossover patients are sicker
   - Higher P_{plat}, ΔP, Lower compliance, more CXR infiltrates
4. High mortality (57%), without crossover (41%)

N Engl J Med 2018; 378: 1965-75.

One-year survivors

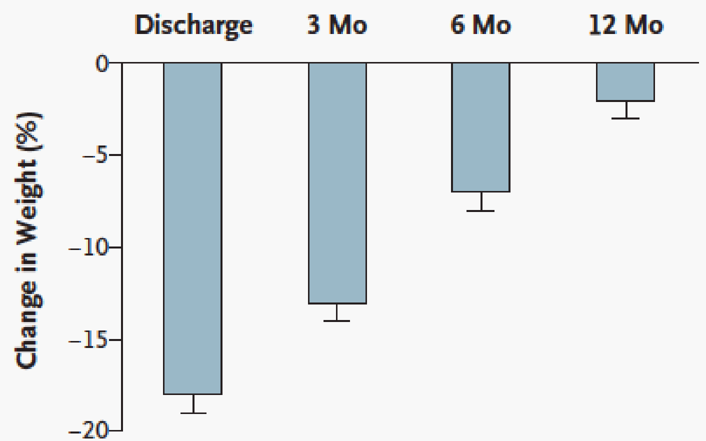


Figure 2. Mean (+SE) Change in Weight from Base Line among Patients with the Acute Respiratory Distress Syndrome at the Time of Discharge from the ICU and at 3, 6, and 12 Months.

Table 2. Recovery of Pulmonary Function among Patients with the Acute Respiratory Distress Syndrome during the First 12 Months after Discharge from the ICU.

Variable	3 Mo (N=71)*	6 Mo (N=77)†	12 Mo (N=80)‡
	median (interquartile range)		
Forced vital capacity (% of predicted)	72 (57–86)	80 (68–94)	85 (71–98)
Forced expiratory volume in one second (% of predicted)	75 (58–92)	85 (69–98)	86 (74–100)
Total lung capacity (% of predicted)§	92 (77–97)	92 (83–101)	95 (81–103)
Residual volume (% of predicted)§	107 (87–121)	97 (82–117)	105 (90–116)
Carbon monoxide diffusion capacity (% of predicted)§¶	63 (54–77)	70 (58–82)	72 (61–86)

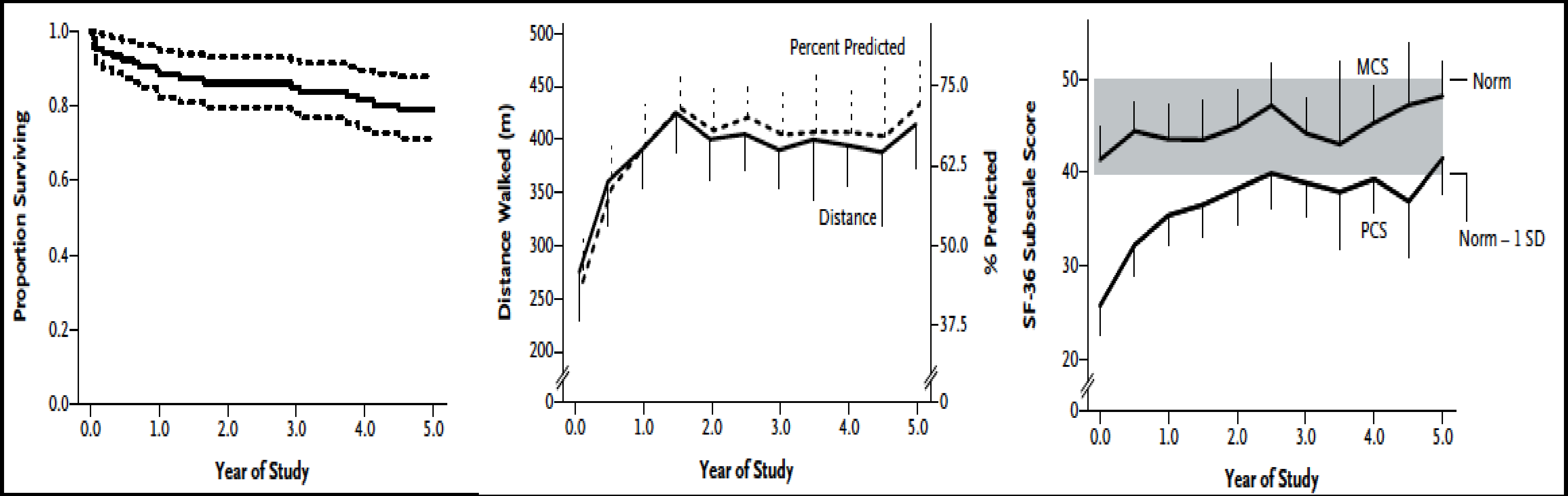
N Engl J Med 2003;348:683-93.

5-year Survivors

Survival

6MWD

SF36



N Engl J Med 2011;364:1293-304.

Thank you!