Management of ARDS

台中榮總 呼吸治療科
詹明澄

Definition of ALI/ARDS

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

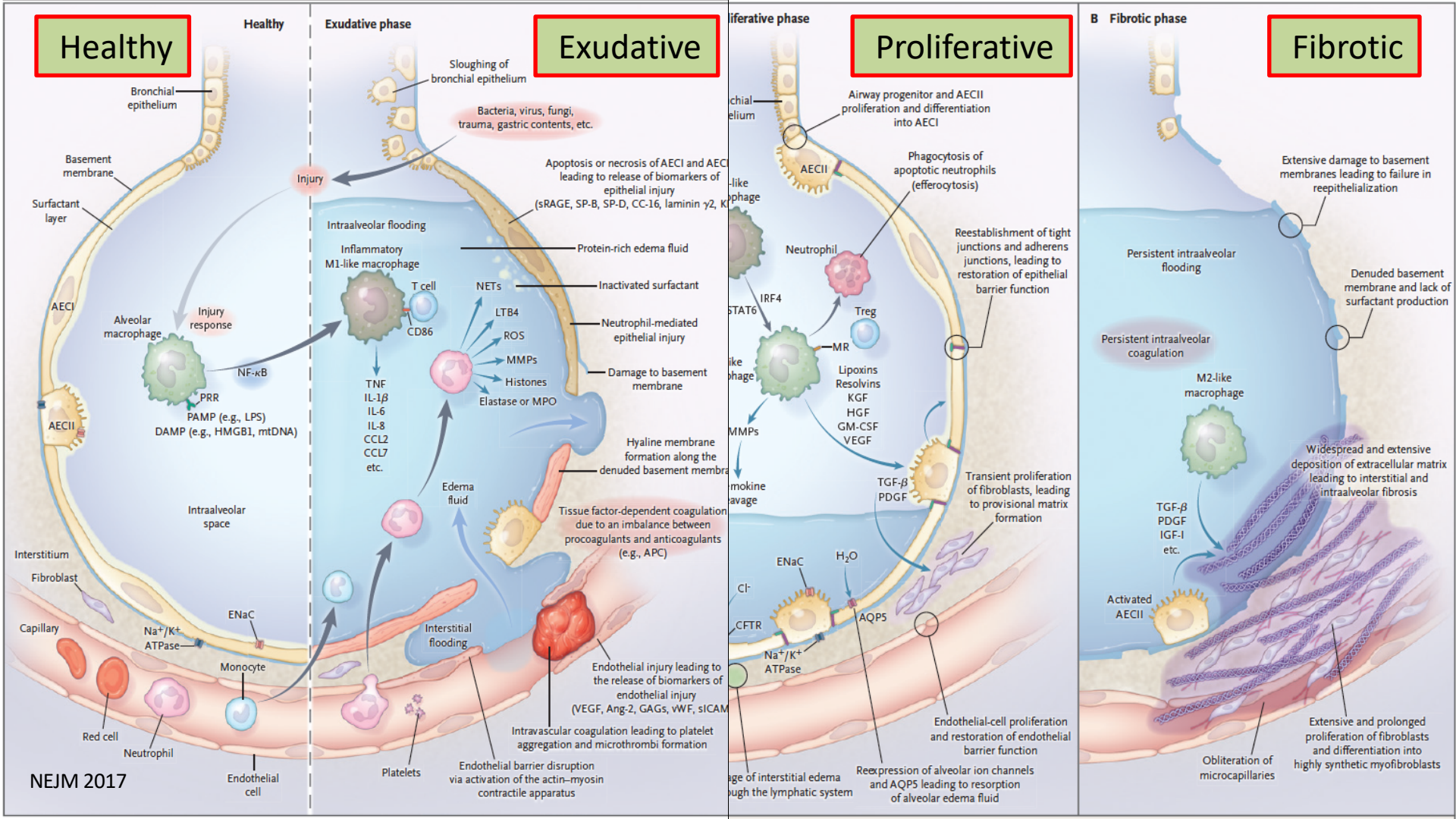
AECC 1994

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


Healthy
Exudative
Proliferative
Fibrotic
Healthy
Exudative phase
B Fibrotic phase
Bronchial epithelium
Basement membrane
Surfactant layer
AECI
AECII
Alveolar macrophage
Injury response
NF-κB
PRR
PAMP (e.g., LPS)
DAMP (e.g., HMGB1, mtDNA)
Intraalveolar space
Interstitium
Fibroblast
Capillary
Na+/K+ ATPase
ENaC
Monocyte
Red cell
Neutrophil
Endothelial cell
Sloughing of bronchial epithelium
Bacteria, virus, fungi, trauma, gastric contents, etc.
Injury
Apoptosis or necrosis of AECI and AECII leading to release of biomarkers of epithelial injury (sRAGE, SP-B, SP-D, CC-16, laminin γ2, K
Intraalveolar flooding
Inflammatory M1-like macrophage
T cell
CD86
Protein-rich edema fluid
NETs
Inactivated surfactant
LTB4
ROS
MMPs
Histones
Elastase or MPO
Neutrophil-mediated epithelial injury
Damage to basement membrane
TNF
IL-1β
IL-6
IL-8
CCL2
CCL7
etc.
Hyaline membrane formation along the denuded basement membra
Edema fluid
Tissue factor-dependent coagulation due to an imbalance between procoagulants and anticoagulants (e.g., APC)
Interstitial flooding
Endothelial injury leading to the release of biomarkers of endothelial injury (VEGF, Ang-2, GAGs, vWF, sICAM
Intravascular coagulation leading to platelet aggregation and microthrombi formation
Platelets
Endothelial barrier disruption via activation of the actin–myosin contractile apparatus
Airway progenitor and AECII proliferation and differentiation into AECI
AECII
Phagocytosis of apoptotic neutrophils (efferocytosis)
Neutrophil
Reestablishment of tight junctions and adherens junctions, leading to restoration of epithelial barrier function
IRF4
Treg
MR
Lipoxins
Resolvins
KGF
HGF
GM-CSF
VEGF
MMPs
TGF-β
PDGF
Transient proliferation of fibroblasts, leading to provisional matrix formation
ENaC
H2O
Cl-
CFTR
AQP5
Na+/K+ ATPase
Endothelial-cell proliferation and restoration of endothelial barrier function
Reexpression of alveolar ion channels and AQP5 leading to resorption of alveolar edema fluid
Extensive damage to basement membranes leading to failure in reepithelialization
Persistent intraalveolar flooding
Denuded basement membrane and lack of surfactant production
Persistent intraalveolar coagulation
M2-like macrophage
Widespread and extensive deposition of extracellular matrix leading to interstitial and intraalveolar fibrosis
TGF-β
PDGF
IGF-I
etc.
Activated AECII
Obliteration of microcapillaries
Extensive and prolonged proliferation of fibroblasts and differentiation into highly synthetic myofibroblasts
NEJM 2017

Barotrauma

Not just air leak

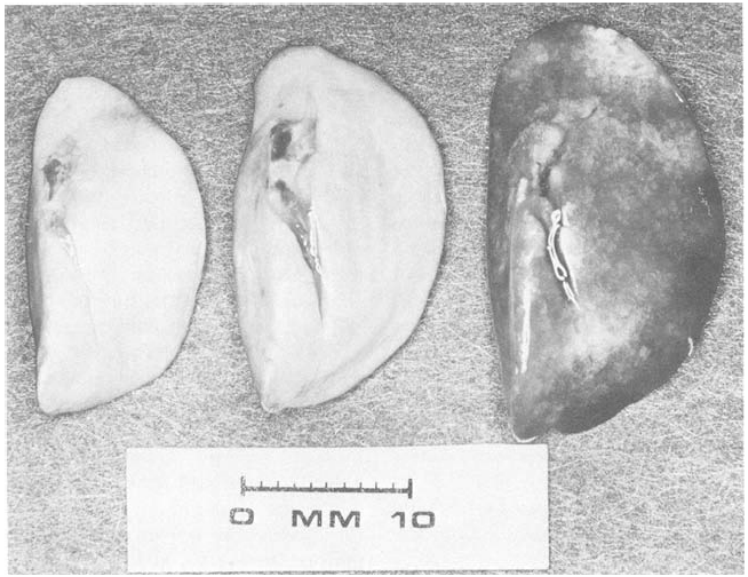


Fig. 3. Comparison of left lungs from rats ventilated with IPPB 14/0, PEEP 45/10, and HIPPB 45/0 (left to right). The perivascular groove is distended with edema in the lungs from rats ventilated with inspiratory pressure of 45 cm H_2O. The dark congested appearance of the lung ventilated with 45/0 is apparent.

Am RevRespir Dis 1974;110:556–565.

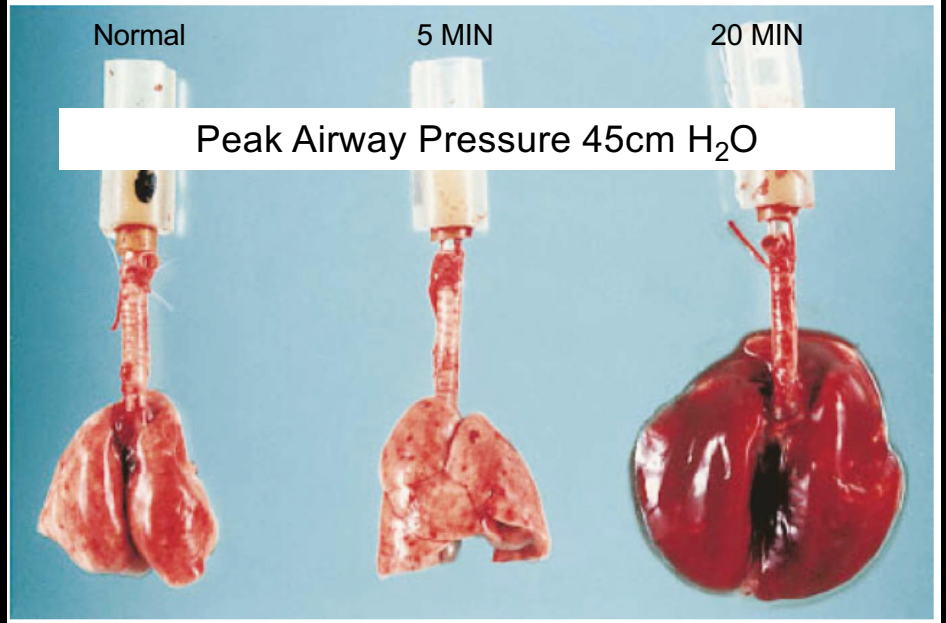


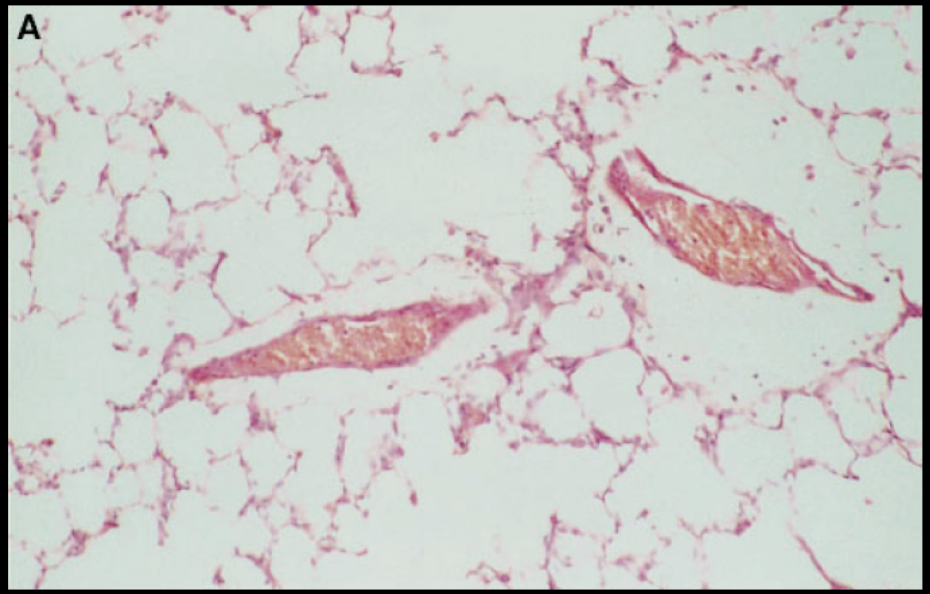
Figure 1 Macroscopic aspect of rat lungs after mechanical ventilation at 45 cm H_2O peak airway pressure. *Left*: normal lungs; *middle*: after 5 min of high airway pressure mechanical ventilation. Note the focal zones of atelectasis (in particular at the left lung apex); *right*: after 20 min, the lungs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

Am J Respir Crit Care Med 1998,157:1-30.

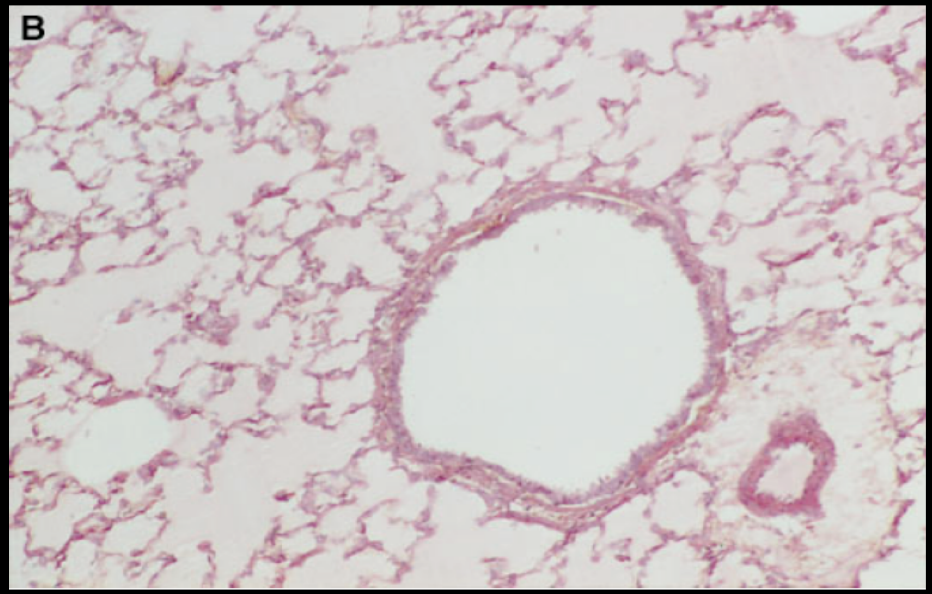
VILI in Light Microscope

AJRCCM 1998

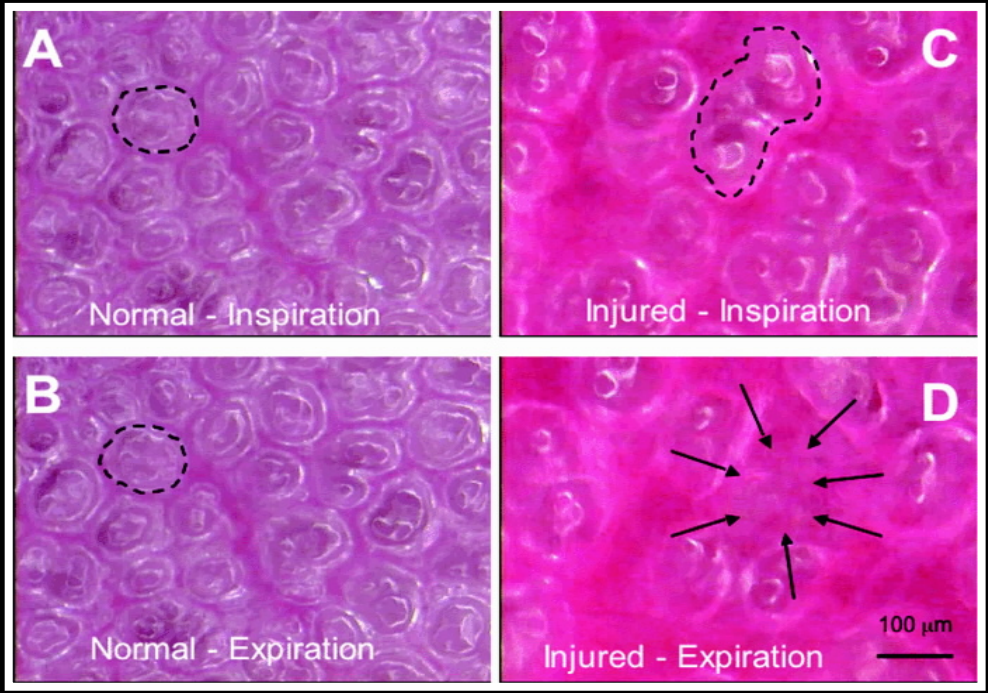
Perivascular cuffing
PC 45cmH_2O, 5ming



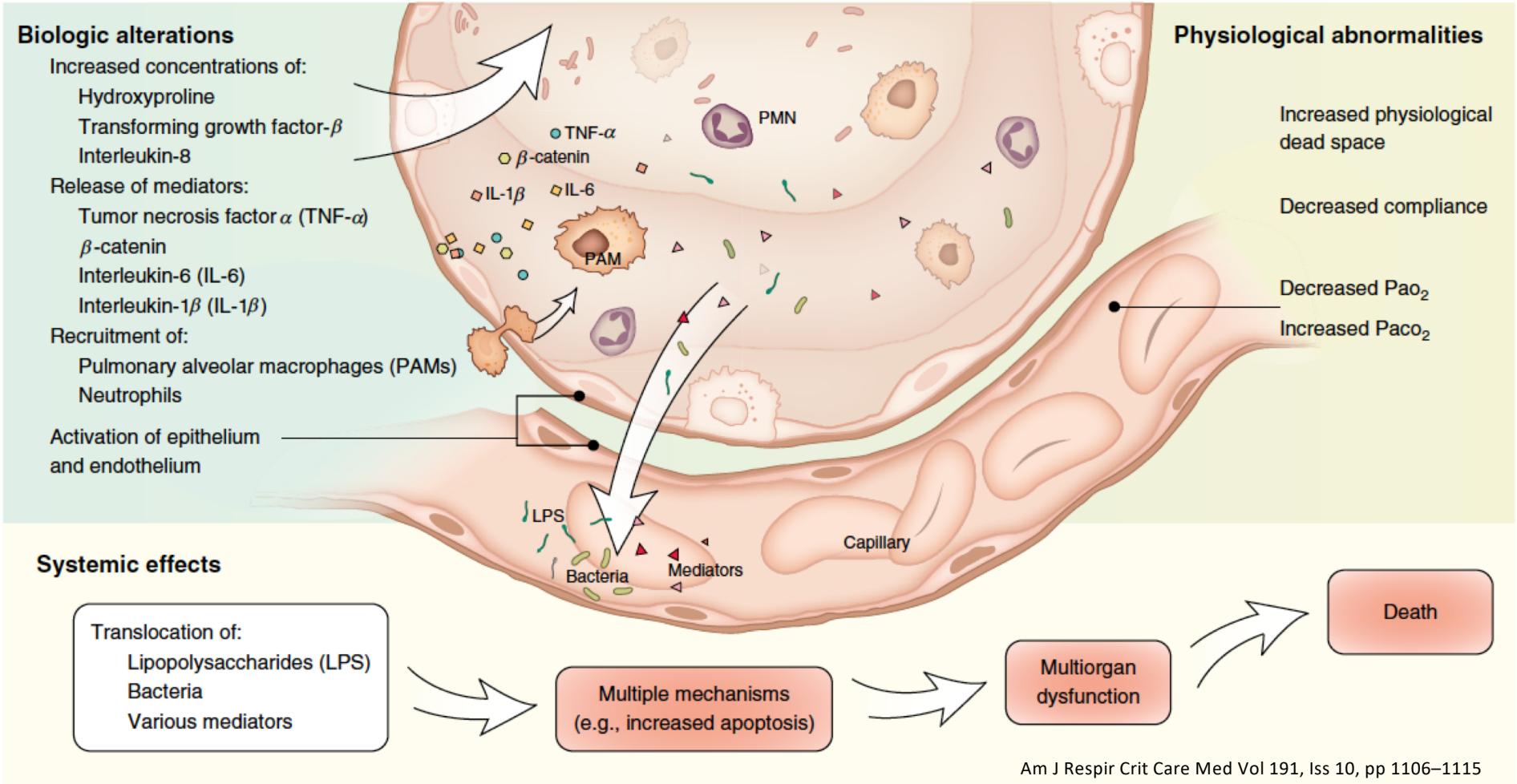
Alveolar edema
PC 45cm H_2O, 20min



Atelectrauma



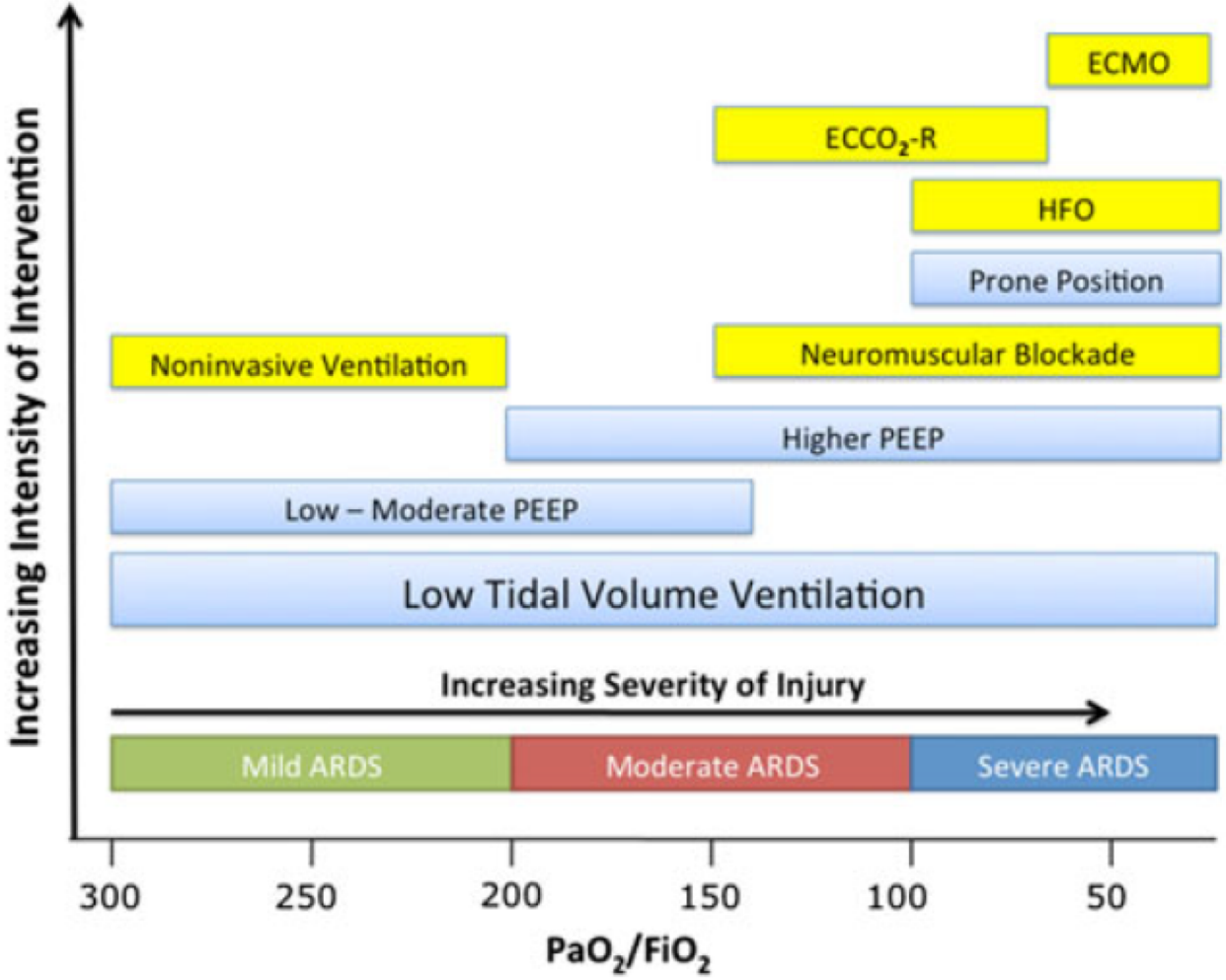
- Opening collapsed airway requires relatively high forces and thus causes epithelium disruption.
- Ventilation at low lung volumes can inhibit production of surfactant and/or lead to surfactant being squeezed out of alveoli.
- Reexpansion of atelectatic regions can be associated with marked increase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



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

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

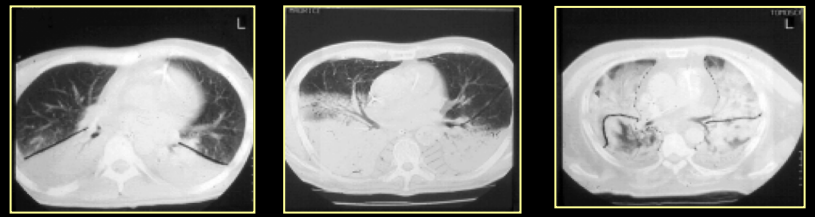
Therapeutic options for ARDS



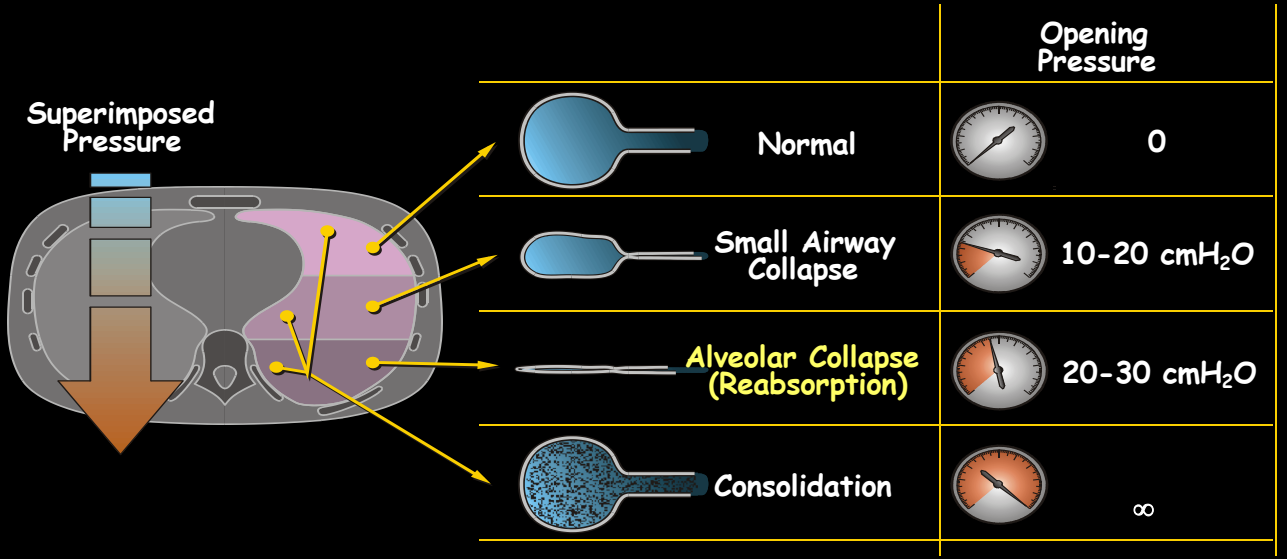
Intensive Care Med (2012) 38:1573–1582

The ARDS Lung

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



Rouby Intensive Care Med 2000

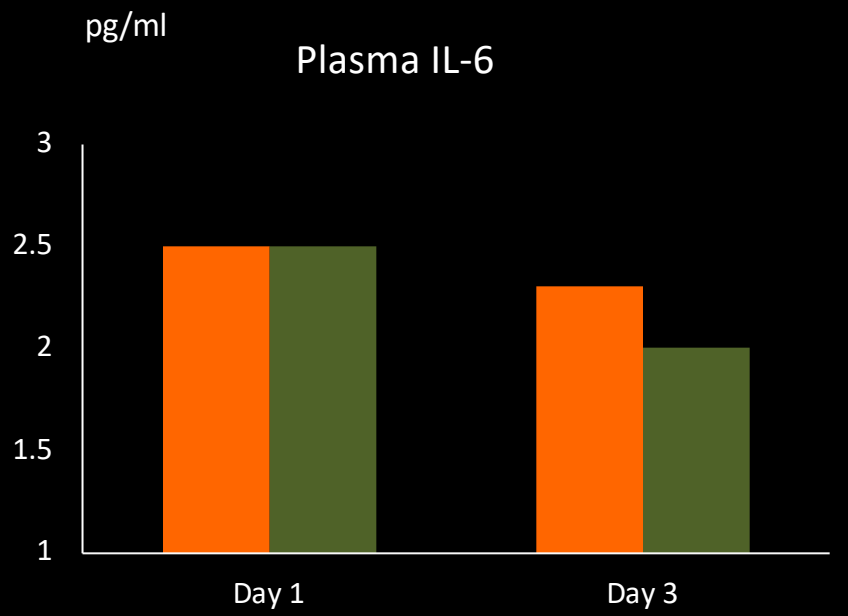


6 vs 12 ml/kg

N Engl J Med 2000;342:1301-8

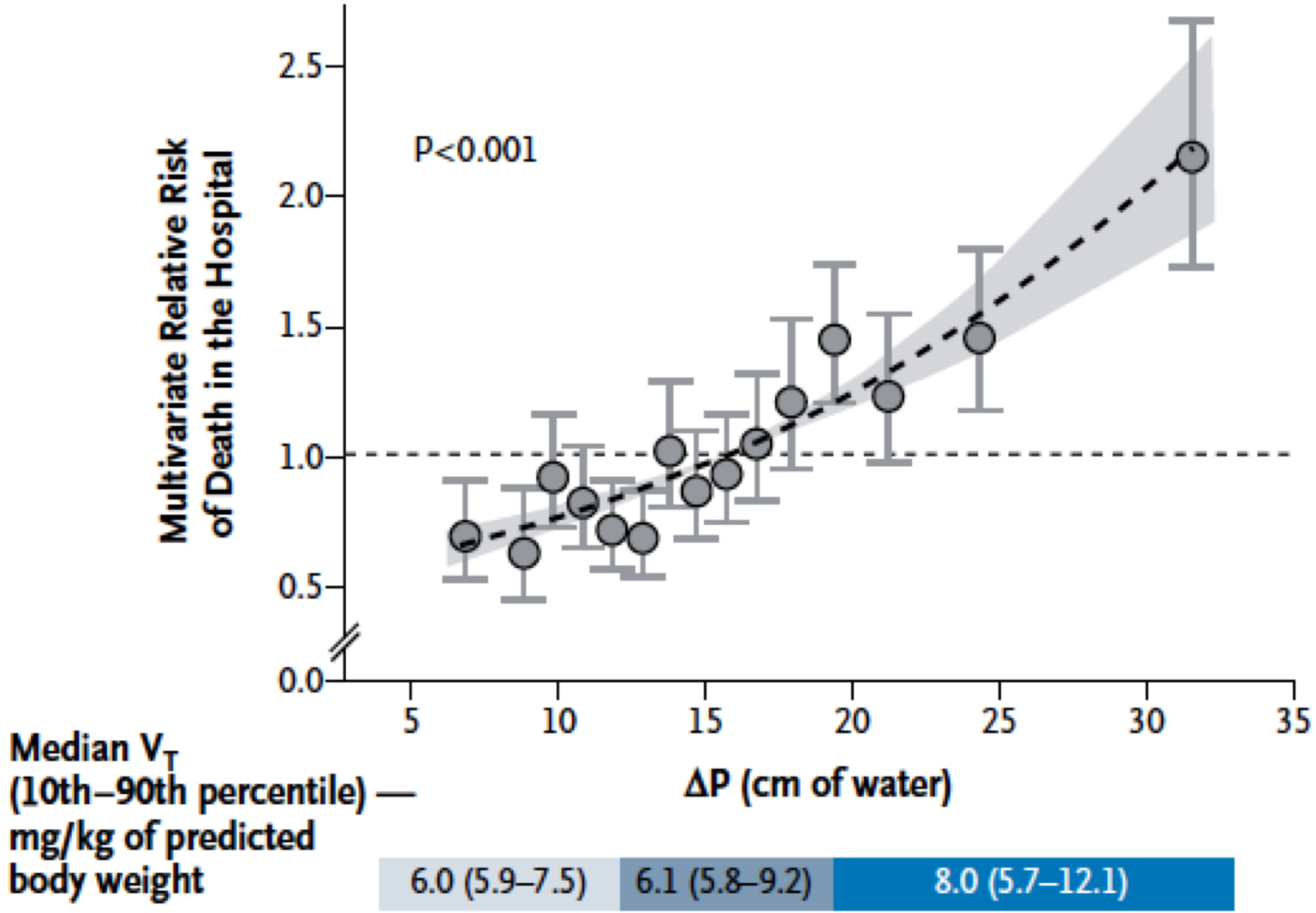
TABLE 4. MAIN OUTCOME VARIABLES.*

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).

Driving pressure vs mortality



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

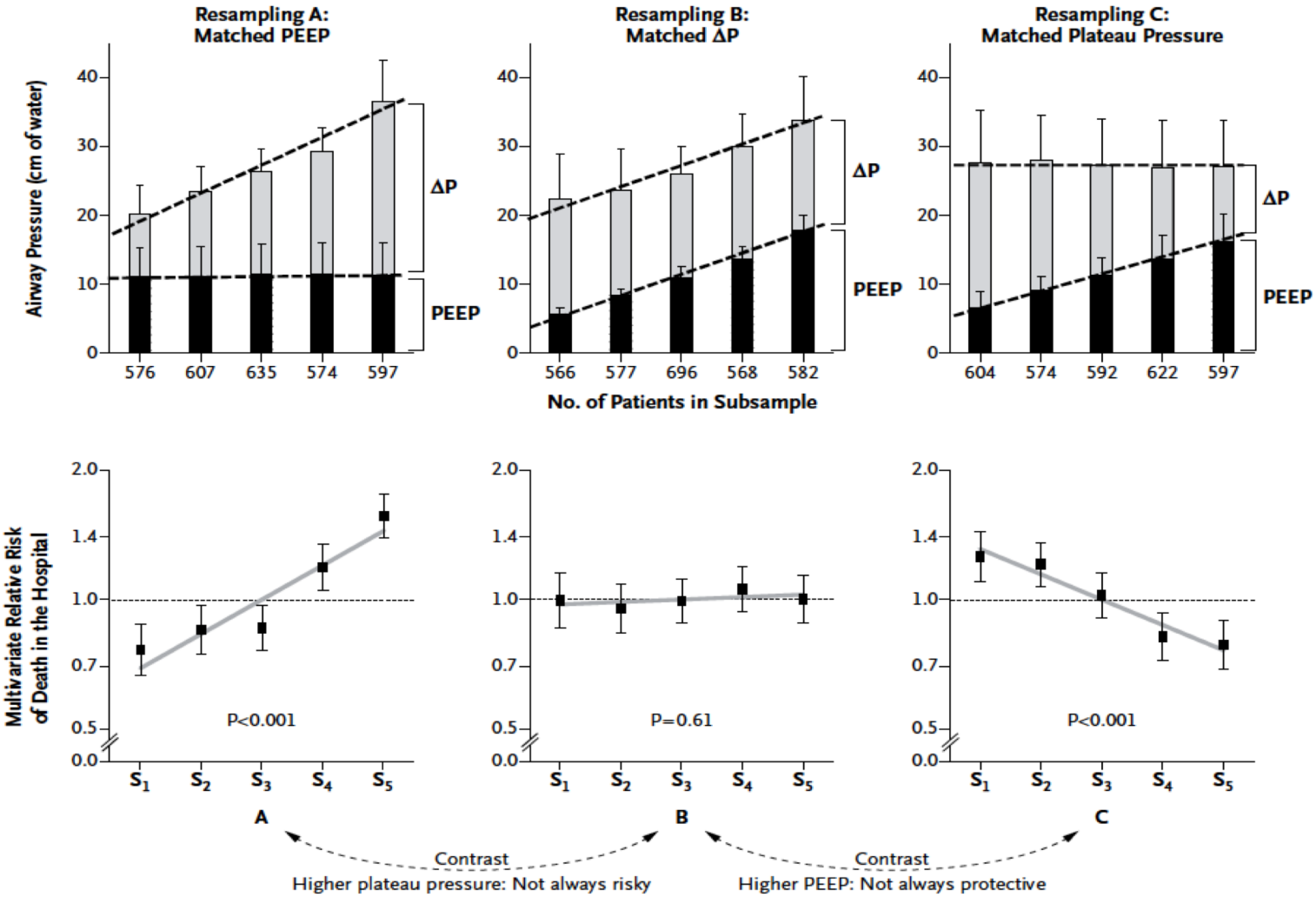
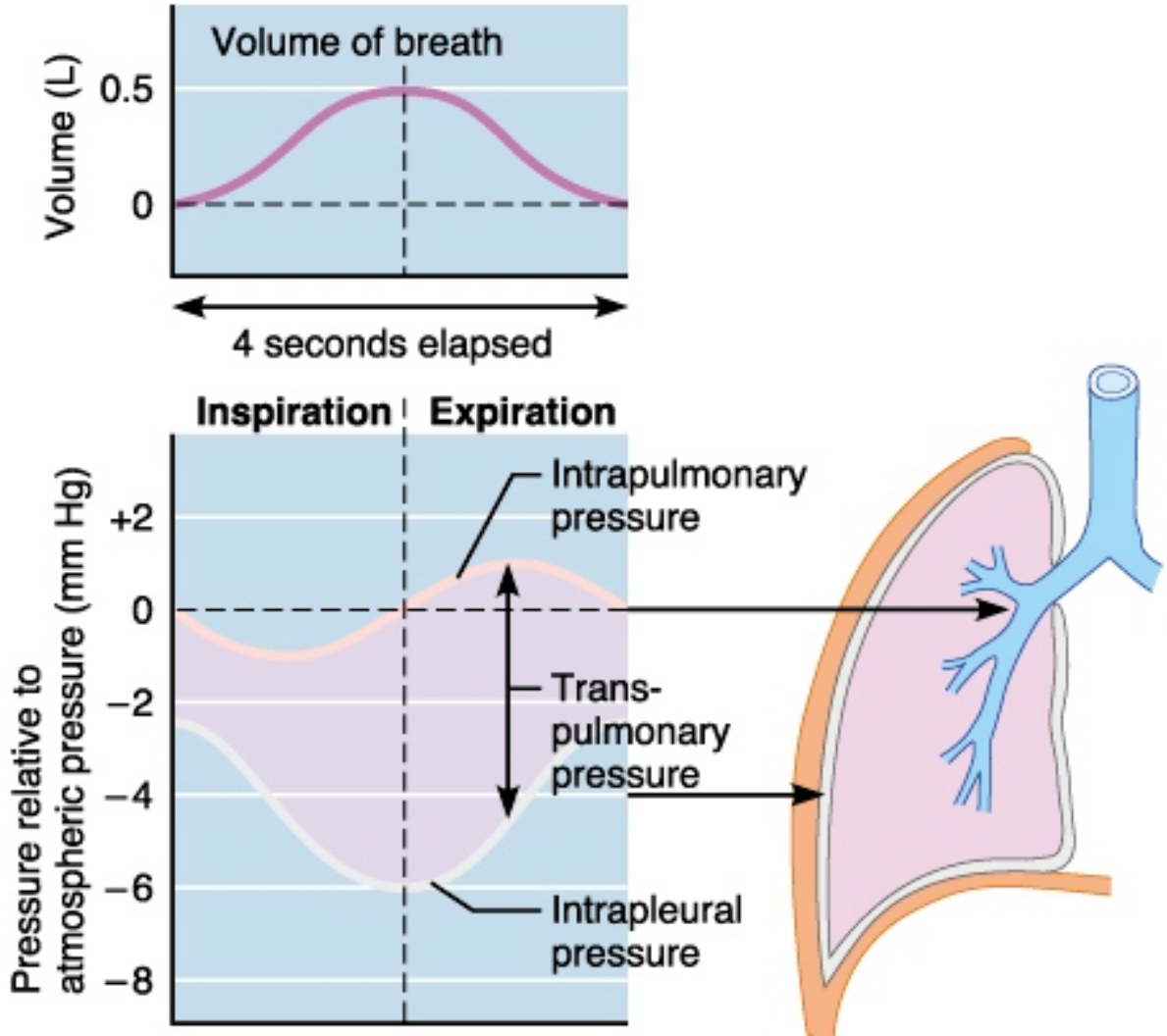

Resampling A:
Matched PEEP
Resampling B:
Matched ΔP
Resampling C:
Matched Plateau Pressure
Airway Pressure (cm of water)
ΔP
PEEP
576 607 635 574 597
566 577 696 568 582
604 574 592 622 597
No. of Patients in Subsample
Multivariate Relative Risk of Death in the Hospital
P<0.001
P=0.61
P<0.001
A
B
C
Contrast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

Table 4. Main Outcome Variables.*

Outcome	Lower-PEEP Group	Higher-PEEP Group	P Value
Death before discharge home (%)†			
Unadjusted	24.9	27.5	0.48
Adjusted for differences in baseline covariates	27.5	25.1	0.47
Breathing without assistance by day 28 (%)	72.8	72.3	0.89
No. of ventilator-free days from day 1 to day 28‡	14.5±10.4	13.8±10.6	0.50
No. of days not spent in intensive care unit from day 1 to day 28	12.2±10.4	12.3±10.3	0.83
Barotrauma (%)§	10	11	0.51
No. of days without failure of circulatory, coagulation, hepatic, and renal organs from day 1 to day 28	16±11	16±11	0.82

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

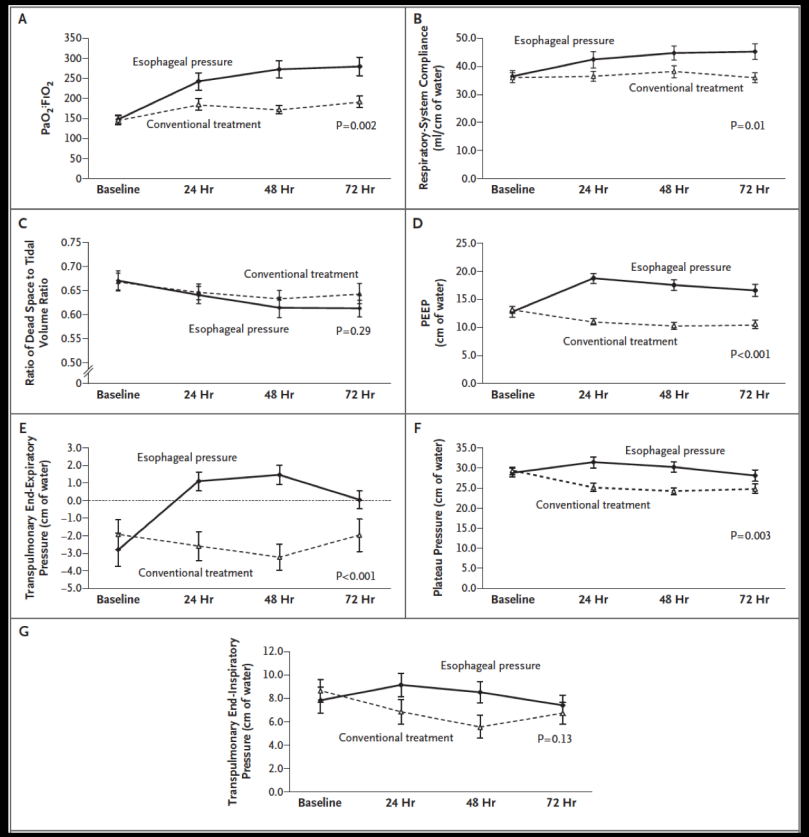


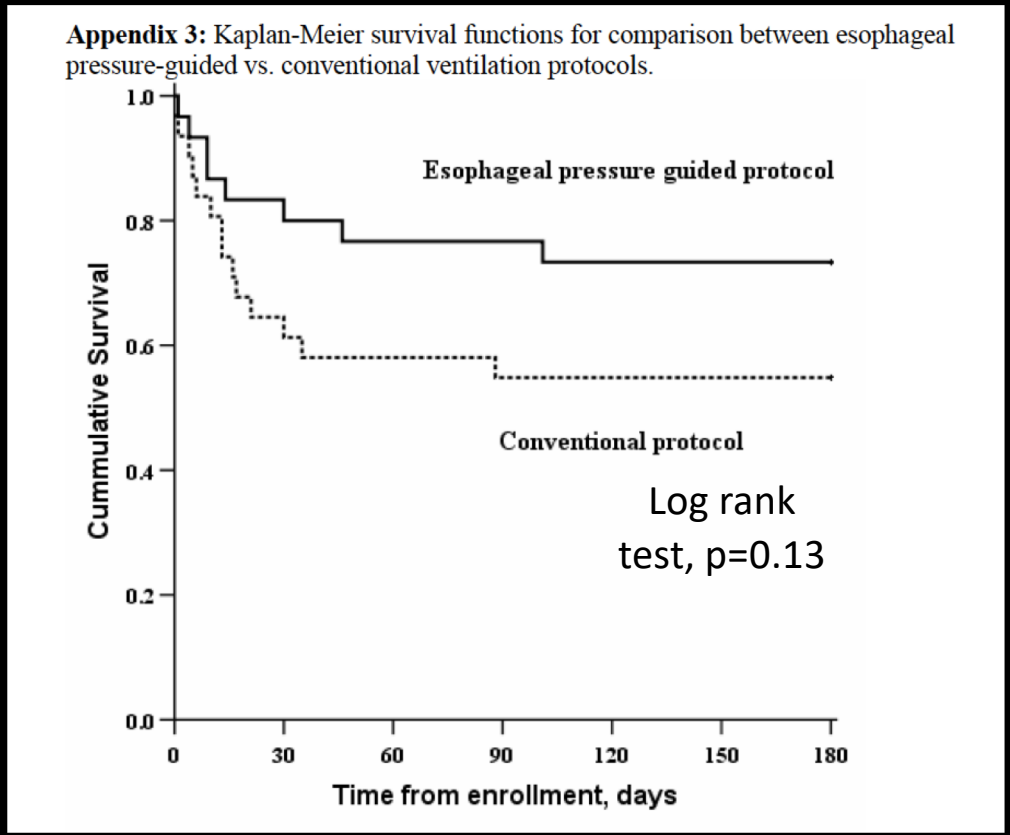
PEEP Guided by Esophageal Balloon

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 P. to Set PEEP

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





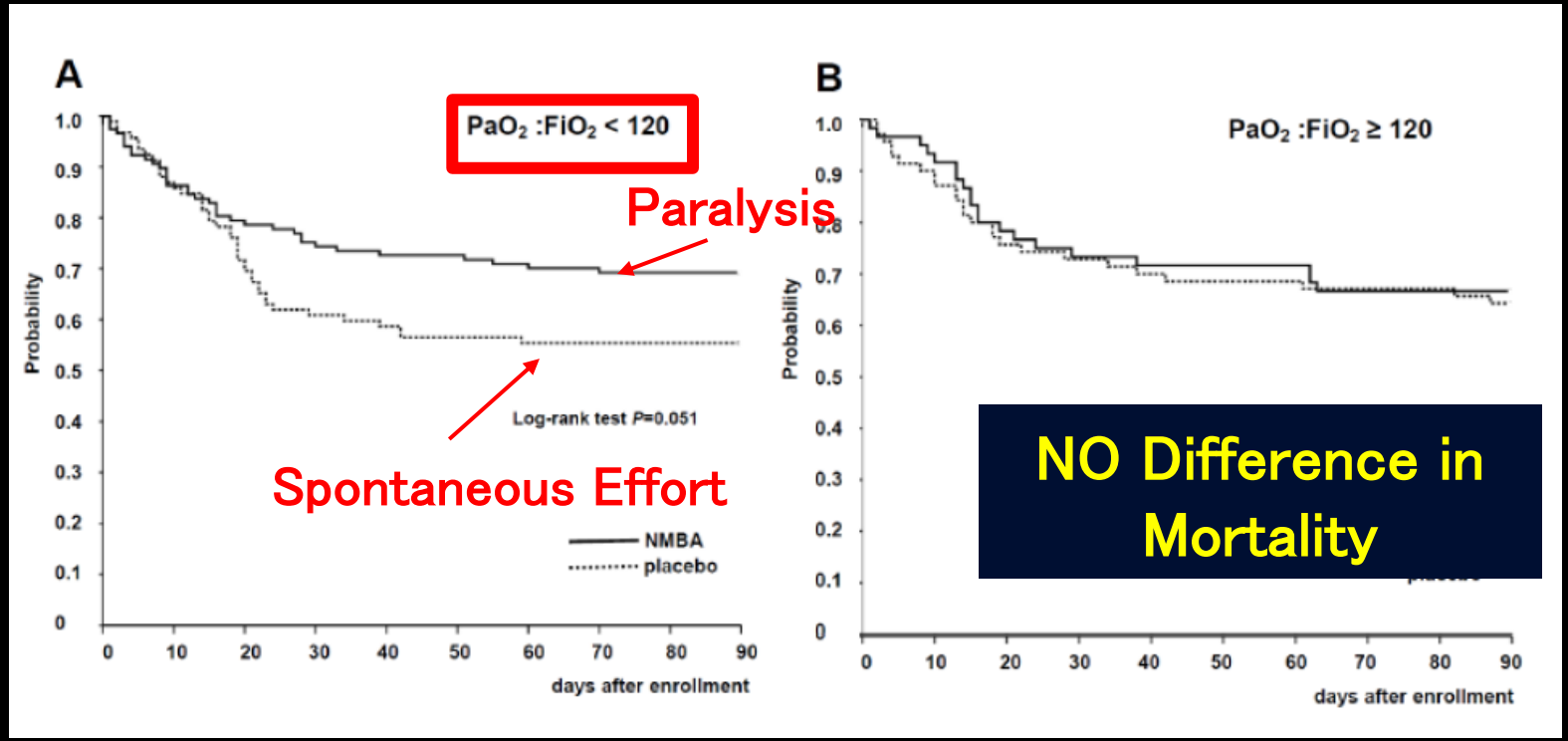
Severe Lung Injury

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

More Severe

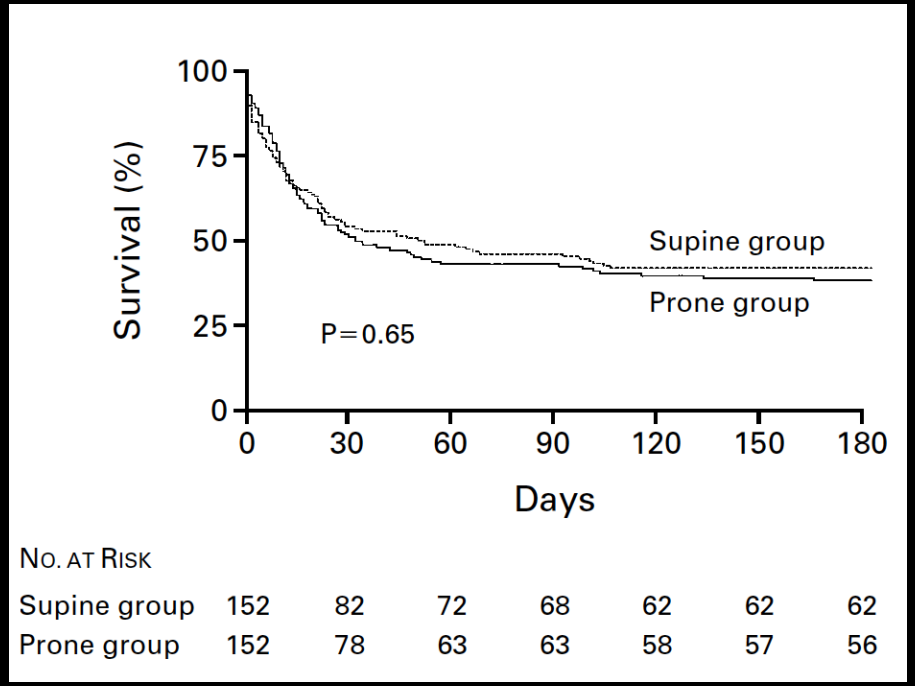
Less Severe

Survival



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

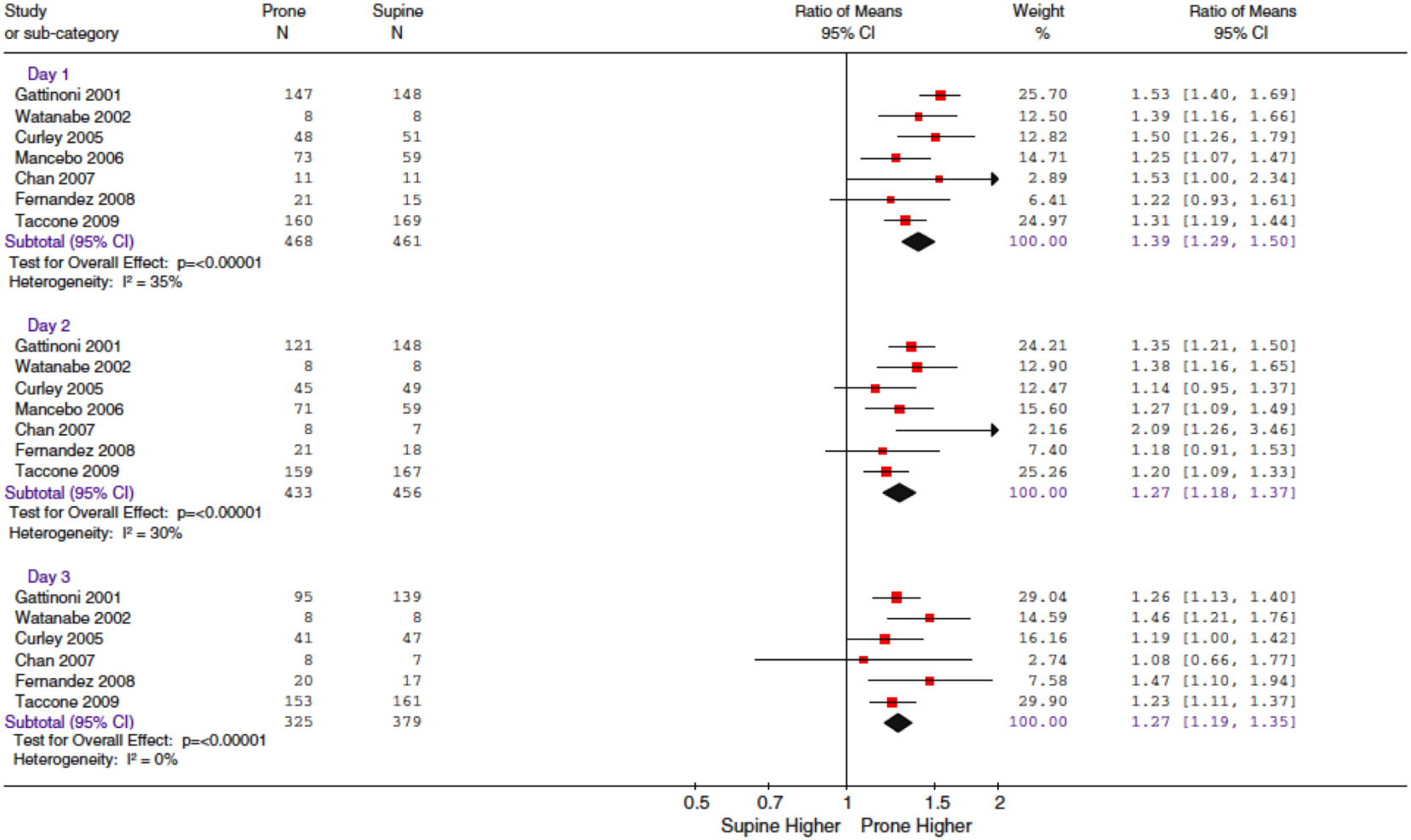
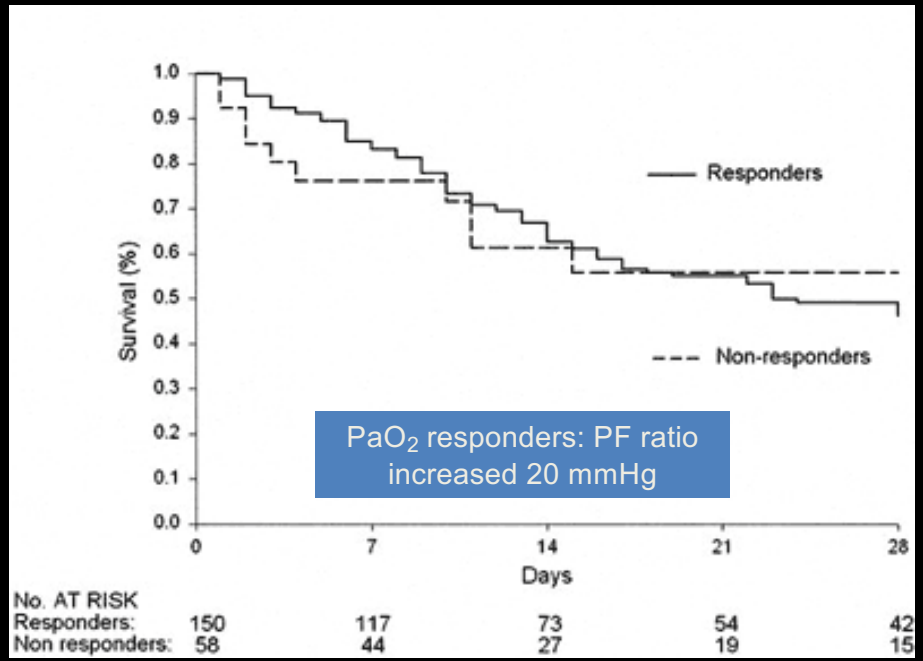
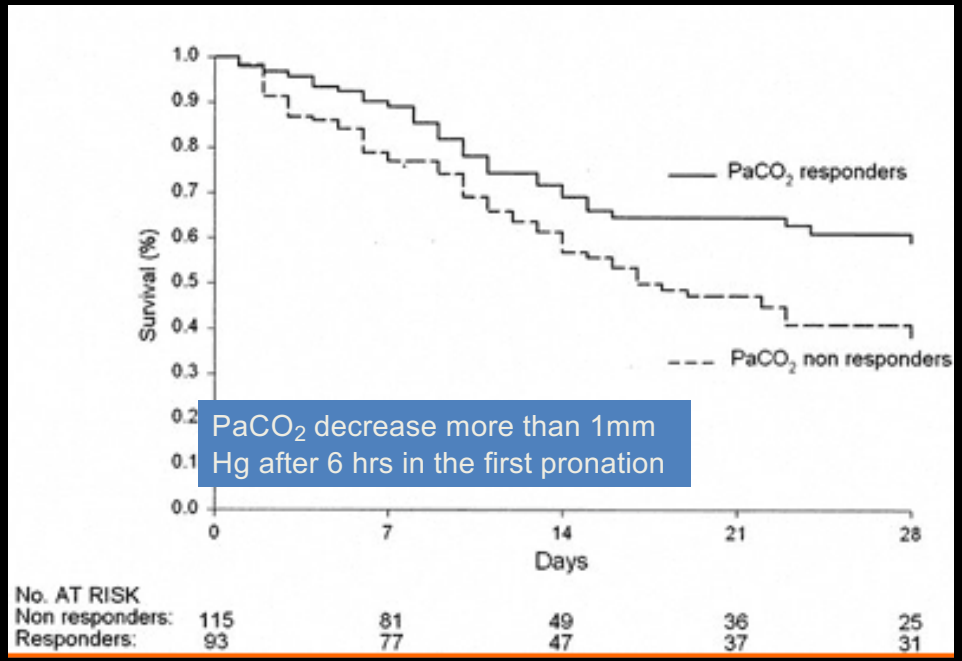


Fig. 4 Effect of prone ventilation on PaO_2 (partial pressure of supine group (at the closest available time). Weight is the

PaO_2 v.s. $PaCO_2$ Responders



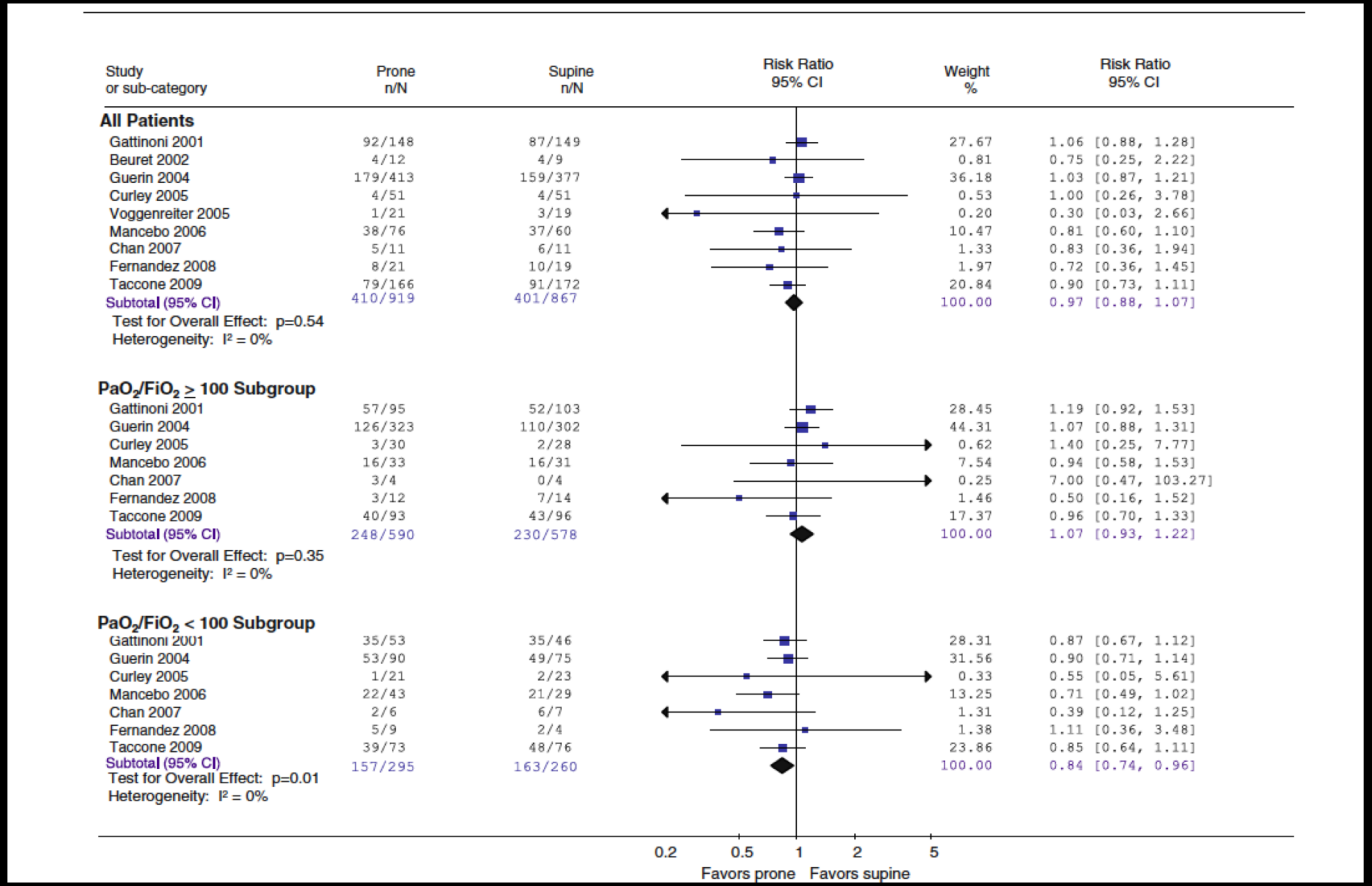
PaO_2 responders: PF ratio increased 20 mmHg



$PaCO_2$ decrease more than 1mm Hg after 6 hrs in the first pronation

Gattinoni et al, Crit Care Med 2003; 31:2727–2733

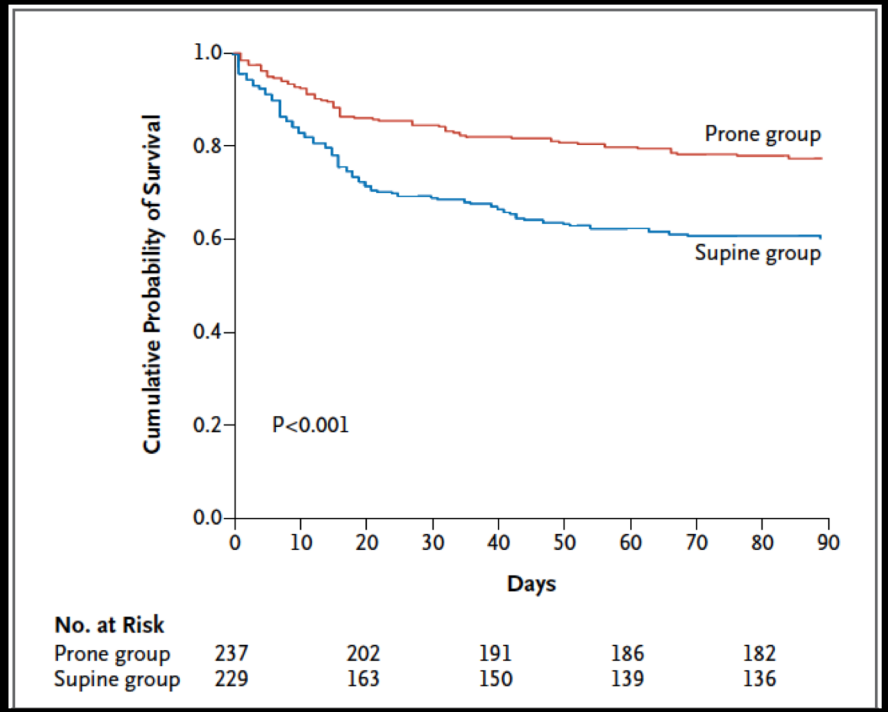
PPV reduces mortality in low PF ratio patients



Intensive Care Med (2010) 36:585–599

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



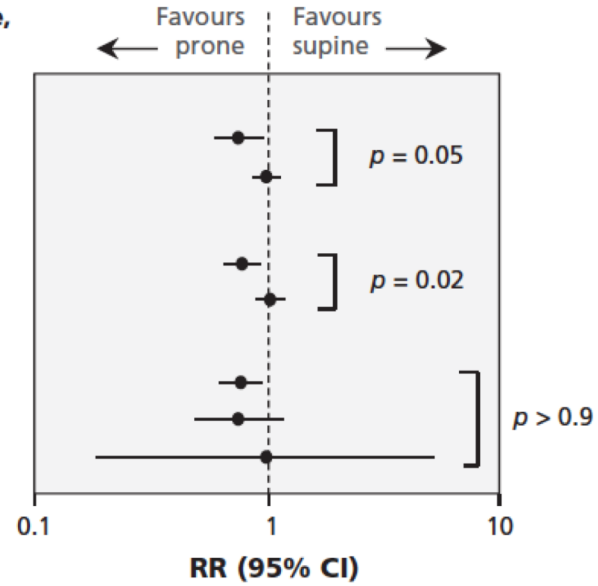
N Engl J Med 2013;368:2159-68.

CMAJ RESEARCH

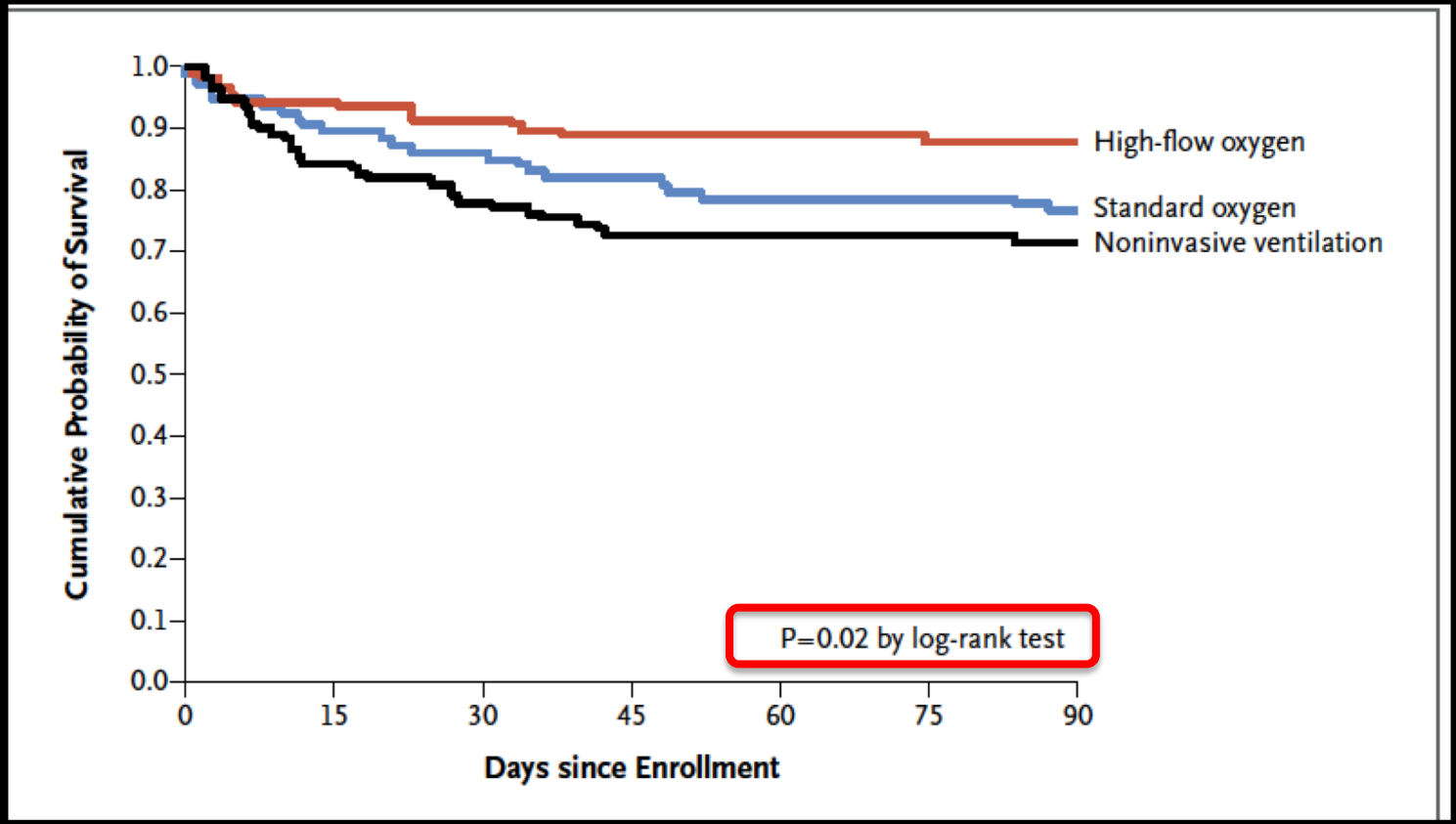
CMAJ 2014. DOI:10.1503/cmaj.140081

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*		RR (95% CI)	I^2 value, %
		Prone	Supine		
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



Nasal High Flow for Acute Hypoxemia



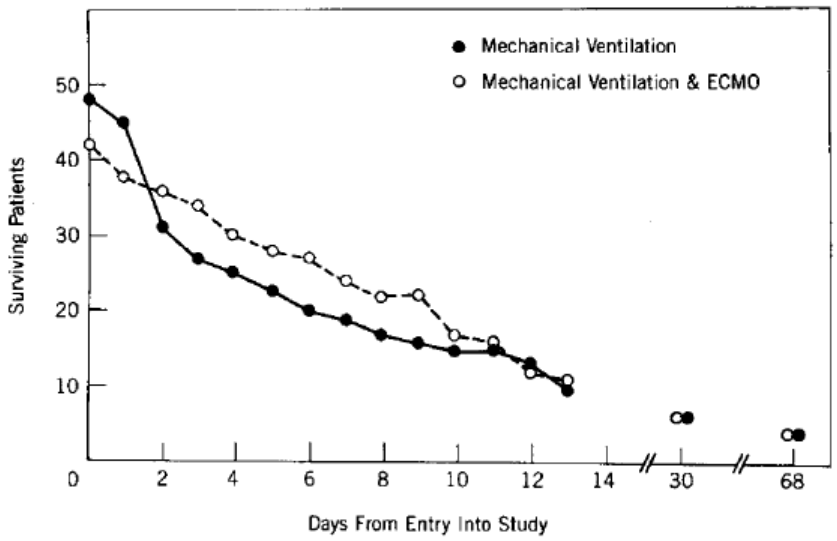
N Engl J Med 2015;372:2185-96.

ExtraCorporeal Life Support (ECLS)

ExtraCorporeal Membrane Oxygenation (ECMO)

ExtraCorporeal CO_2 Removal (ECCO2R)

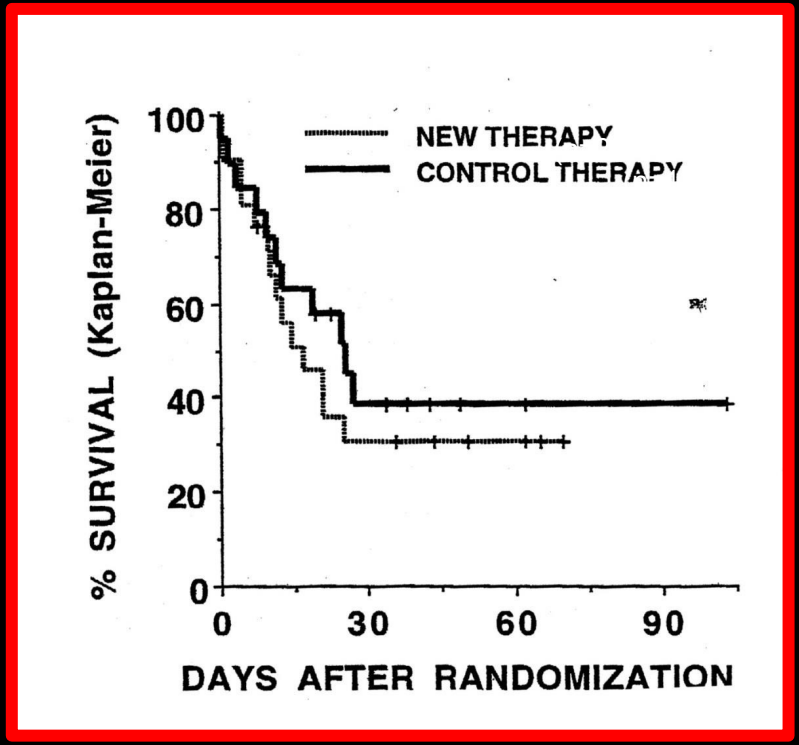
Patient Outcome			
Therapy*	Dead—Respiratory Improvement Never Occurred	Dead After Respiratory Improvement	Survived After Respiratory Improvement
ECMO and MV	34	4	4
MV (control)	41	3	4



Zapol W. JAMA 1979:242:2193-6

Salt Lake City study

PCIRV + ECCO2R



Morris A.H. AJRCCM 1994, ***149:295–305***

ECMO volumes and indications

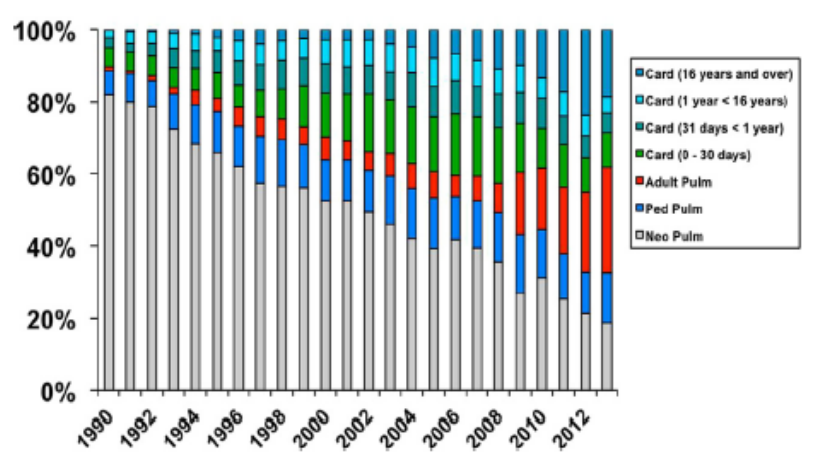


Figure 8. Cases in the Extracorporeal Life Support Organization Registry, July 2013. (From the Extracorporeal Life Support Organization Registry, reprinted with permission.)

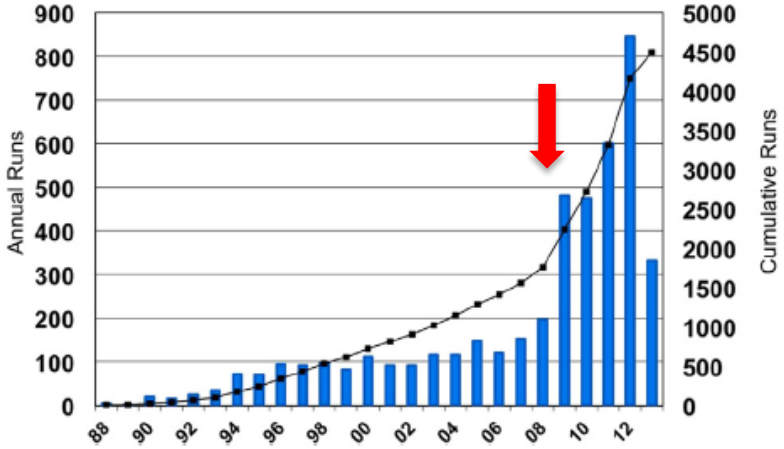


Figure 9. Adult respiratory cases, Extracorporeal Life Support Organization Registry July 2013. (From the Extracorporeal Life Support Organization Registry, reprinted with permission.)

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

Adherence to protective ventilation strategy

	ECMO	Conventional	
Treatment by low-volume low-pressure ventilation strategy at any time	84 (93%)	63 (70%)	<0·0001
Time under strategy (days)	23·9 (20·4)	15·0 (21·1)	<0·0001

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)
Sa_{O_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)

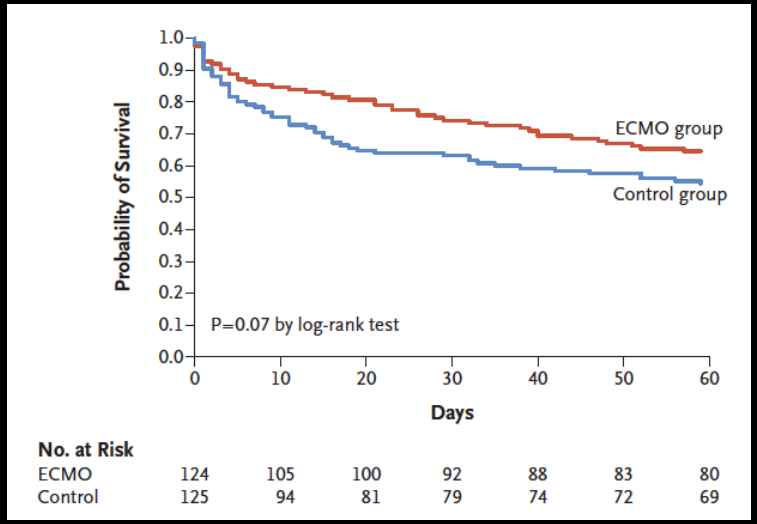
ECMO for 2009 Influenza H1N1 Severe ARDS

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*



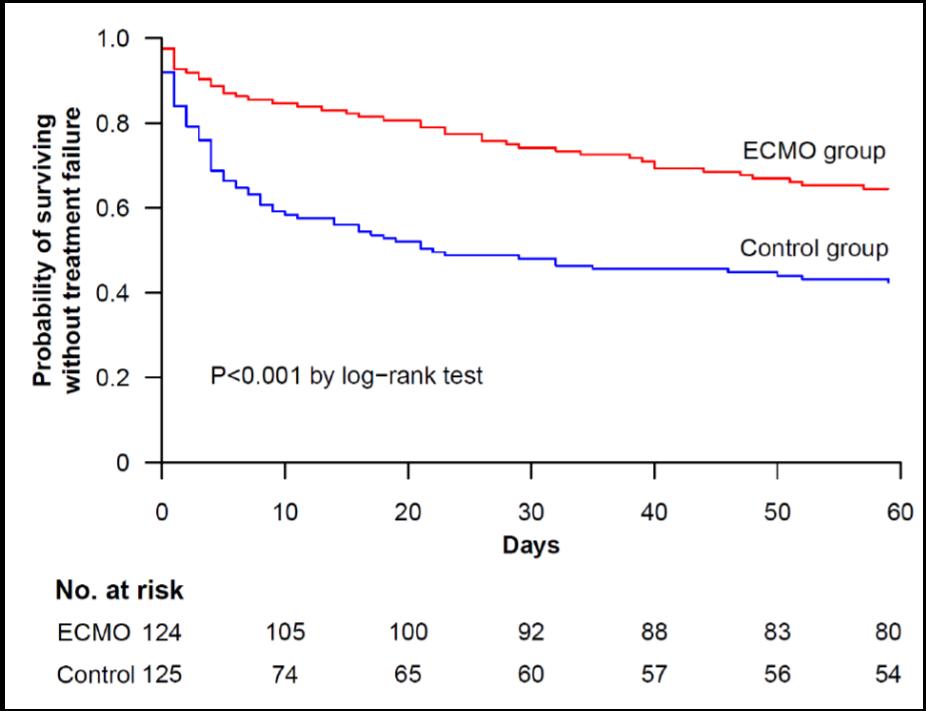
1. Very sick patients
   - P/F ratio < 80 mmHg
   - CRS < 30 cmH_2O
   - Driving pressure > 16 cmH_2O
   - SOFA > 10
2. Strict study design
   - 100% ECMO in study group
   - Optimal care in control group
     - Low tidal volume, 90% prone, 100% NM blockade

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.

Meta-analysis of ECMO for ARDS

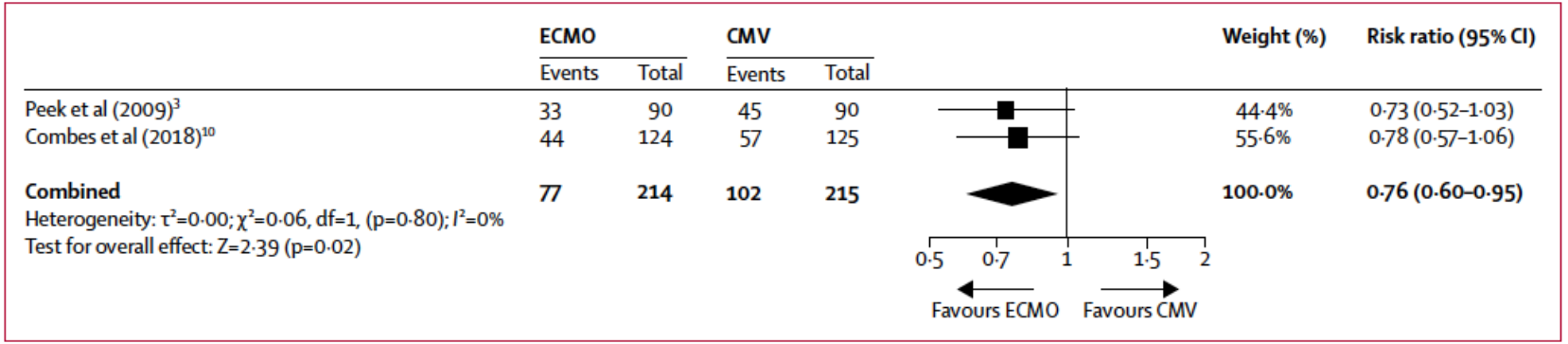
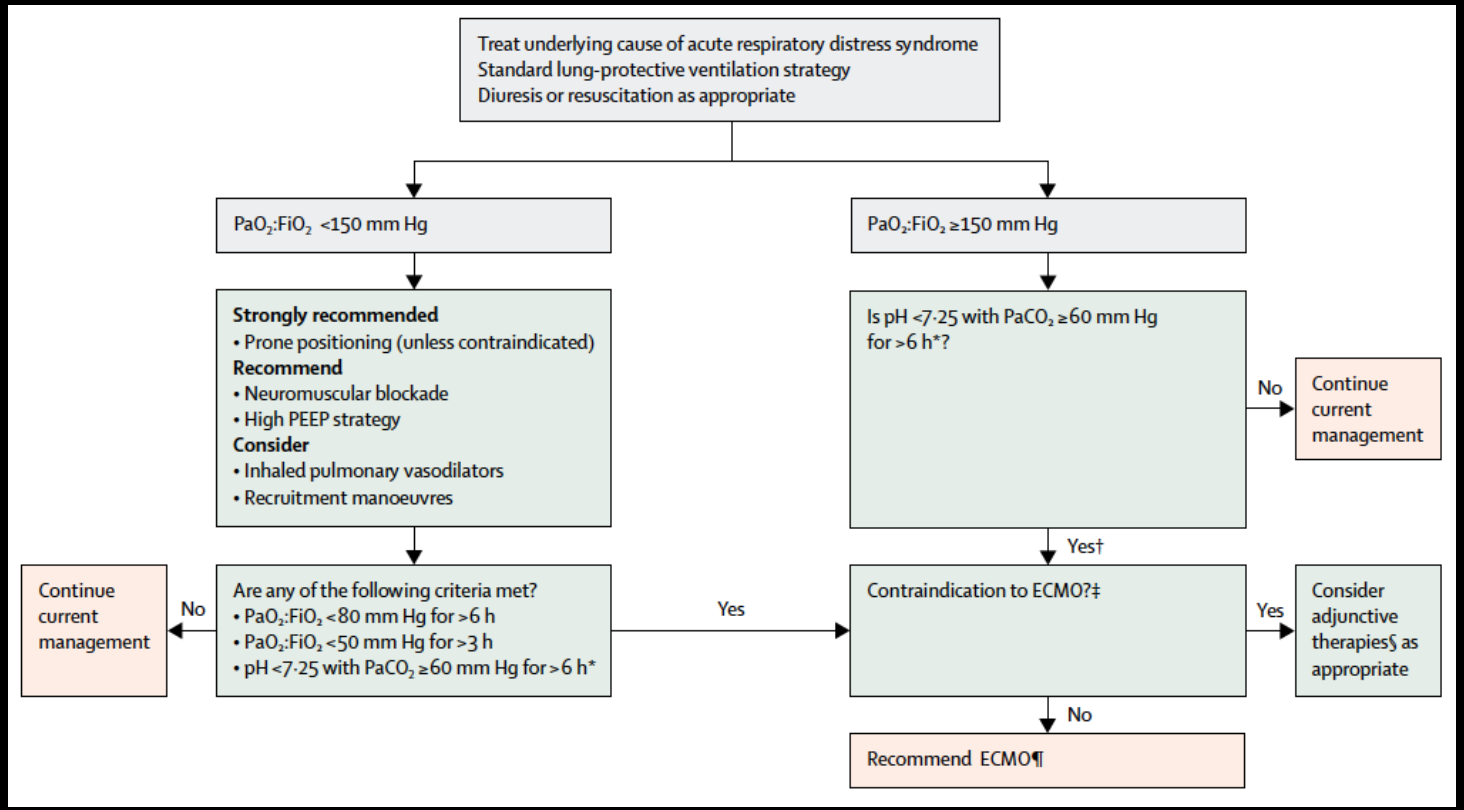


Figure 3: **Forest plot of mortality at latest follow-up in randomised controlled trials of ECMO *vs* CMV in adults with severe acute respiratory distress syndrome**
6-month mortality or death before discharge was the latest follow-up timepoint in Peek et al's trial, whereas 60-day mortality was the latest timepoint in Combes et al's trial. Risk ratios were calculated with a random-effects model. ECMO=extracorporeal membrane oxygenation. CMV=conventional mechanical ventilation. df=degree of freedom.

Interpretation: Compared with conventional mechanical ventilation, use of venovenous ECMO in adults with severe acute respiratory distress syndrome was associated with reduced 60-day mortality. However, venovenous ECMO was also associated with a moderate risk of major bleeding.

Lancet Respir Med 2019;7: 163–72

Management Algorithm of ECMO for ARDS

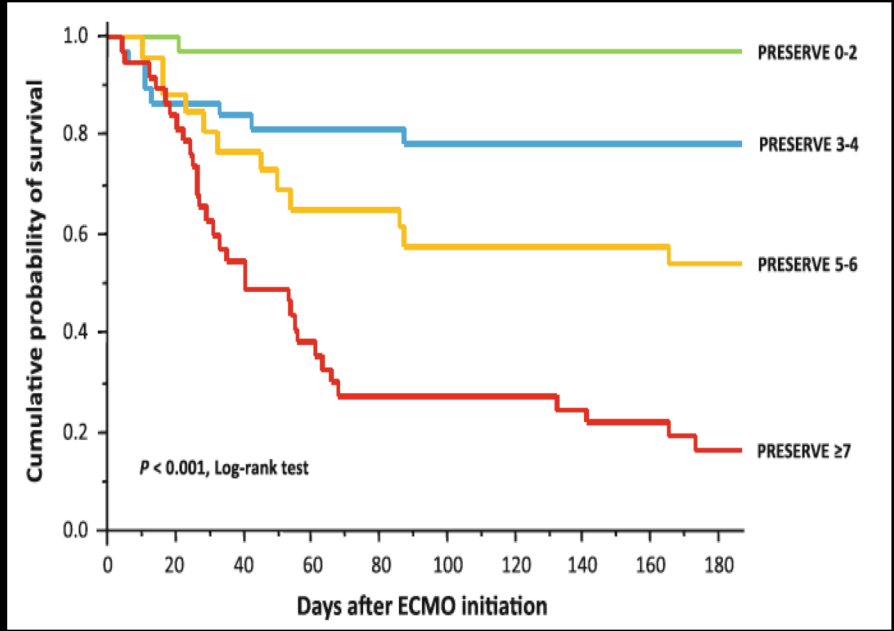


The Lancet Respiratory Medicine 2019/01

PRESERVE study

prediction of successful ECMO for ARDS

Parameter	Score
Age (years)	
<45	0
45–55	2
>55	3
Body mass index >30	−2
Immunocompromised	2
SOFA >12[a]	1
MV >6 days	1
No prone positioning before ECMO	1
PEEP < 10 cm H_2O	2
Plateau pressure >30 cm H_2O	2
Total score[c]	0–14

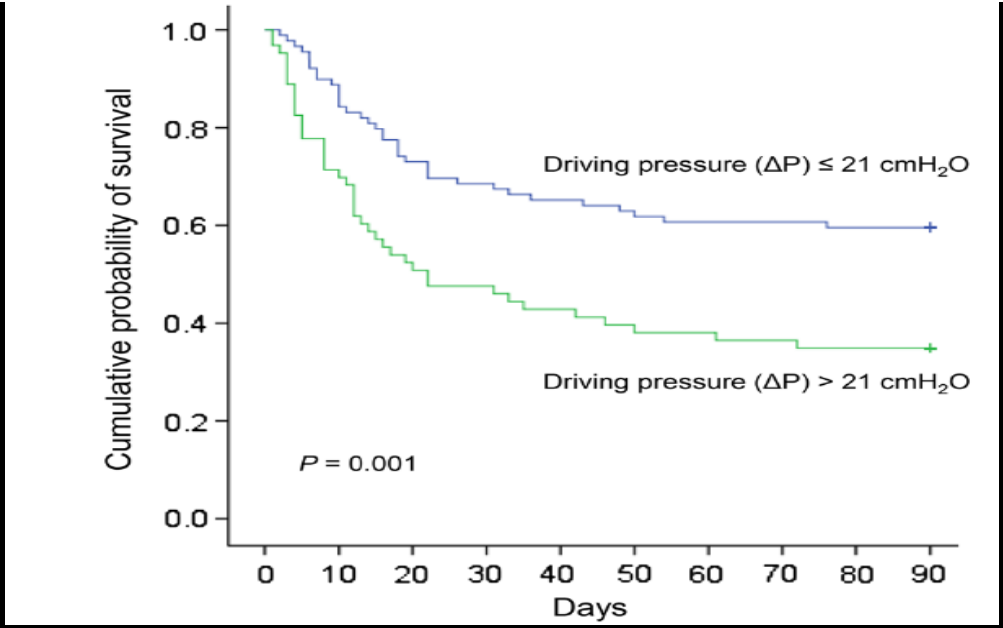


Intensive Care Med (2013) 39:1704–1713

Dynamic Driving Pressure for ARDS with ECMO

Table 2 Cox proportional hazards regression model with ICU mortality as outcome

Factors	Hazard ratio (95% CI)	*p* value
Multivariate analysis		
Immunocompromised	1.957 (1.216–3.147)	0.006
APACHE II score	1.039 (1.005–1.073)	0.023
ARDS duration before ECMO	1.002 (1.000–1.003)	0.029
Mean dynamic driving pressure from day 1 to 3 on ECMO	1.070 (1.026–1.116)	0.002



Chiu *et al. Ann. Intensive Care (2017) 7:12*

Table 3 Outcome parameters of the study

	All patients			Subgroup: PaO_2/FIO_2 <150		
	avECCO$_2$-R	Control	*p*	avECCO$_2$-R	Control	*p*
Ventilator-free-days-28	10.0 ± 8	9.3 ± 9	0.779	11.3 ± 7.5	5.0 ± 6.3	0.033
Ventilator-free-days-60	33.2 ± 20	29.2 ± 21	0.469	40.9 ± 12.8	28.2 ± 16.4	0.033
Non-pulmonary organ failure free days-60	21.0 ± 14	23.9 ± 15	0.447	24.1 ± 7.5	29.0 ± 17.7	0.428
Lung injury score on day 10	2.2 ± 0.6	2.1 ± 0.5	0.854	2.3 ± 0.8	2.2 ± 0.5	0.601
Length of stay in hospital (days)	46.7 ± 33	35.1 ± 17	0.113	42.0 ± 16.6	40.3 ± 15.7	0.815
Length of stay in ICU (days)	31.3 ± 23	22.9 ± 11	0.144	25.9 ± 13.1	31.0 ± 12.7	0.258
In-hospital mortality	7/40 (17.5 %)	6/39 (15.4 %)	1.000	1/21 (4.8 %)	1/10 (10 %)	0.563

Table 4 The serum level of tumor necrosis factor (TNF), interleukin 6 (IL-6), and interleukin 8 (IL-8) in treatment and control patients (median values and 25/75 percentiles)

TNF (pg/ml)	Before begin of the study	24 h	48 h	72 h
avECCO$_2$-R ($n = 20$)	19.8 (13.8–23)	20 (13.2–23.6)	15.3 (13.7–21.4)	22.5 (12.8–33.2)
Control ($n = 15$)	20.5 (14.2–26.8)	21 (13.9–48.6)	15.9 (13.6–28)	15.2 (12.7–25)
IL-6 (pg/ml)				
avECCO$_2$-R ($n = 20$)	163 (86–419)	85 (50–193)$^{\$}$	53 (20–109)$^{\$\$}$	60 (35–155)$^{\$}$
Control ($n = 15$)	97 (84–214)	111 (52–171)	102 (58–166)	64 (18–90)
IL-8 (ng/l)				
avECCO$_2$-R ($n = 20$)	72 (23–98)	65 (30–100)	71 (28–94)	81 (43–120)
Control ($n = 15$)	34 (23–49)	36 (24–126)	45 (29–529)	25 (17–191)

$^{\$}$ $p < 0.05$ in comparison with before
$^{\$\$}$ $p < 0.01$ in comparison with before

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.