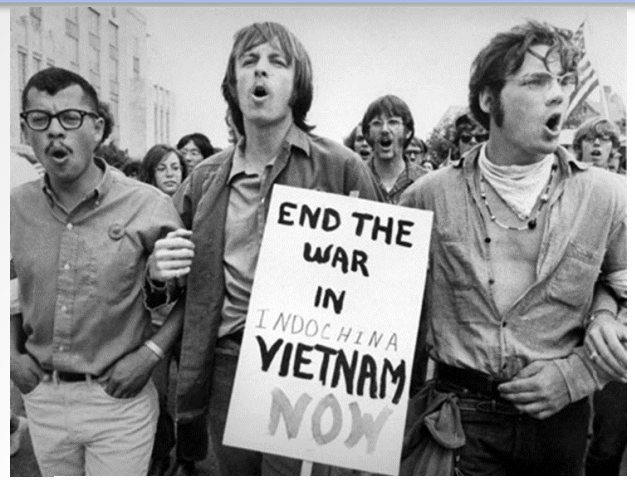
Σύνδρομο οξείας Αναπνευστικής Δυσχέρειας (Acute Respiratory Distress Syndrome-ARDS)

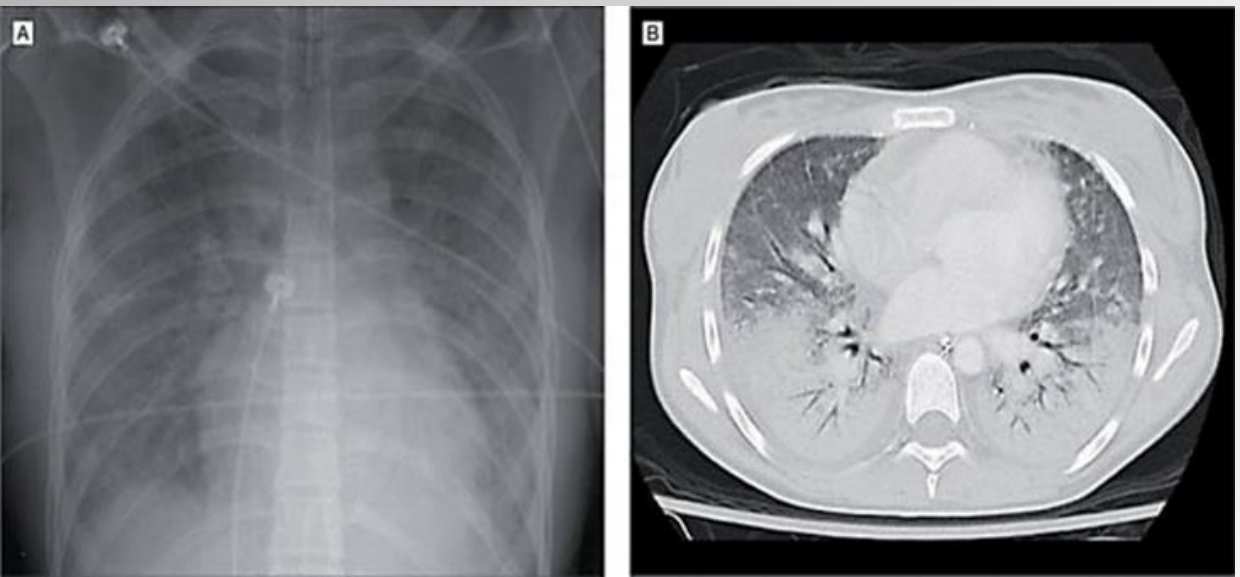
Αντωνία Κουτσούκου

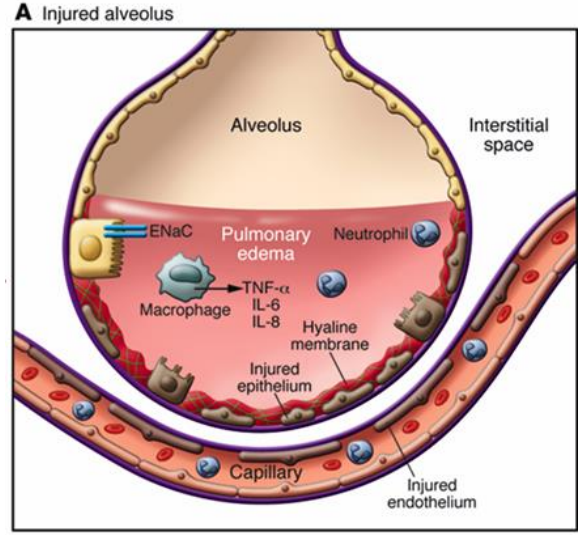
Καθηγήτρια

Σύνδρομο οξείας αναπνευστικής δυσχέρειας, Acute Respiratory Distress Syndrome, ARDS

12 ασθενείς με οξεία αναπνευστική δυσχέρεια, κυάνωση, μείωση της πνευμονικής ενδοτικότητας και διάχυτα διηθήματα στην Ro θώρακος

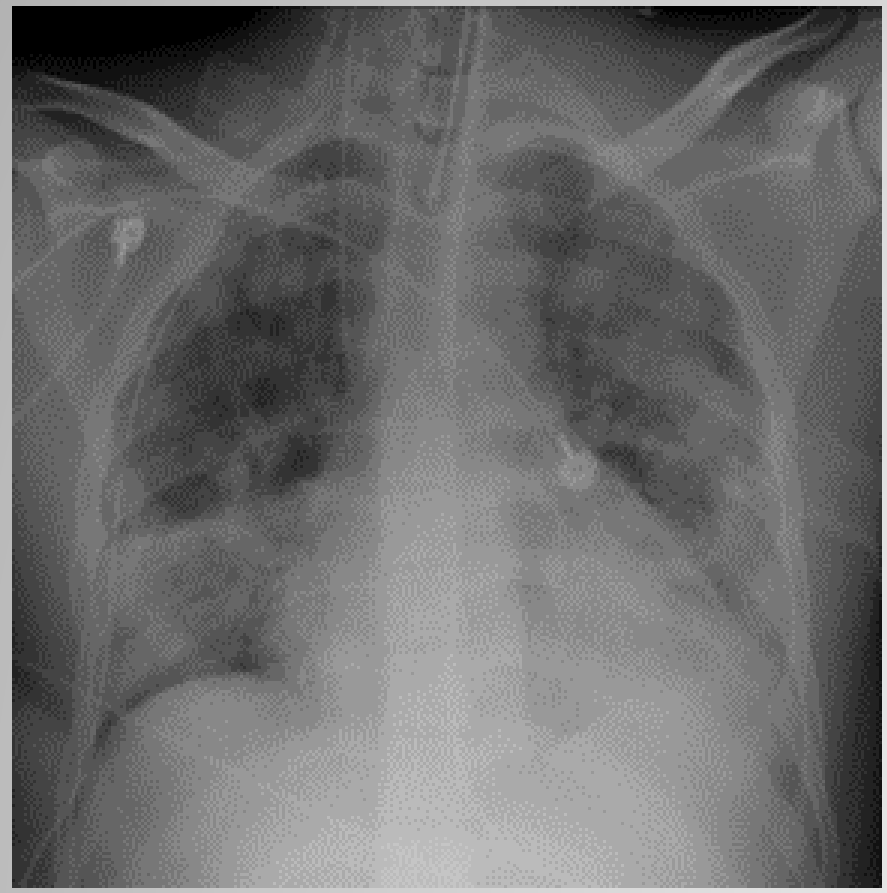






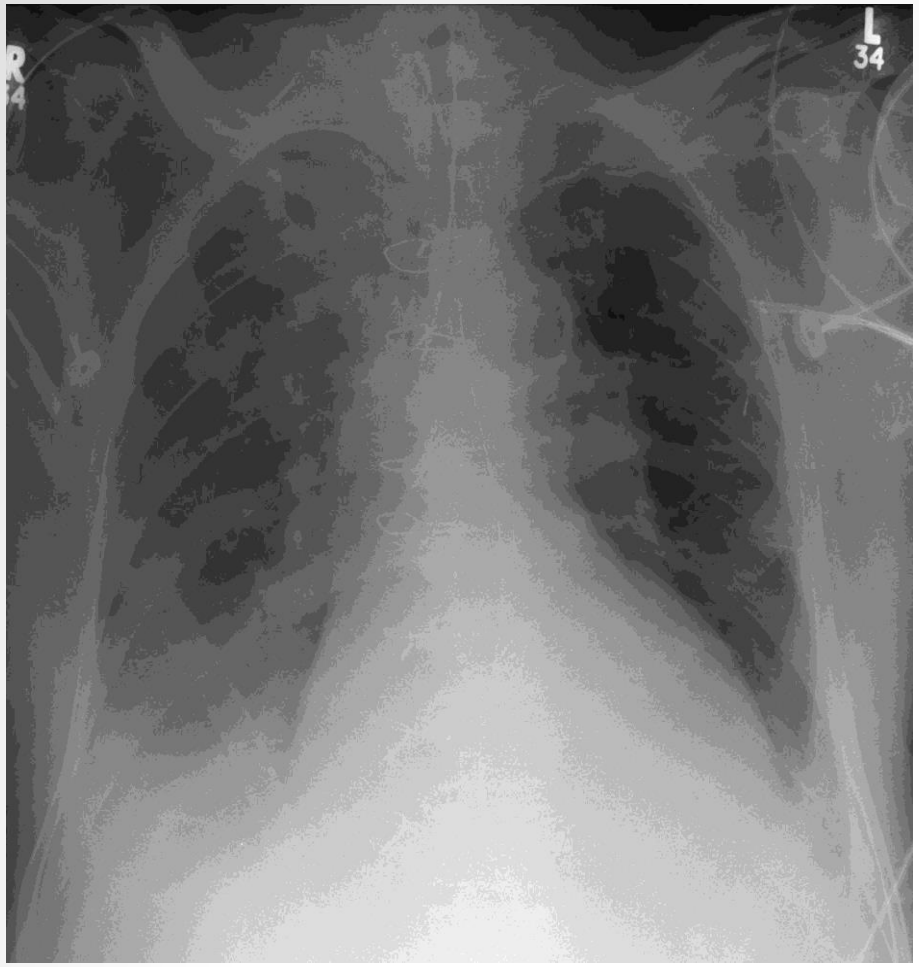
Ashbaugh, The Lancet, 1967 290: 7511; 319 – 323

The Berlin Definition 2012

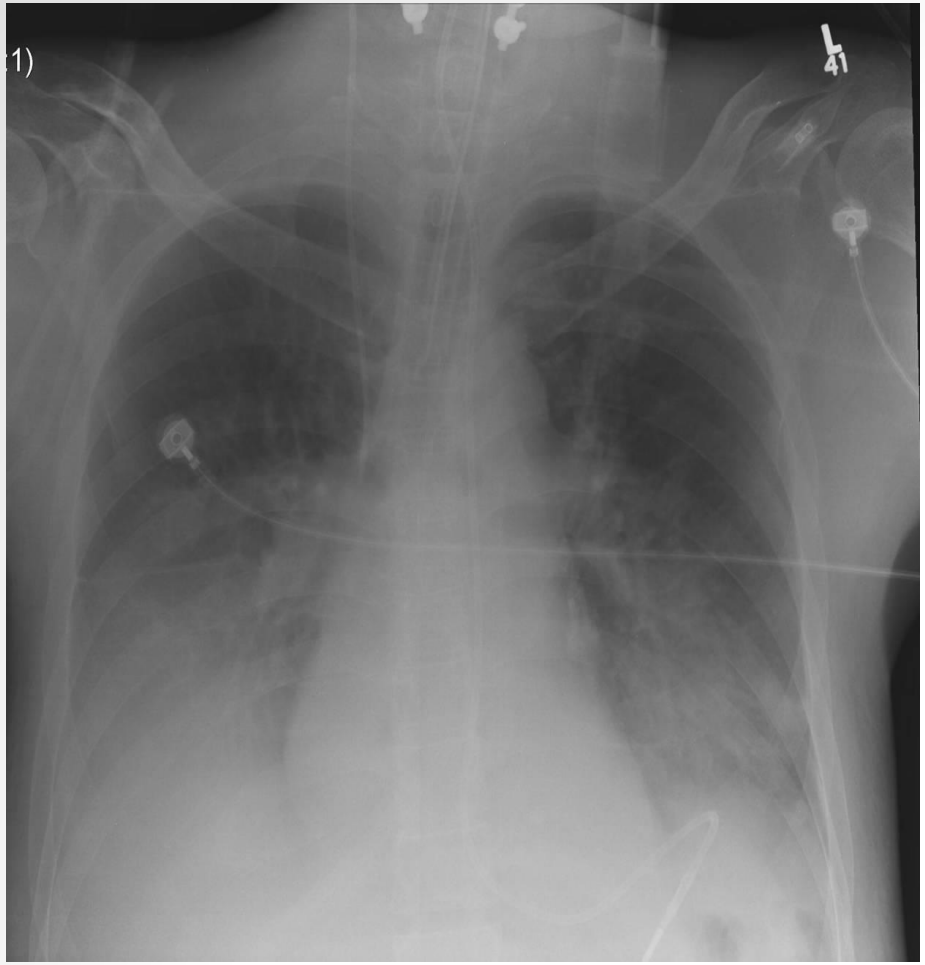


- **Οξεία εναρξη αναπνευστικής ανεπάρκειας (εντός 7 ημερών) μετά από ένα εκκλυτικό αίτιο «καταστροφικό γεγονός»**
- **Αμφοτερόπλευρα διηθήματα στη Ro θώρακος (που δεν εξηγούνται από συλλογές, όζους ή ατελεκτασίες)**
- **Αναπνευστική ανεπάρκεια που δεν εξηγείται πλήρως από καρδιακή ανεπάρκεια ανεπάρκειας**
- **PaO_2/FiO_2 (PEEP≥ 5cm H2O)**
- **$300 > PaO_2/FiO_2 \geq 200$ Ήπιο ARDS**
- **$200 > PaO_2/FiO_2 \geq 100$ Μέτριο ARDS**
- **$PaO_2/FiO_2 < 100$ Βαρύ ARDS**

2012 The Berlin Definition

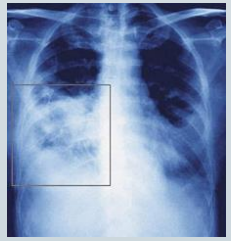


2012 The Berlin Definition

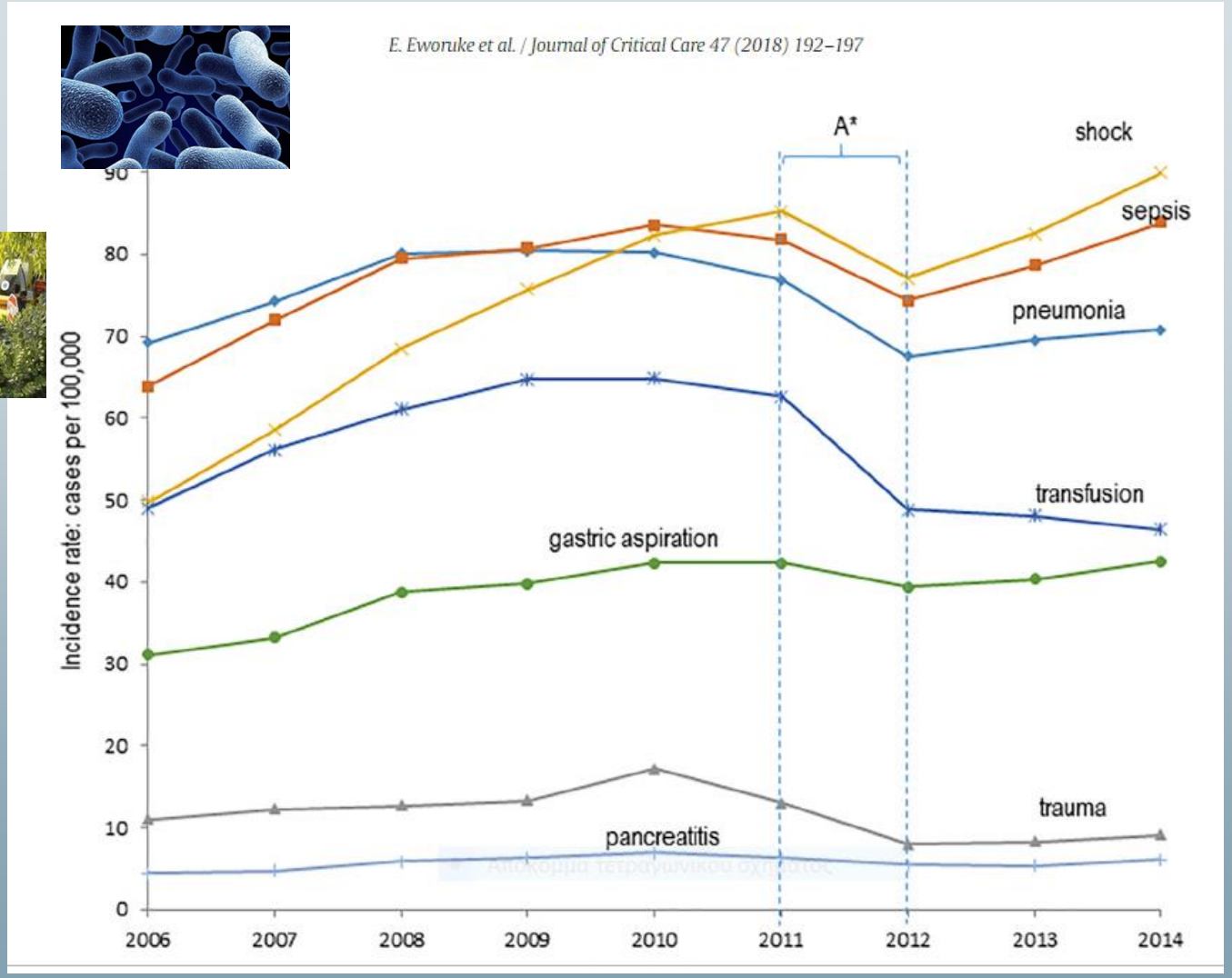


Κλινικές καταστάσεις που οδηγούν σε ARDS

- Πνευμονία
- Σήψη
- Σοβαρό τραύμα
- Εισρόφηση
- Πνευμονική θλάση
- Μεταγγίσεις-TRALI
- Οξεία παγκρεατίτιδα
- Εισπνοή τοξικών αερίων
- Εγκαύματα
- Μη-Καρδιογενές shock
- Δηλητηριάσεις
- Παρ 'ολίγον πνιγμός



Ferguson Crit Care 2007



Επιδημιολογία

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries

Giacomo Bellani, MD, PhD; John G. Laffey, MD, MA; Tài Pham, MD; Eddy Fan, MD, PhD; Laurent Brochard, MD, HDR; Andres Esteban, MD, PhD; Luciano Gattinoni, MD, FRCP; Frank van Haren, MD, PhD; Anders Larsson, MD, PhD; Daniel F. McAuley, MD, PhD; Marco Ranieri, MD; Gordon Rubenfeld, MD, MSc; B. Taylor Thompson, MD, PhD; Hermann Wrigge, MD, PhD; Arthur S. Slutsky, MD, MASc; Antonio Pesenti, MD; for the LUNG SAFE Investigators and the ESICM Trials Group

459 ICUs
50 countries, 5 continents
29144 pts (3022, ARDS, 10.4%)

ICU Incidence of ARDS

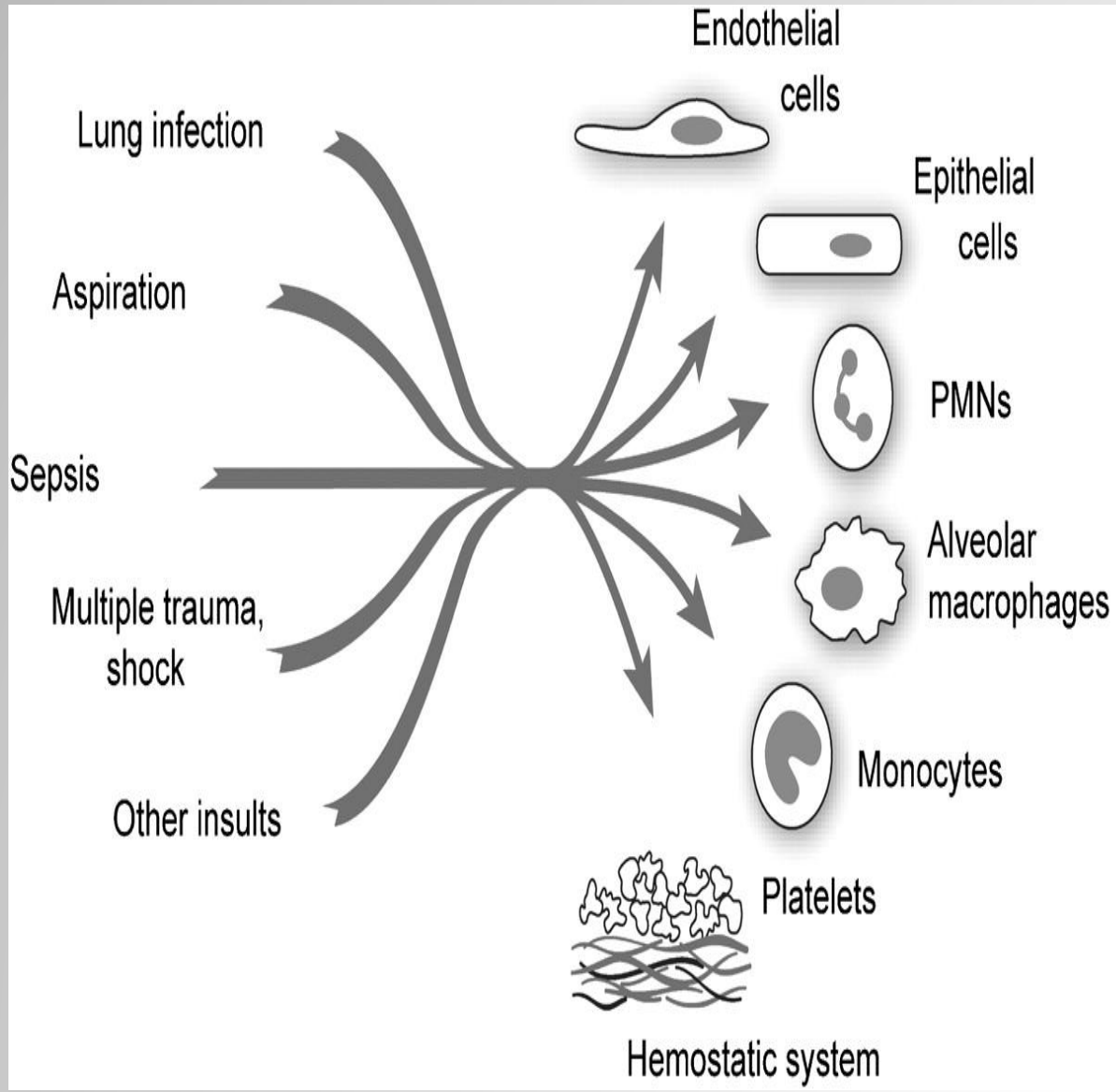
ARDS represented 10.4% (95% CI, 10.0%-10.7%) of total ICU admissions and 23.4% (95% CI, 21.7%-25.2%)of all patients requiring mechanical ventilation and constituted 0.42 cases/ ICU bed over 4 weeks. There was some geographic variation,

Recognition of ARDS

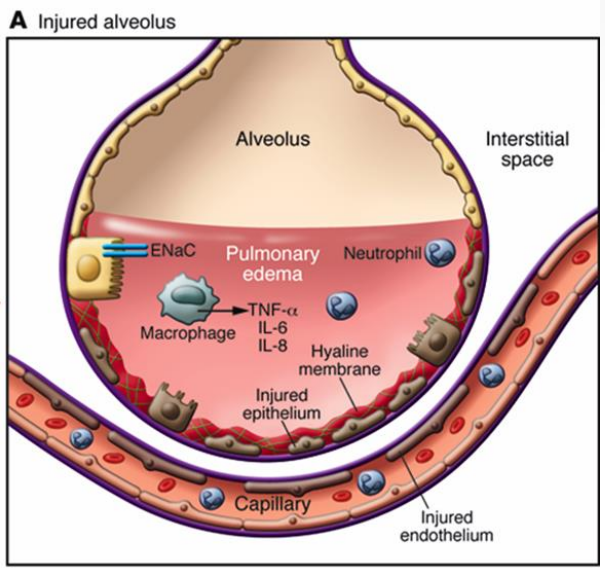
ARDS was underdiagnosed, with 60.2% of all patients with ARDS being clinician-recognized. Clinician recognition of ARDS ranged from 51.3% (95% CI, 47.5%-55.0%) for mild ARDS to 78.5% (95% CI, 74.8%-81.8%) for severe ARDS

- Bellani et al, JAMA 2016

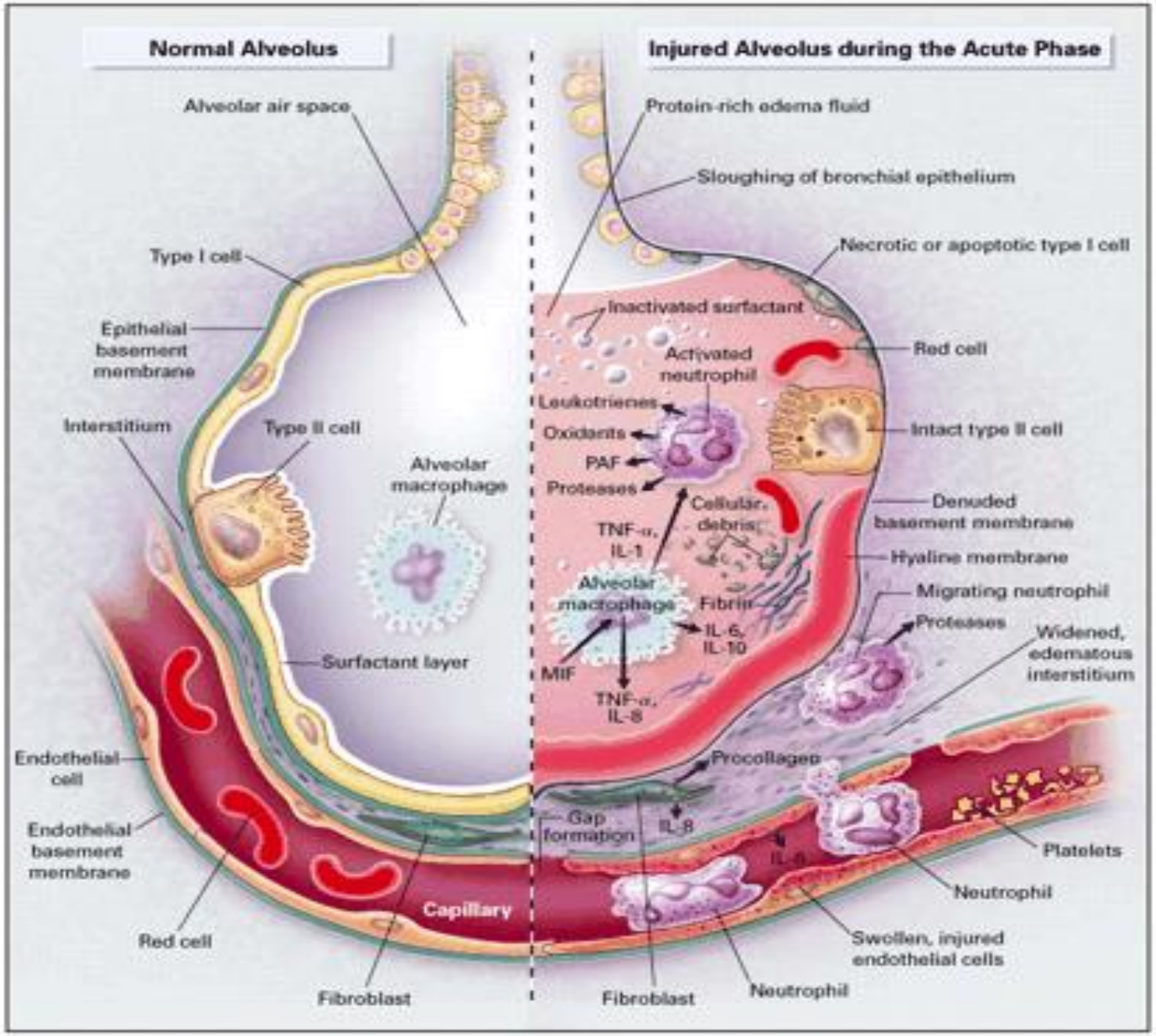
ARDS -παθογένεια



INJURY

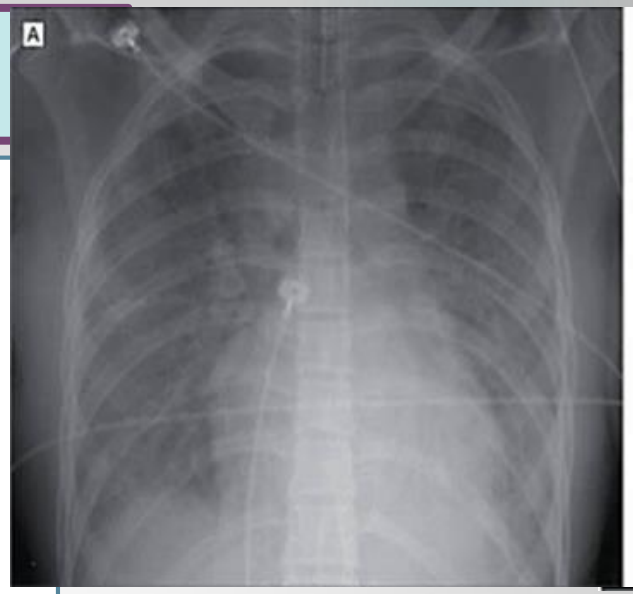


- Alveolar-capillary membrane injury
- Inflammation
- Increased permeability pulmonary edema


Normal Alveolus
Alveolar air space
Type I cell
Epithelial basement membrane
Interstitium
Type II cell
Alveolar macrophage
Surfactant layer
Endothelial cell
Endothelial basement membrane
Capillary
Red cell
Fibroblast
Injured Alveolus during the Acute Phase
Protein-rich edema fluid
Sloughing of bronchial epithelium
Necrotic or apoptotic type I cell
Inactivated surfactant
Activated neutrophil
Red cell
Leukotrienes
Oxidants
PAF
Proteases
Intact type II cell
Cellular debris
TNF-α, IL-1
Denuded basement membrane
Hyaline membrane
Alveolar macrophage
Fibrin
Migrating neutrophil
Proteases
IL-6, IL-10
MIF
TNF-α, IL-8
Widened, edematous interstitium
Procollagen
Gap formation
IL-8
Platelets
Neutrophil
Swollen, injured endothelial cells
Fibroblast
Neutrophil

Οξεία εξιδρωματική Φάση (1η-3η ημέρα)

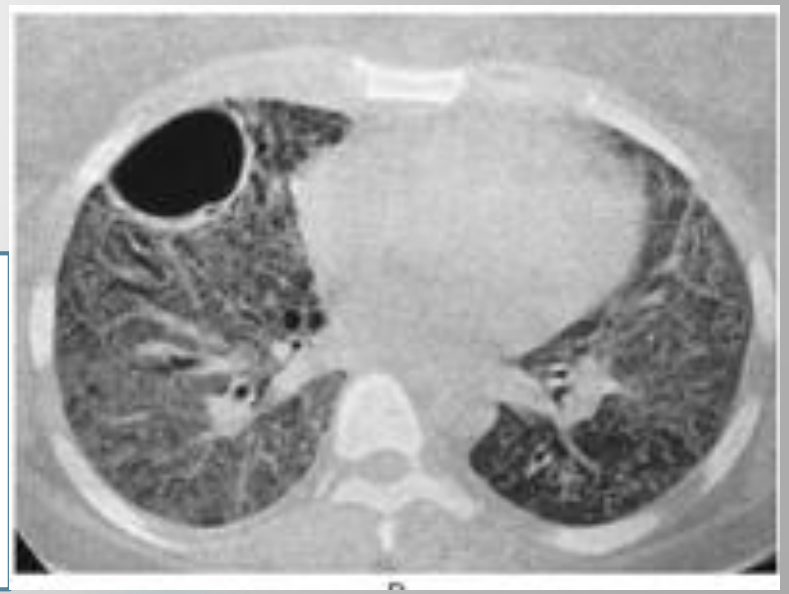
- Οξεία έναρξη αν. ανεπάρκειας (Σημαντική υποξυγοναιμία που δεν βελτιώνεται με τη χορήγηση O2)
- *Ro* θώρακος: αμφοτερόπλευρα διηθήματα συρρέοντα ή ασύμμετρα, πιθανόν πλευριτικές συλλογές
- CT θώρακος: κυψελιδικά διηθήματα και ατελεκτατικές βλάβες, ιδίως στις υποκείμενες περιοχές

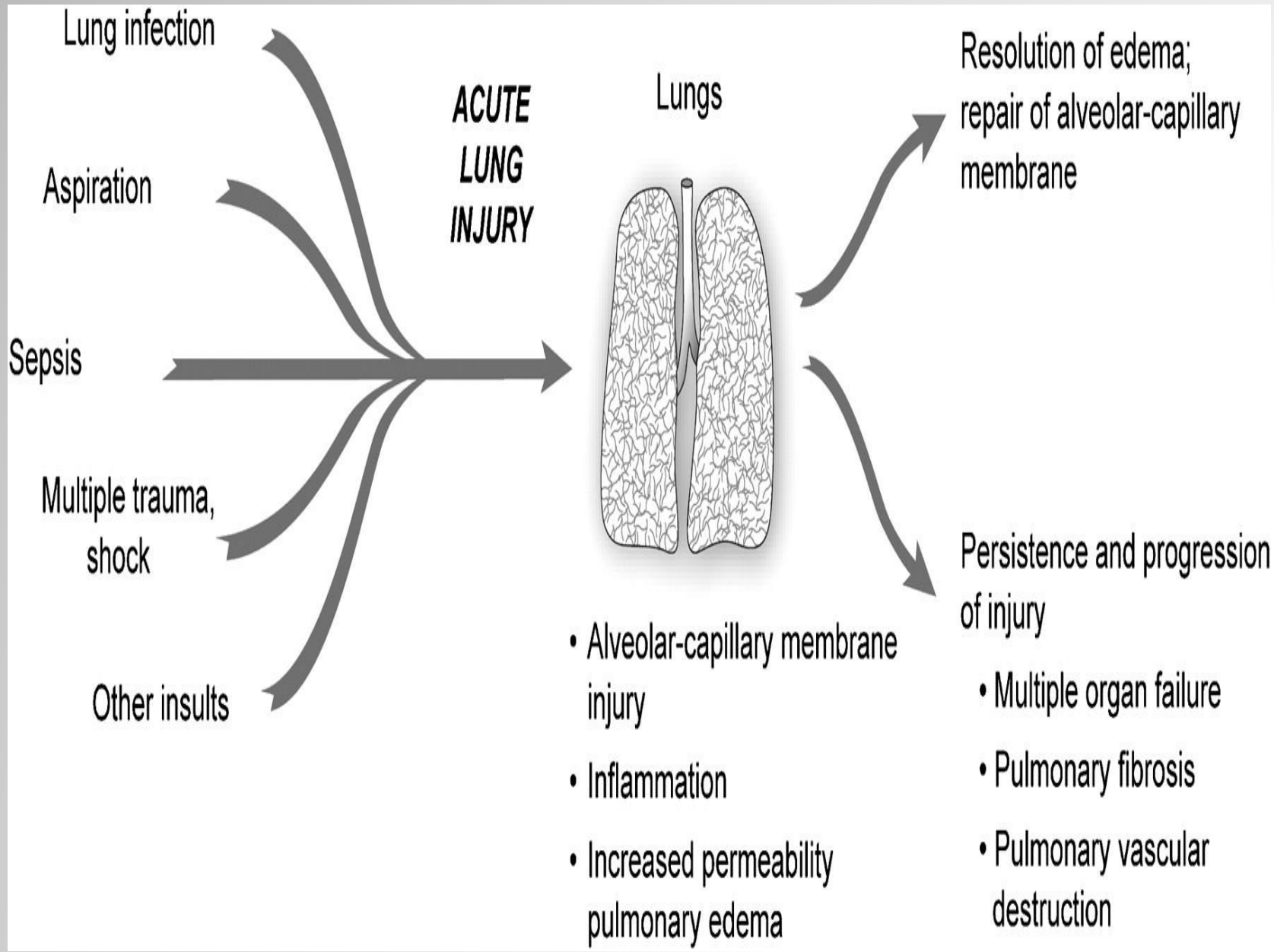


Φάση της υπερπλασίας(3-7 ημέρες)

Ινωτική φάση (>7 ημέρες)

Εμμένουσα υποξυγοναιμία, Υπερκαπνία (αύξηση του νεκρού χώρου)
Πνευμονική υπέρταση
Ro θώρακος: Γραμμοειδείς σκιάσεις (εξελισσόμενη ίνωση), πνευμοθώρακας
CT θώρακος: Διάχυτες διάμεσες σκιάσεις, bullae



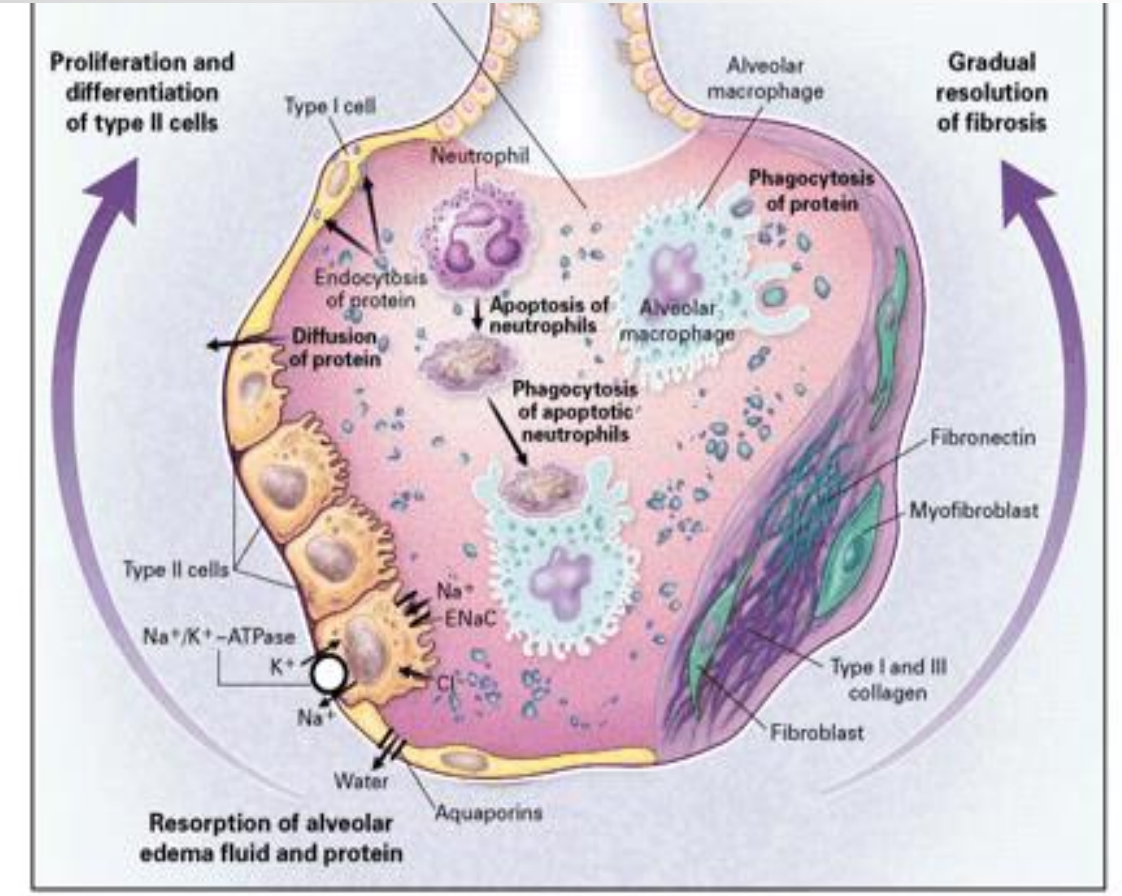

Lung infection
Aspiration
Sepsis
Multiple trauma, shock
Other insults
ACUTE LUNG INJURY
Lungs
• Alveolar-capillary membrane injury
• Inflammation
• Increased permeability pulmonary edema
Resolution of edema; repair of alveolar-capillary membrane
Persistence and progression of injury
• Multiple organ failure
• Pulmonary fibrosis
• Pulmonary vascular destruction

Κυψελιδικό οίδημα: ενεργός μεταφορά Na και Cl από τις κυψελίδες στο διάμεσο χώρο (το νερό ακολουθεί παθητικά)

Μη διαλυτές πρωτείνες: μέσω φαγοκυτταρώσεως από τα μακροφάγα

Διαλυτές πρωτεΐνες: μέσω διαχύσεως μεταξύ των επιθηλιακών κυττάρων

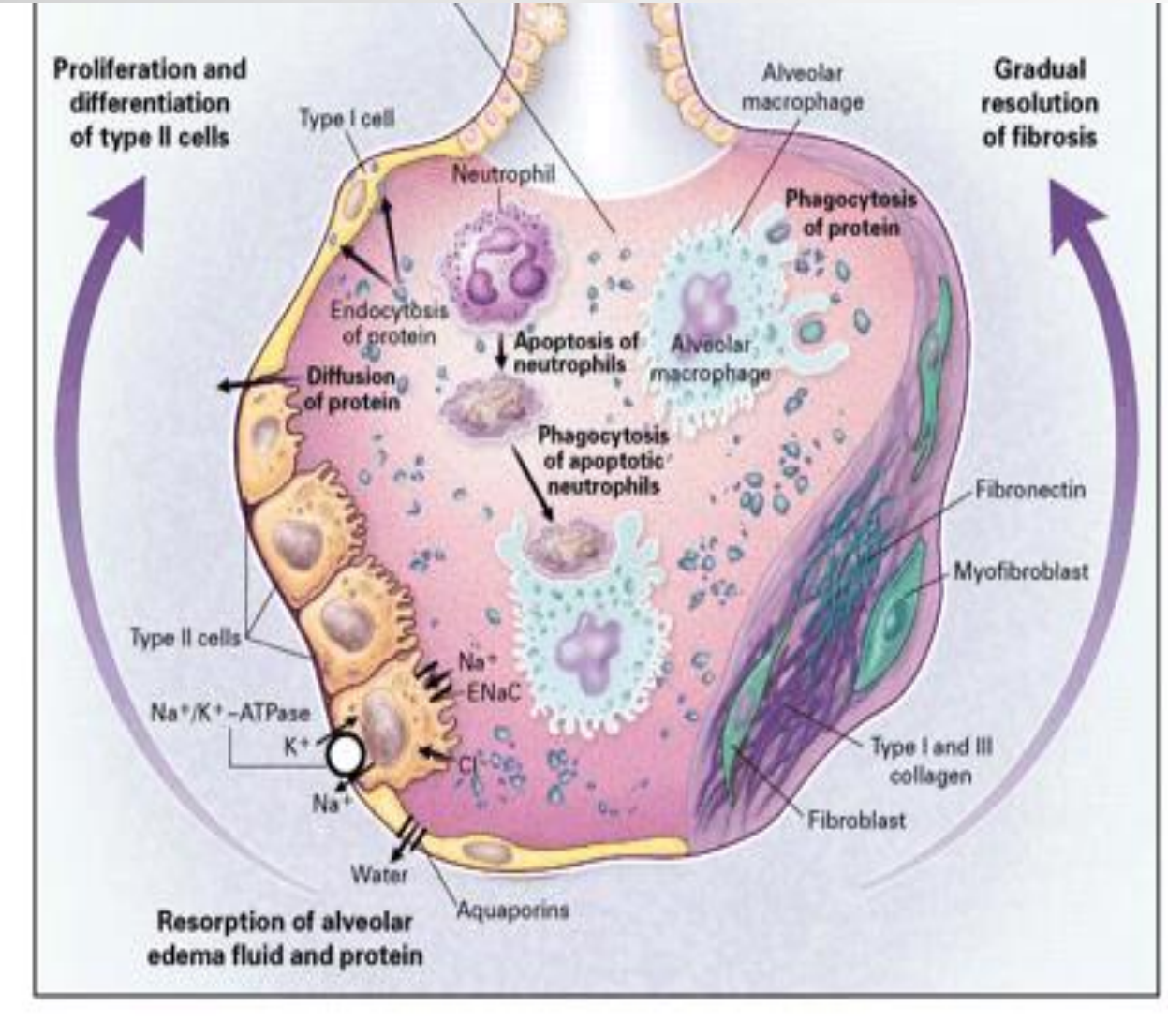
Λύση της βλάβης



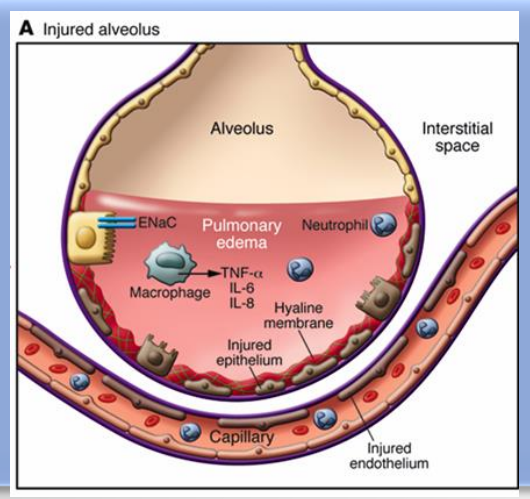
Λύση της βλάβης

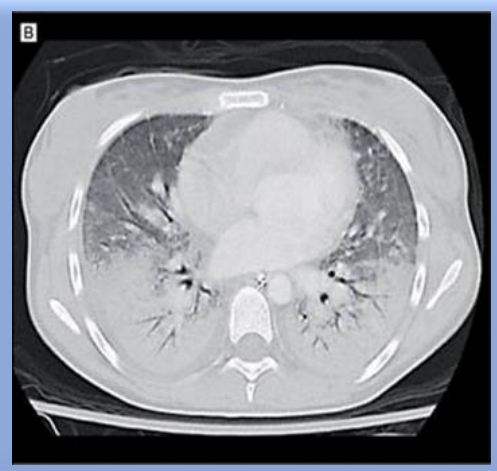
Φλεγμονώδη κύτταρα: μέσω αποπτώσεως

Τα κυψελιδικά κύτταρα τύπου II πολλαπλασιάζονται για να καλύψουν τη βασική μεμβράνη και εν συνεχεία διαφοροποιούνται σε κυψ. κύτταρα τύπου I



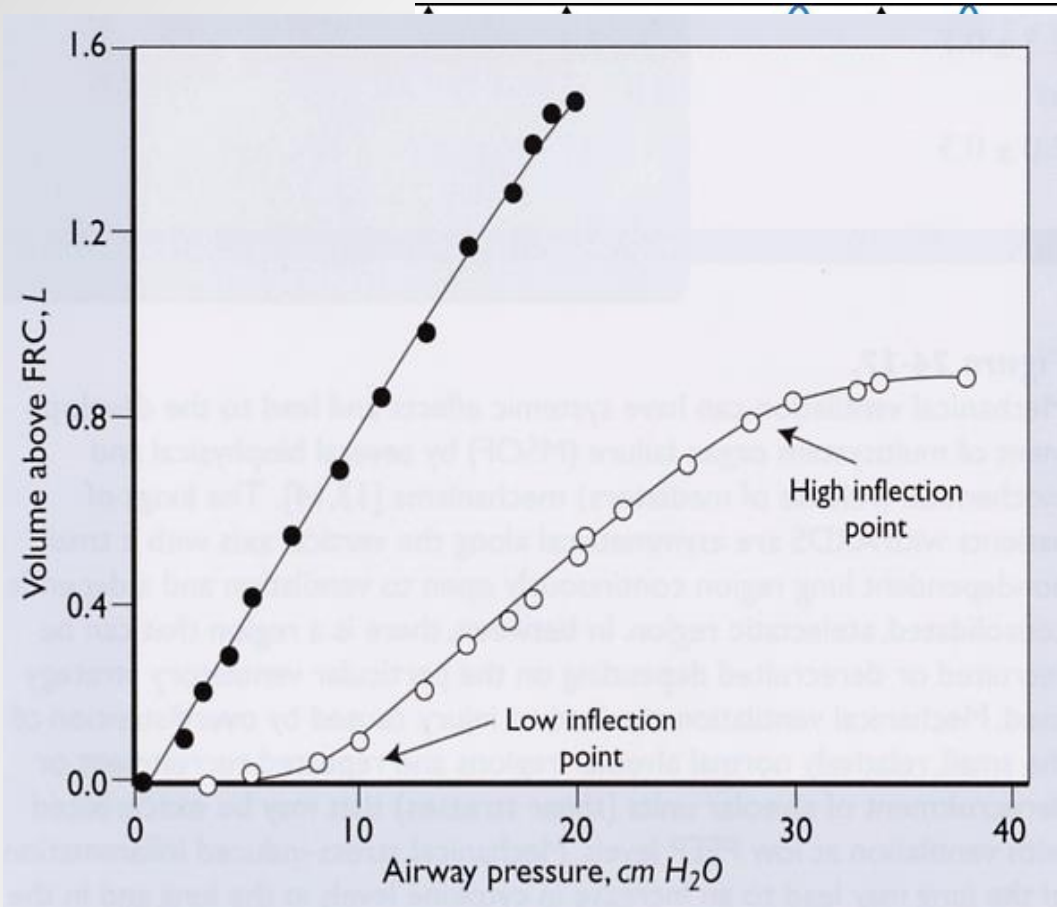
ARDS -φυσιολογία

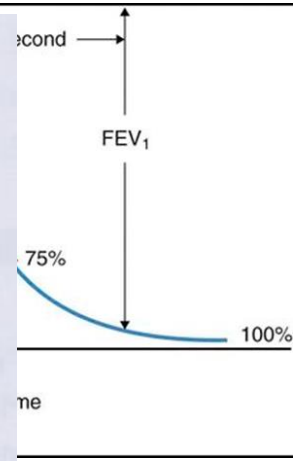




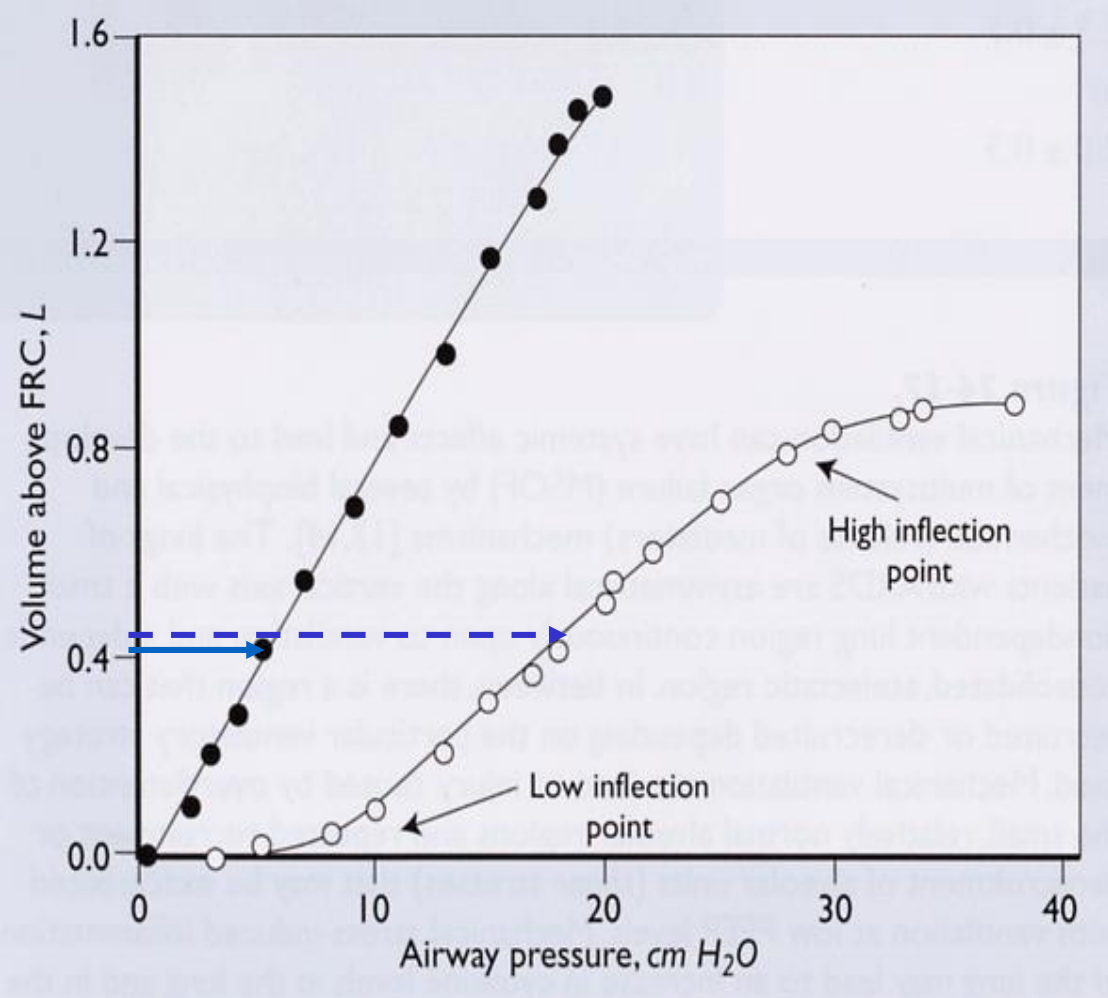
- **Ανταλλαγή των αερίων**
- **↓PaO2:** ↑shunt, διαταραχές V/Q
- **↑ PaCO2:** ↑VD/VT, ↑ παραγωγή CO2

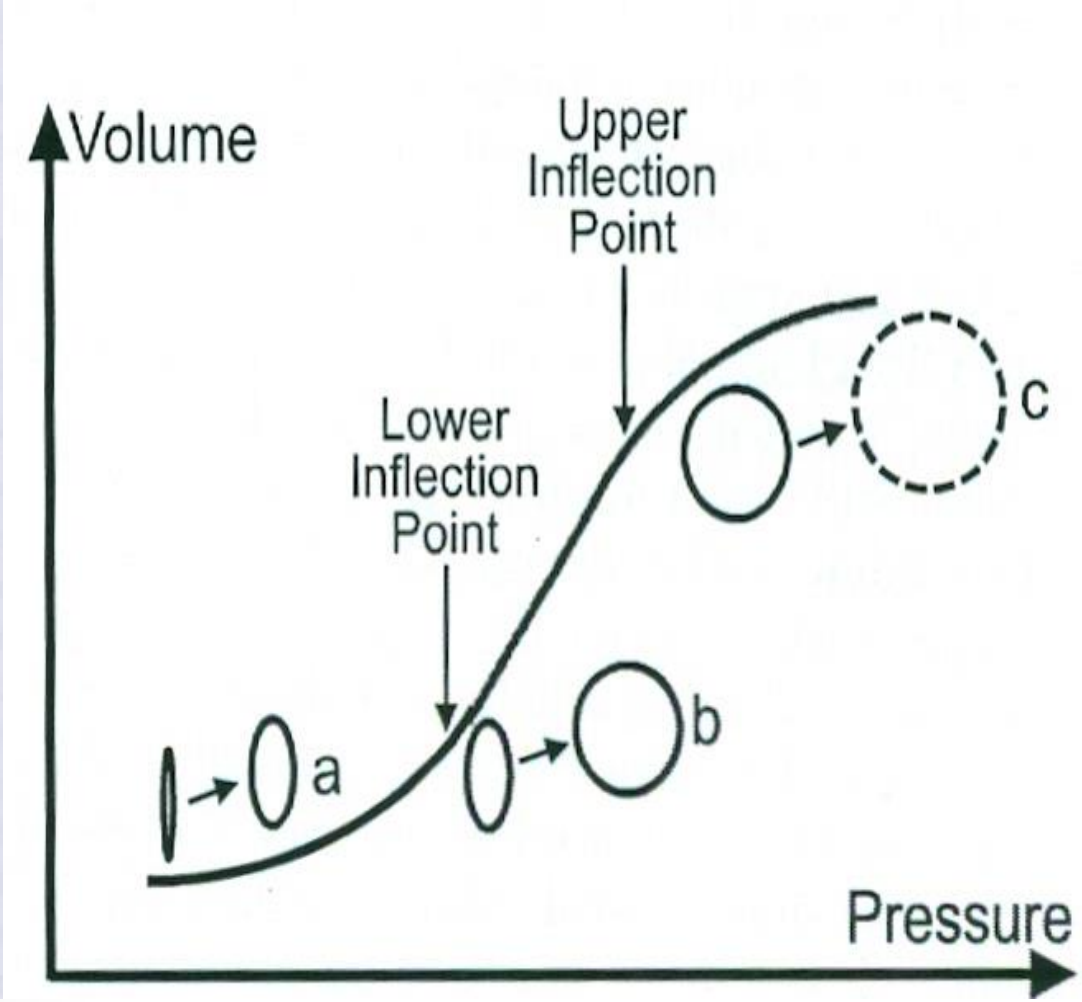
- **↓ Πνευμονικού όγκου (baby lung)**
- ↓ FRC
- ↓ VC
- ↓ Ενδοτικότητας





Ενδοτικότητα- Compliance ARDS





ARDS -φυσιολογία

- <u>Πνευμονική κυκλοφορία</u>

↑ PVR: απόφραξη αγγείων
πάχυνση τοιχώματος
συμπίεση εκ των έξω
αγγειοδραστικές ουσίες
υποξία

Οι ασθενείς με ARDS χαρακτηρίζονται από βαριά **υποξυγοναιμία**, και χρειάζονται **μηχανική υποστήριξη** της αναπνοής

Οι ασθενείς με ARDS χαρακτηρίζονται από βαριά υποξυγοναιμία, και χρειάζονται **μηχανική υποστήριξη** της αναπνοής

ΑΞΟΝΕΣ ΣΤΟΧΕΥΣΗΣ ΤΟΥ ΜΗΧΑΝΙΚΟΥ ΑΕΡΙΣΜΟΥ ΣΤΟ ARDS

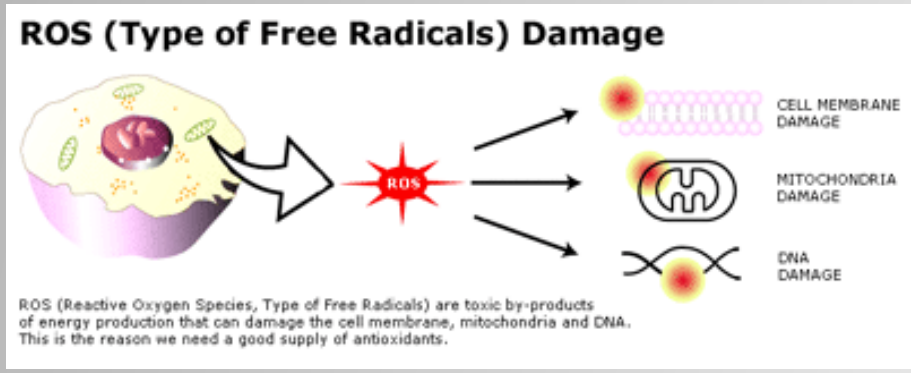
- **Επαρκής οξυγόνωση (**PaO_2 55-80 mm Hg, SaO_2: 88-95%)

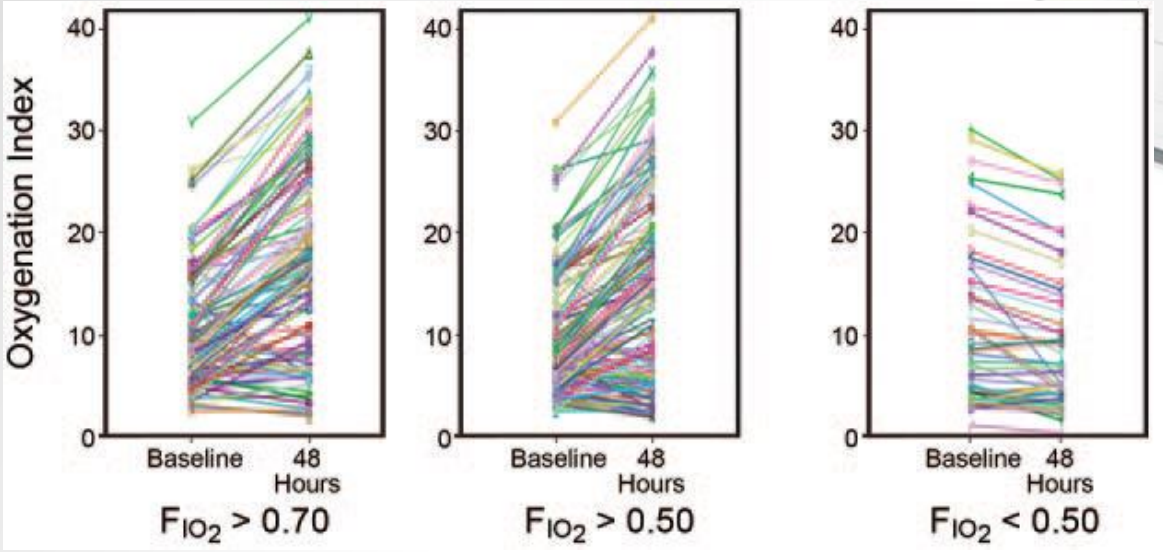
- **Ελαχιστοποίηση των βλαβών** που προκαλεί ο αναπνευστήρας *(Ventilator Induced Lung Injury-VILI)*

Μηχανικός αερισμός στο ARDS

1. Επαρκής οξυγόνωση

- a. ↑ FiO_2- Τοξικότητα





- OI = (FiO_2×mean airway pressure)/PaO_2

Rachmale, Respir Care 2012

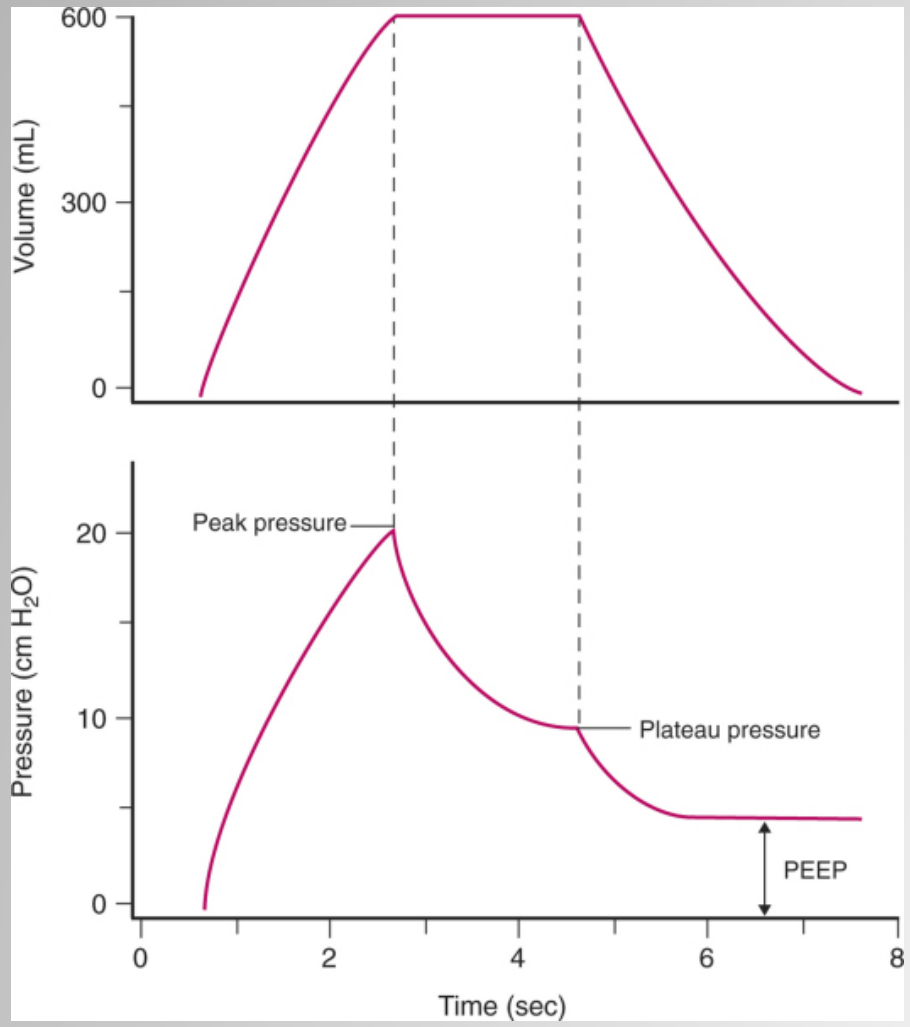
Μηχανικός αερισμός στο ARDS

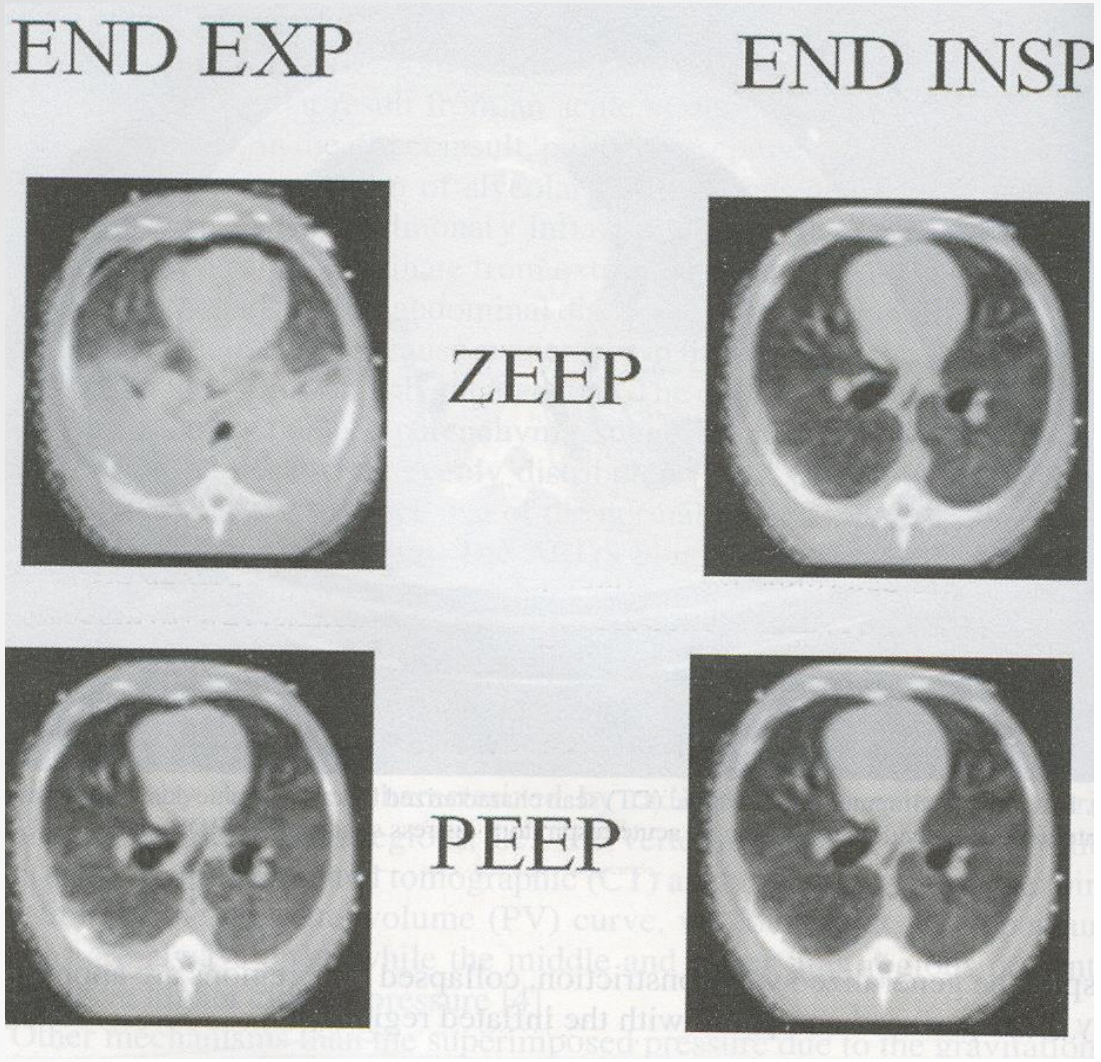
1. Επαρκής οξυγόνωση: SaO_2 >88-95%

- ↑ FiO_2- Τοξικότητα

  - Αύξηση του λειτουργικού όγκου του πνεύμονα (που συμμετέχει στην ανταλλαγή των αερίων)

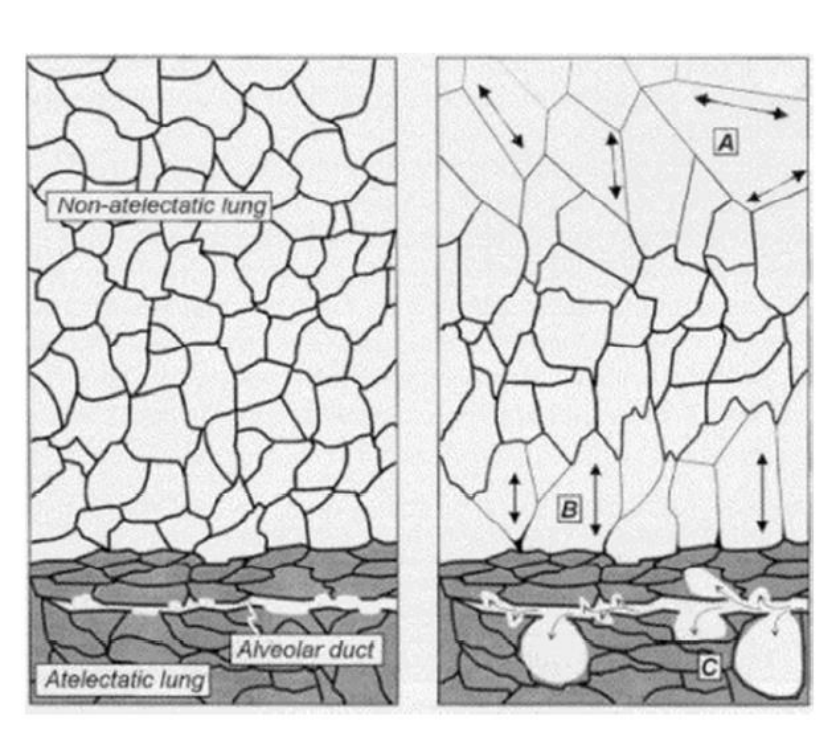
Positive End-Expiratory Pressure- PEEP

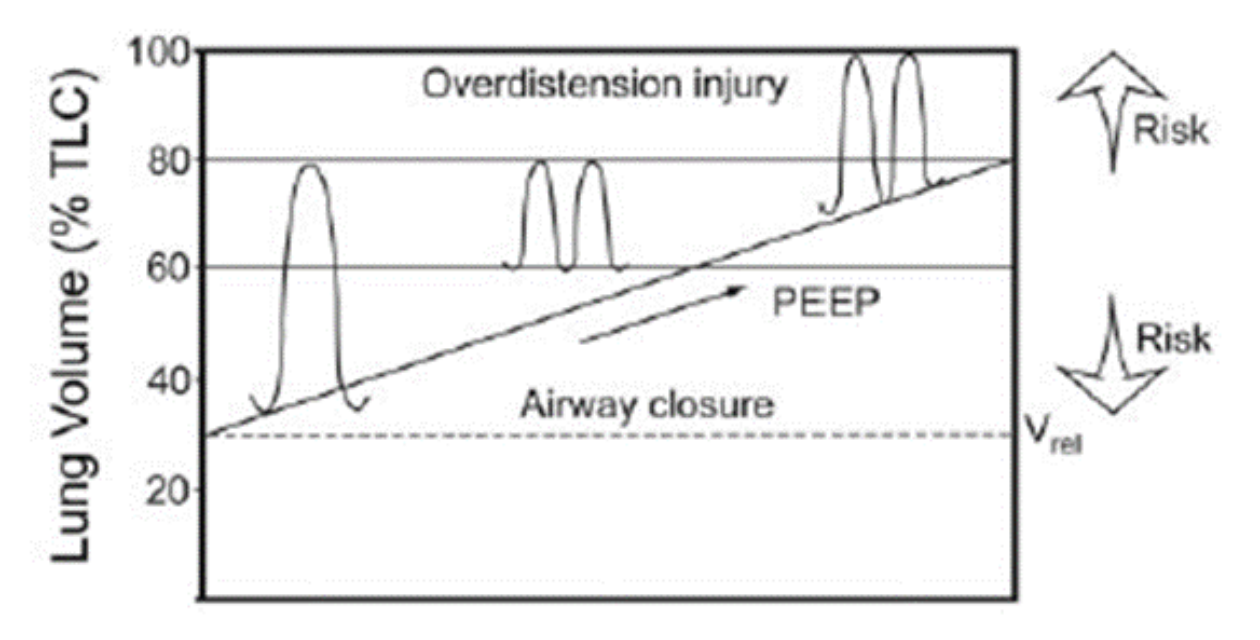




Μηχανικός αερισμός στο ARDS

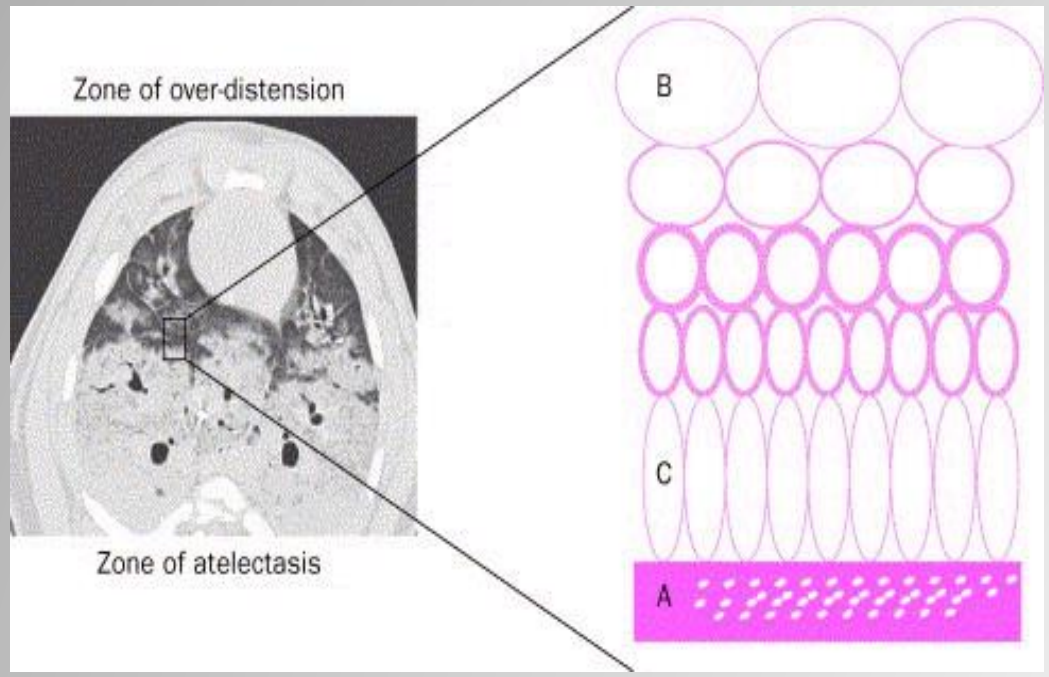
2. Αποφυγή των βλαβών που προκαλεί ο αναπνευστήρας
(Ventilator Induced Lung Injury-VILI)

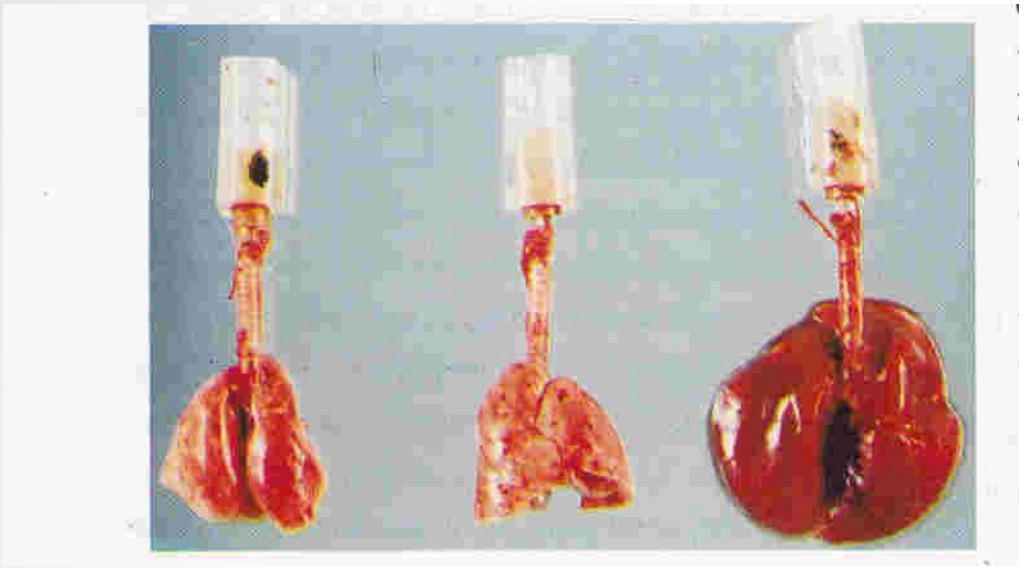




2. Ventilator Induced Lung Injury (VILI)

Hubmayr J Appl Physiol, 2005

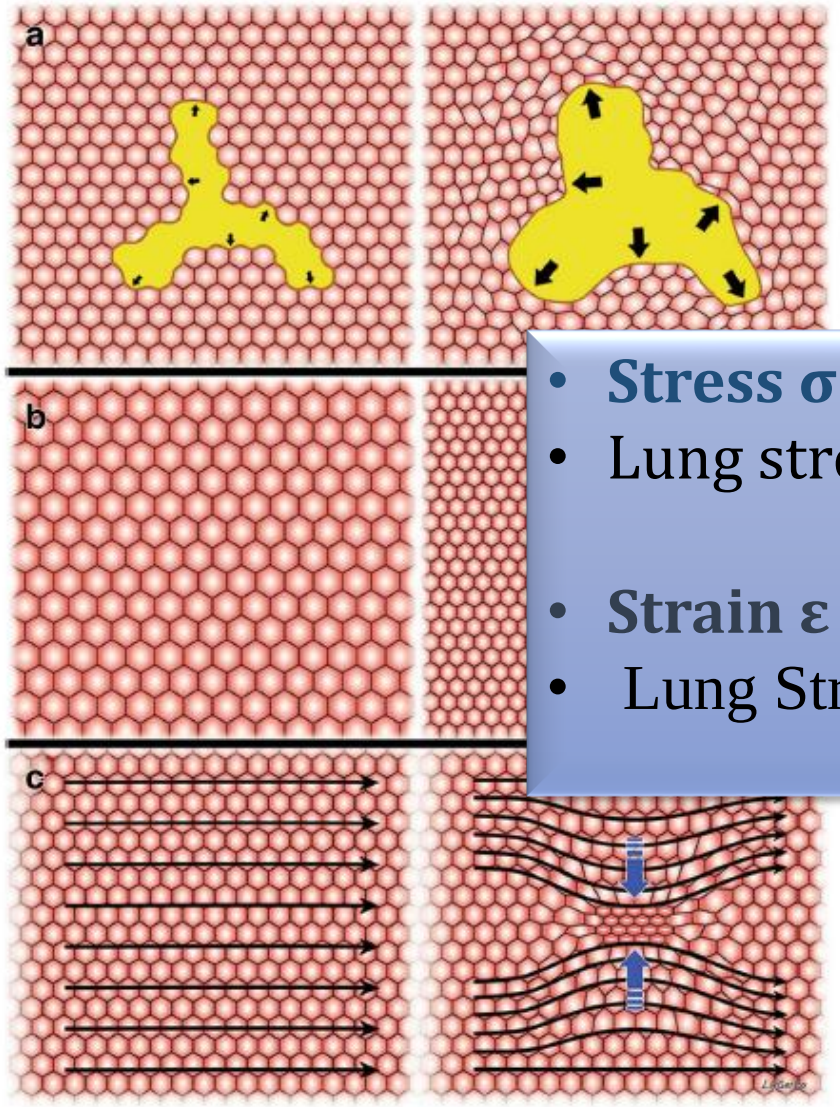


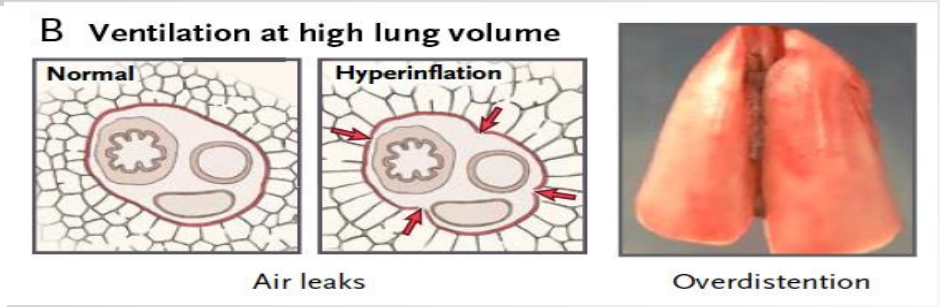


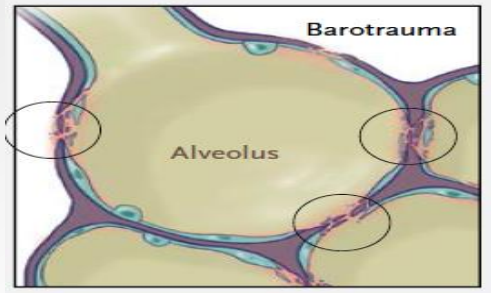
- **Περιοχική υπερδιάταση**

Περιοδική σύγκλειση-επανέκπτυξη μικρών αεραγωγών και κυψελίδων

Ventilation Induced Lung Injury

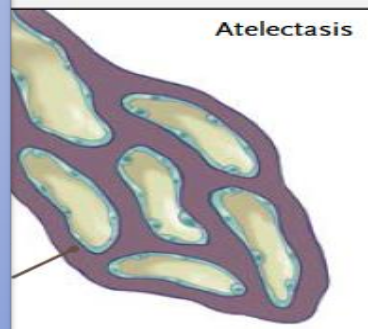


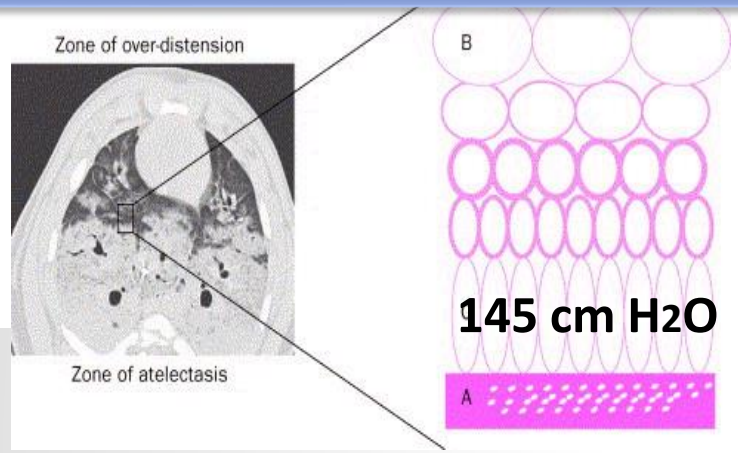




- **Stress σ** = $\Delta F/\Delta S$
- Lung stress = Transpulmonary pressure, (P_L)

- **Strain ε** = $\Delta L/L_0$ (V_T/EELV)
- Lung Strain=V_T/FRC



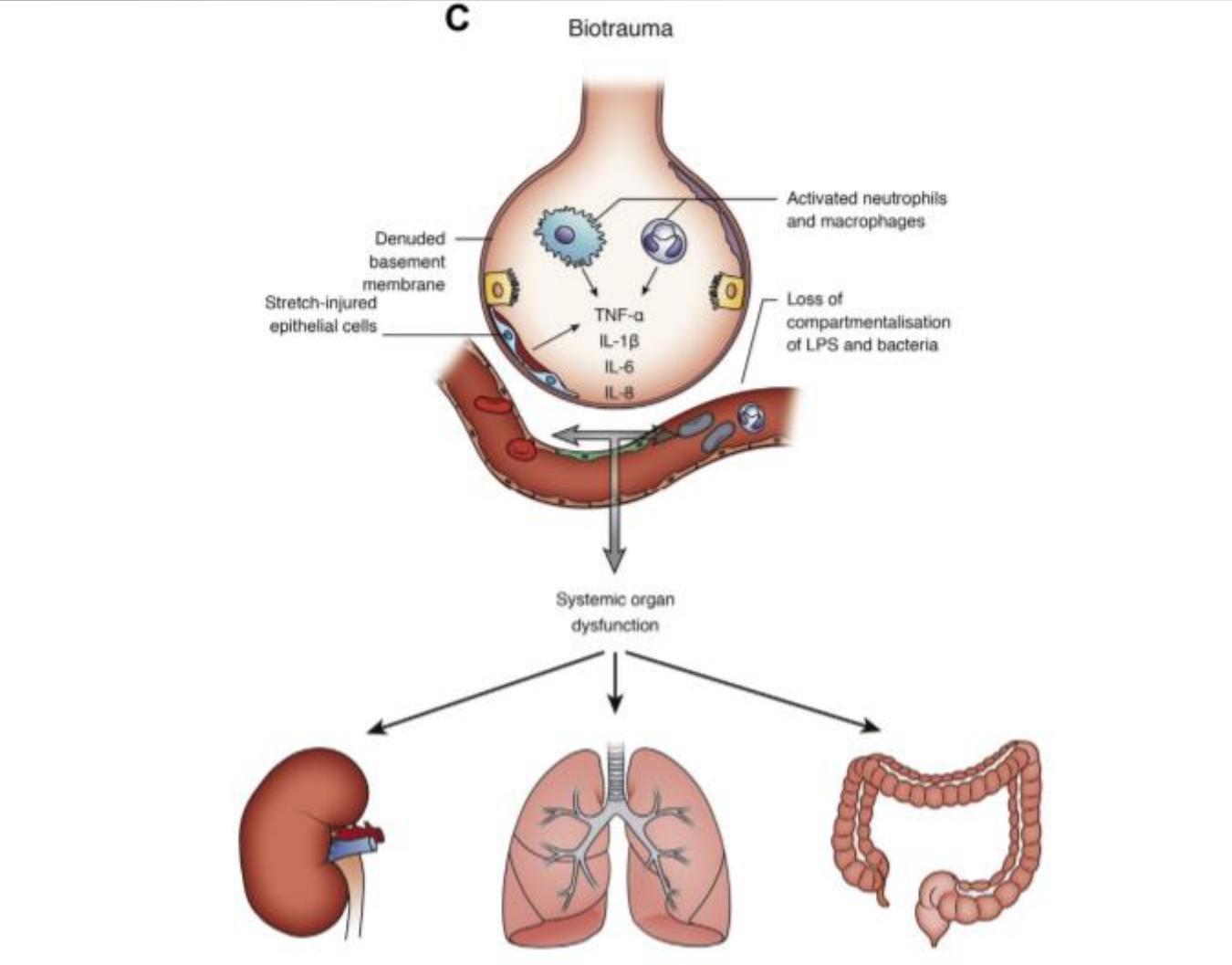


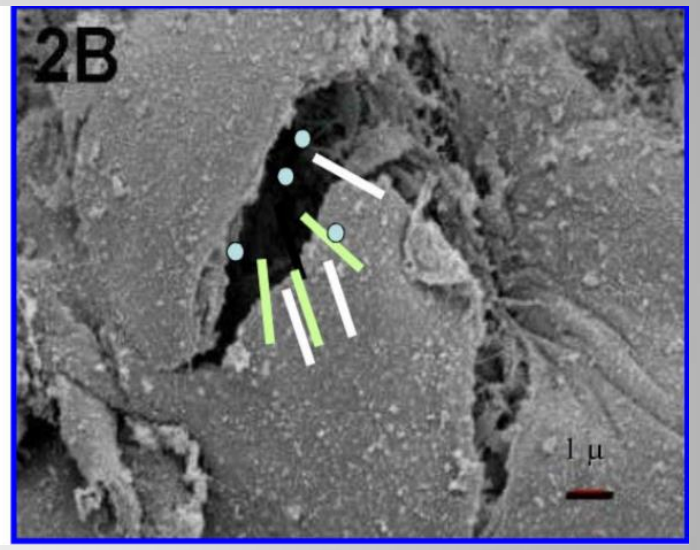
Stress raisers or concentrators

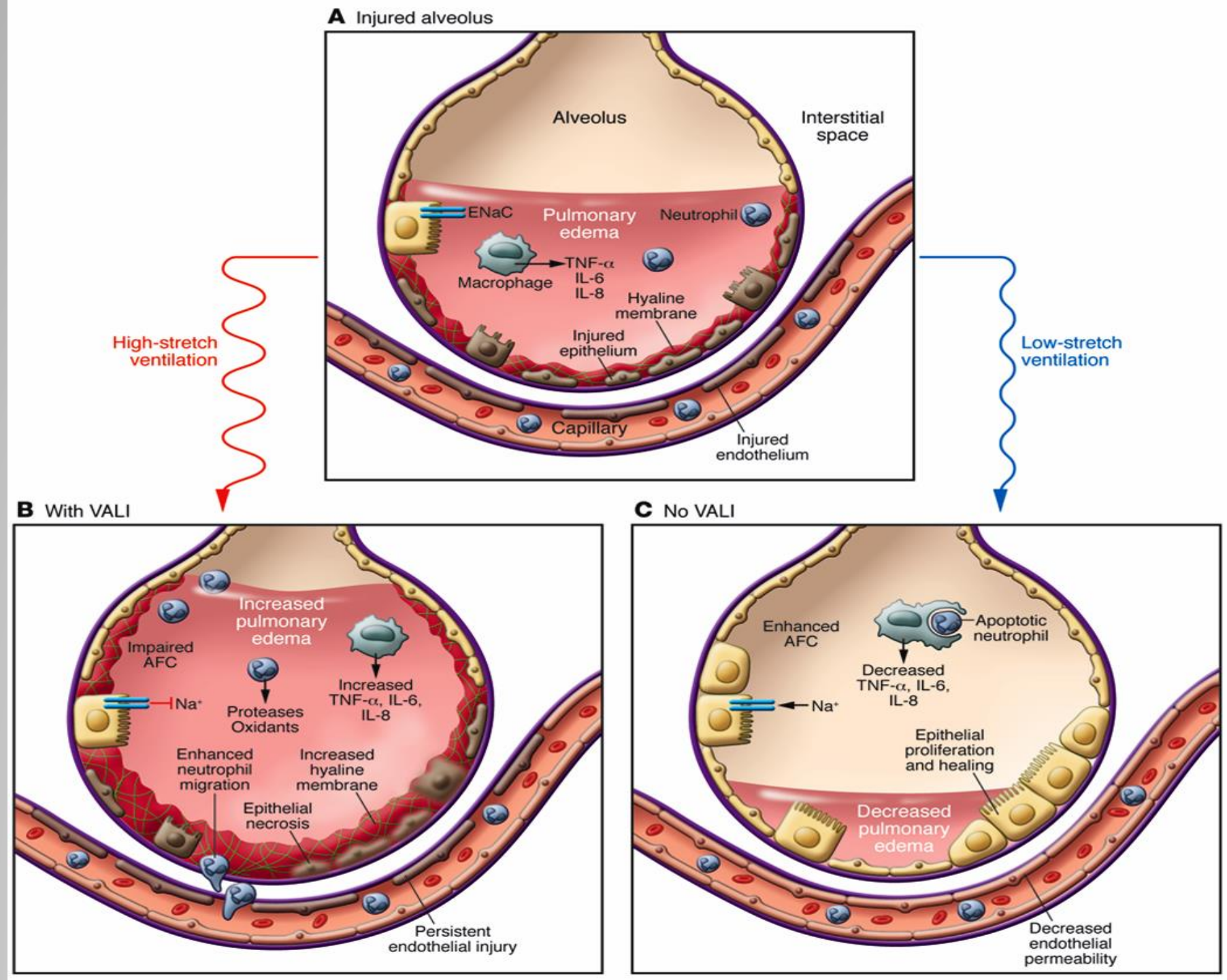
(Πολλαπλασιαστικές εφαπτόμενες δυνάμεις)

Nieman Intens Care Med Exper 2017

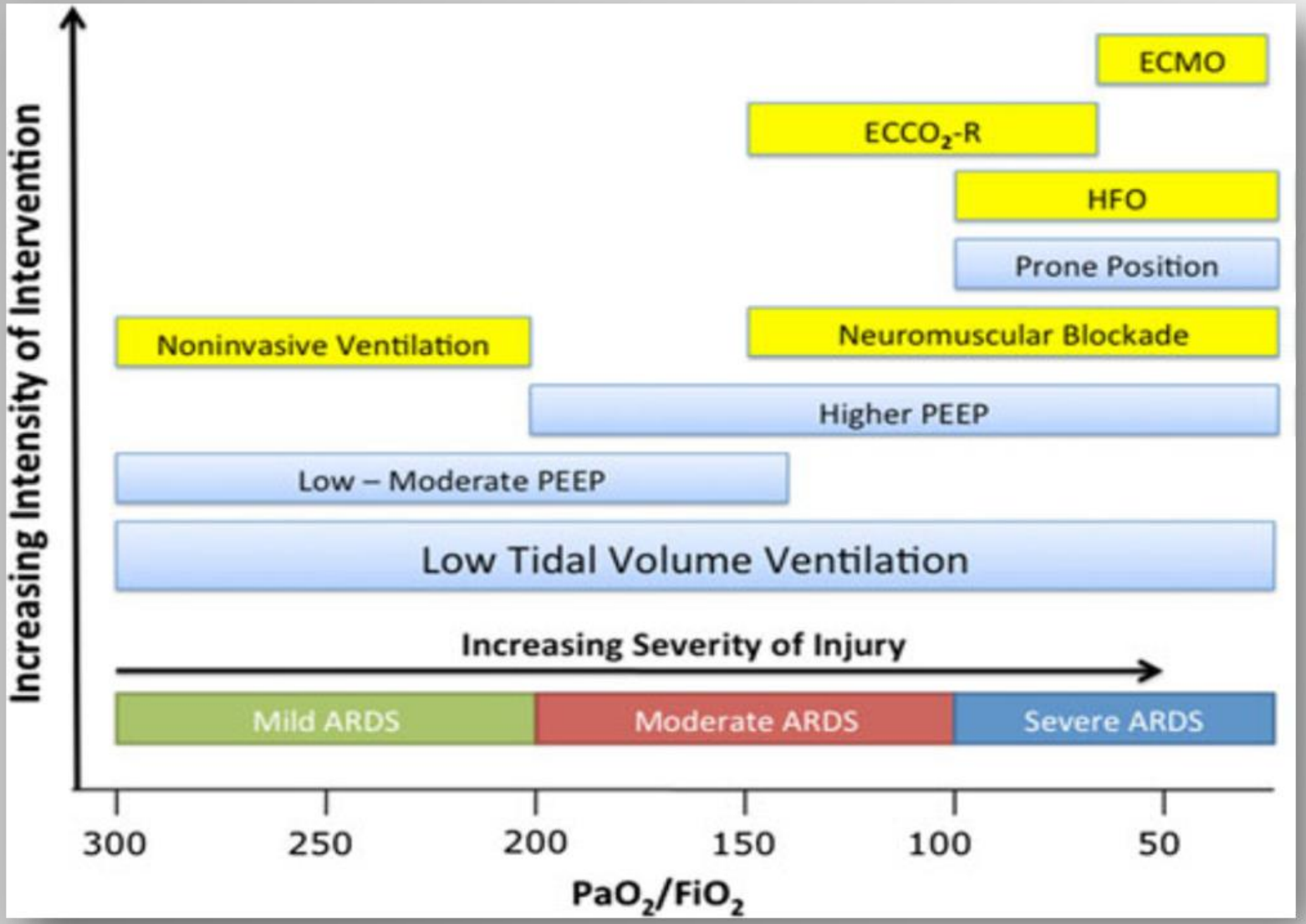
Ventilation Induced Lung Injury
Biotrauma






A Injured alveolus
Alveolus
Interstitial space
ENaC
Pulmonary edema
Neutrophil
Macrophage
TNF-α
IL-6
IL-8
Hyaline membrane
Injured epithelium
Capillary
Injured endothelium
High-stretch ventilation
Low-stretch ventilation
B With VALI
Increased pulmonary edema
Impaired AFC
Na+
Proteases
Oxidants
Increased TNF-α, IL-6, IL-8
Enhanced neutrophil migration
Increased hyaline membrane
Epithelial necrosis
Persistent endothelial injury
C No VALI
Enhanced AFC
Apoptotic neutrophil
Decreased TNF-α, IL-6, IL-8
Na+
Epithelial proliferation and healing
Decreased pulmonary edema
Decreased endothelial permeability

ARDS: Θεραπευτική αντιμετώπιση



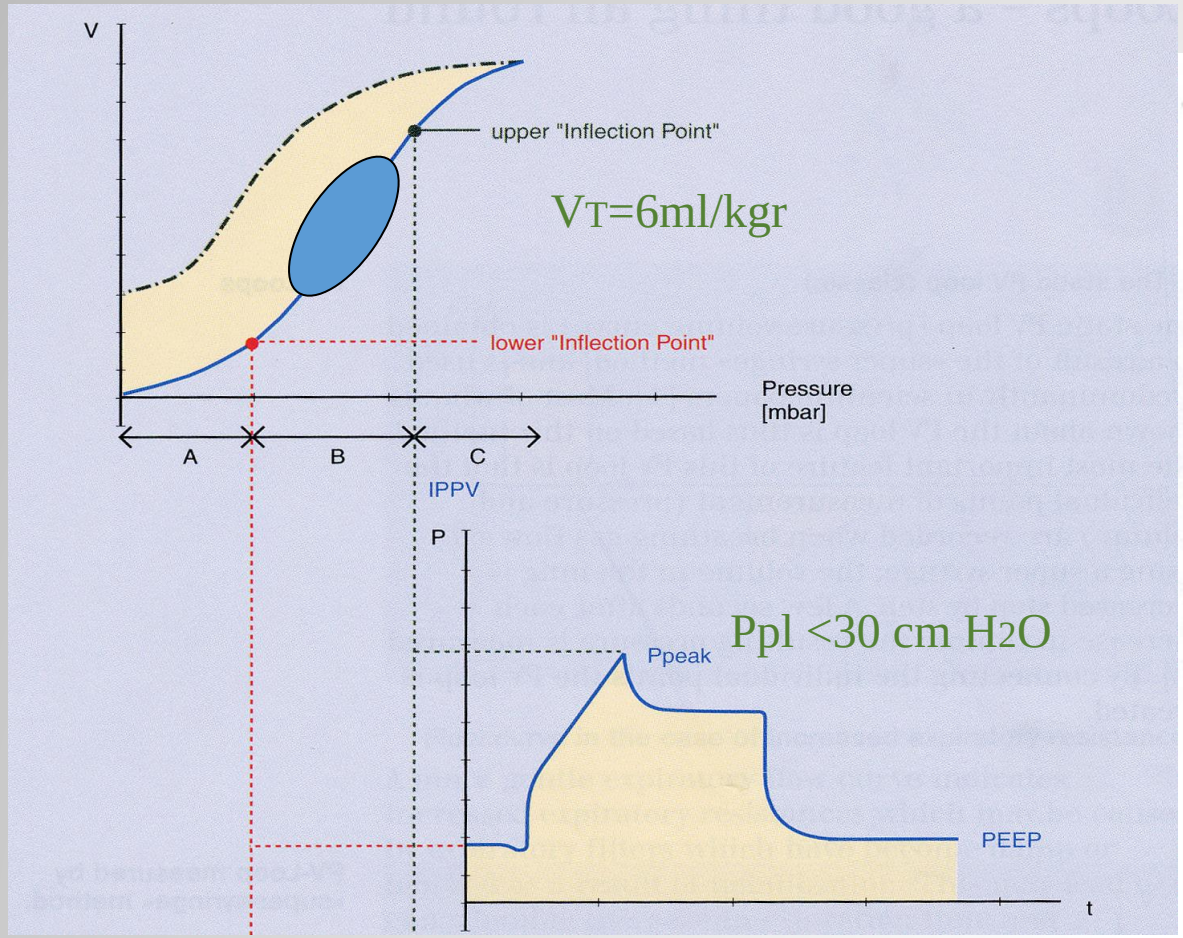
ARDS: Lung protective ventilation

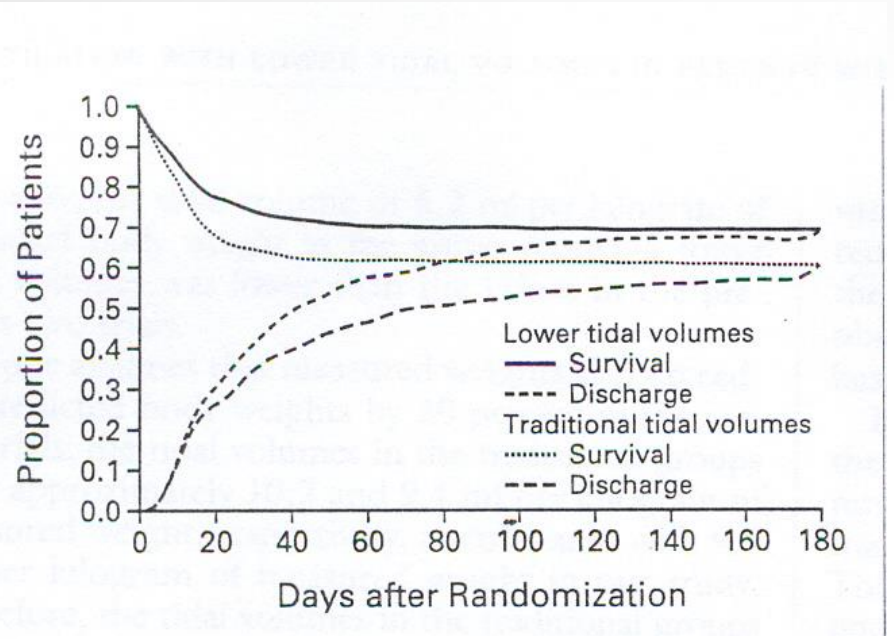
ARDSnet, N Engl J Med 2000

Tv: 6mL/kgPBW

Pplat: ≤30 cm H_2O

RR: 6-35/min
pH: 7.30-7.45



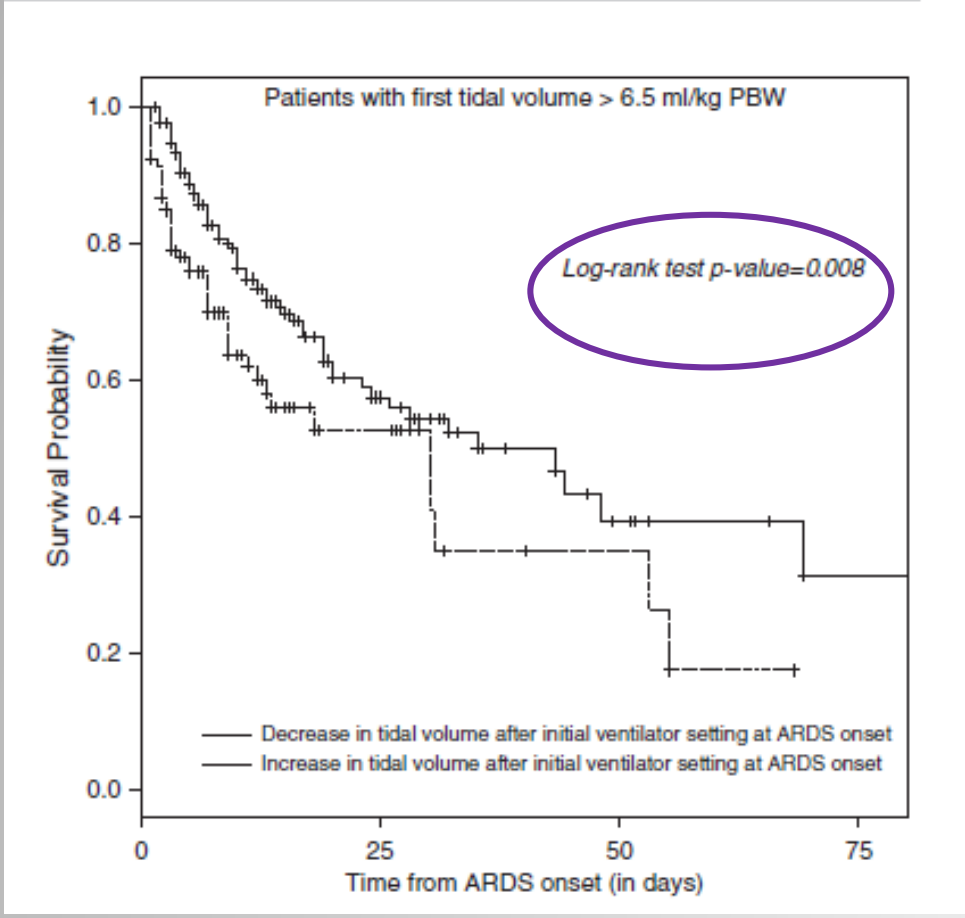


Traditional ventilation: **39,8%**
(Pplat<50cm H2O, VT=12 mL/Kg)
Lung protective ventilation: **30.1%**
(Pplat<30cm H2O, VT=6mL/Kg)
Mortality rate: 20% reduction

FiO_2-PEEP ⇒ PaO_2:55-80 mm Hg or SaO_2: 88-95%

ARDS: Lung protective ventilation

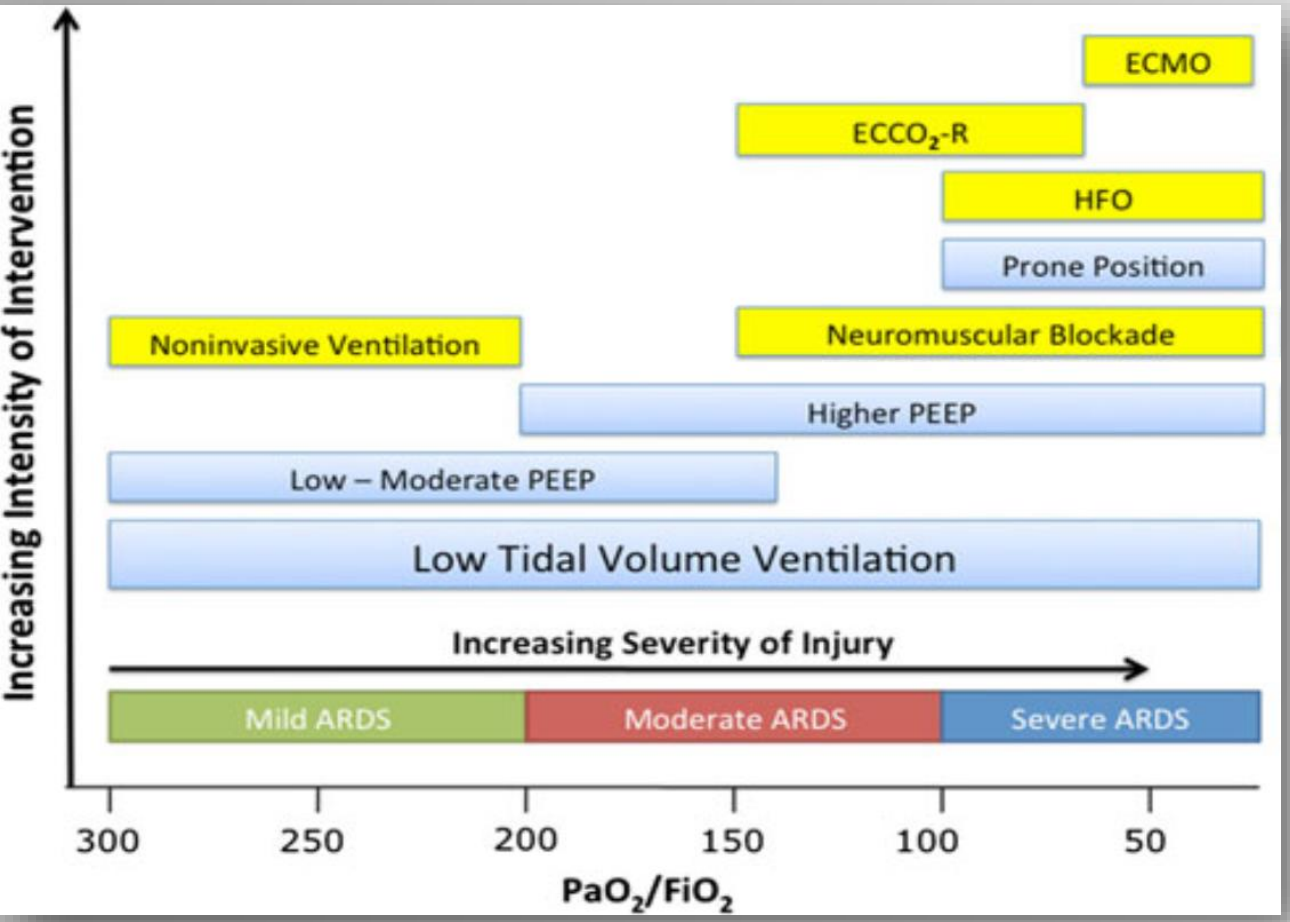
Έγκαιρη εφαρμογή προστατευτικού αερισμού



Πολυκεντρική μελέτη
482 ασθενείς με ARDS
11.558 μετρήσεις VT (δυο φορές την ημέρα)

Needham, AJRCCM 2015

ARDS: Lung protective ventilation



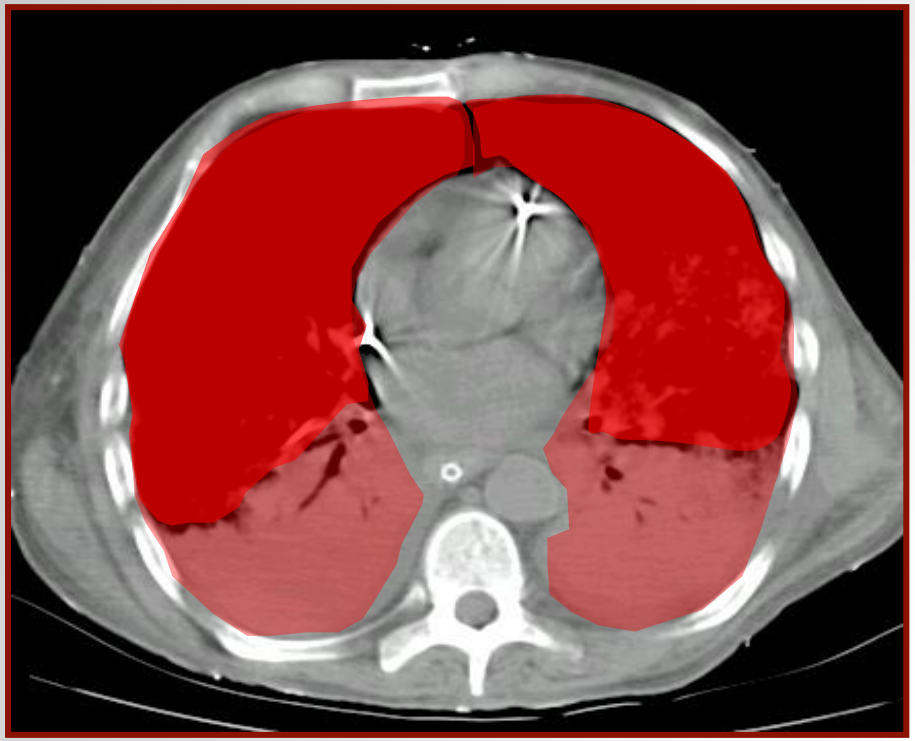
Long-Simmering Questions For the Bedside

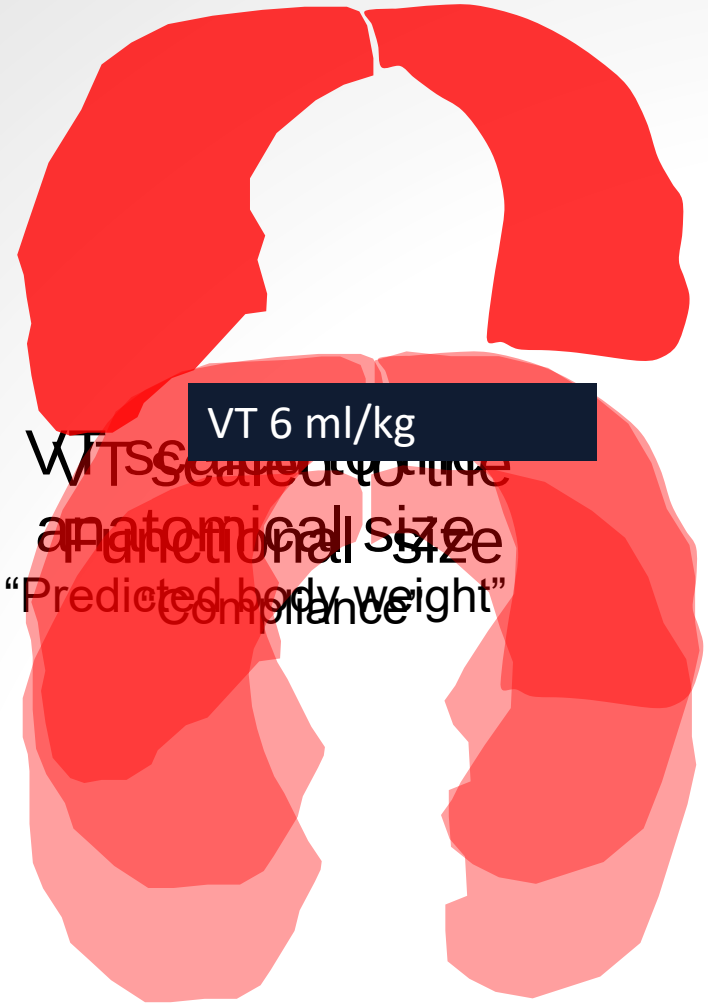
- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*

The ARDS definition Task Force: JAMA 2012

Marini J. Crit Care 2015

Lung Protection:
Scaling the delivered tidal volume

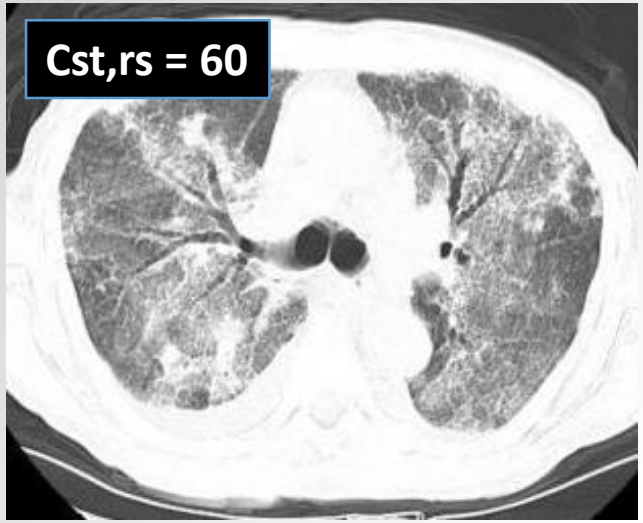


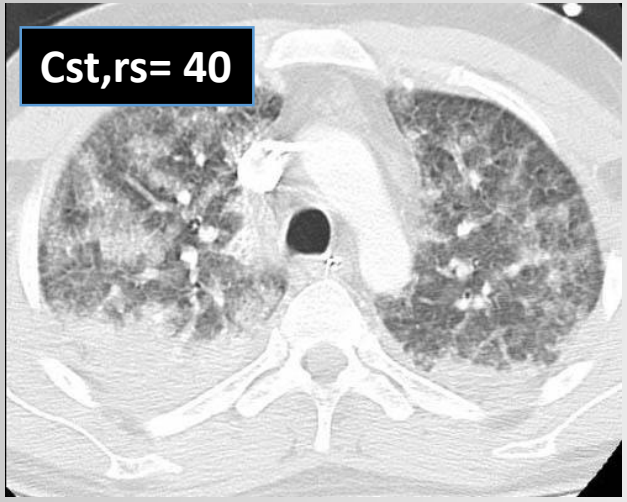


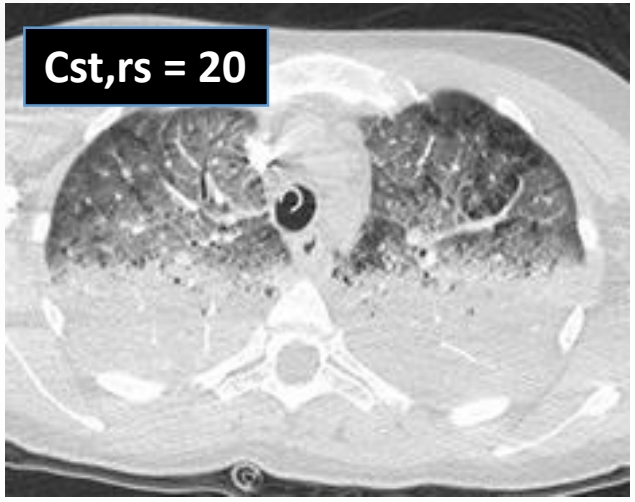
Ideal Body Weight= 70 Kg

V_T= 420 ml (6 ml/kg IBW)

- ↓ Lung stress, Transpulmonary pressure,
- ↓ Lung Strain=VT/FRC







Pelosi P for PROVENet

Μηχανικός αερισμός στο ARDS: Τι αλλάζει?

- ↓ Lung stress, Transpulmonary pressure,
- ↓ Lung Strain=VT/FRC

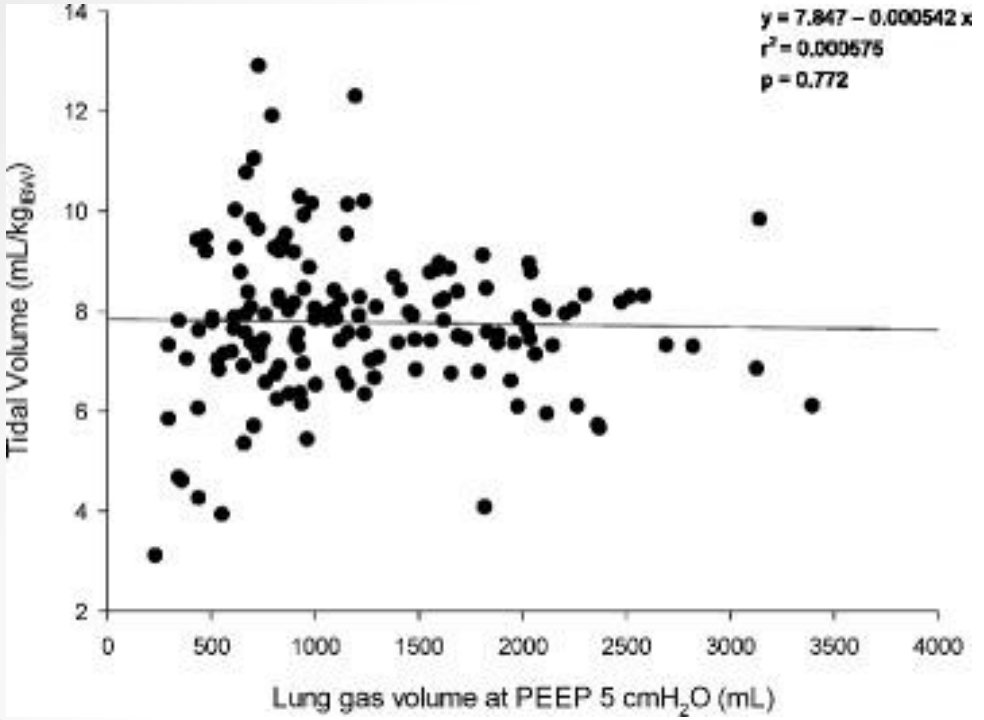
Lung protective ventilation

1. Pplat < 30 cm H_2O
2. VT = 6 mL/Kg PBW
3. High PEEP

Chiumello, Crit Care 2016

Τι συσχετίζεται με την έκβαση?

- Η ρύθμιση των παραμέτρων του αναπνευστήρα
- Οι μηχανικές παράμετροι του πνεύμονα (απότοκοι των ρυθμίσεων του αναπνευστήρα)

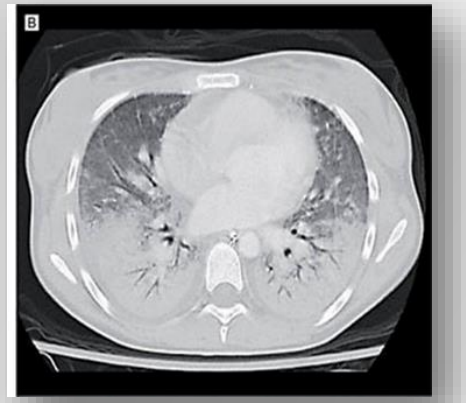


Μηχανικός αερισμός στο ARDS: Τι αλλάζει? Driving Pressure

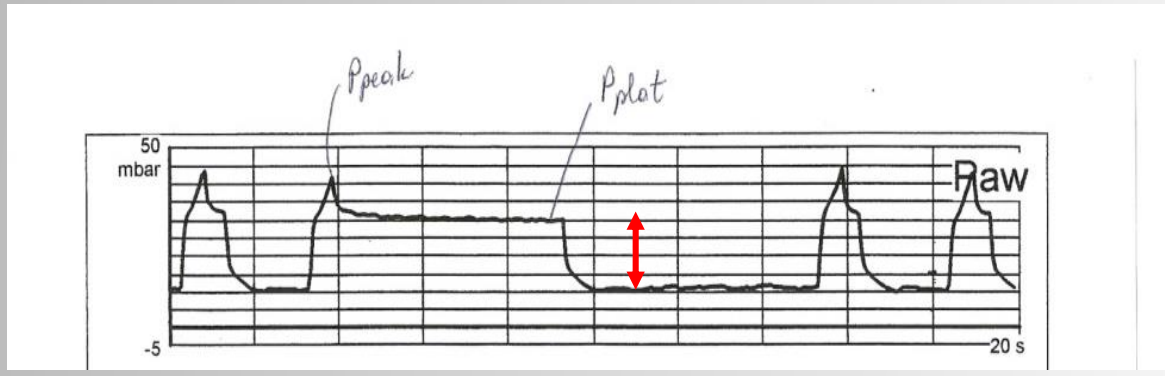
Lung protective ventilation

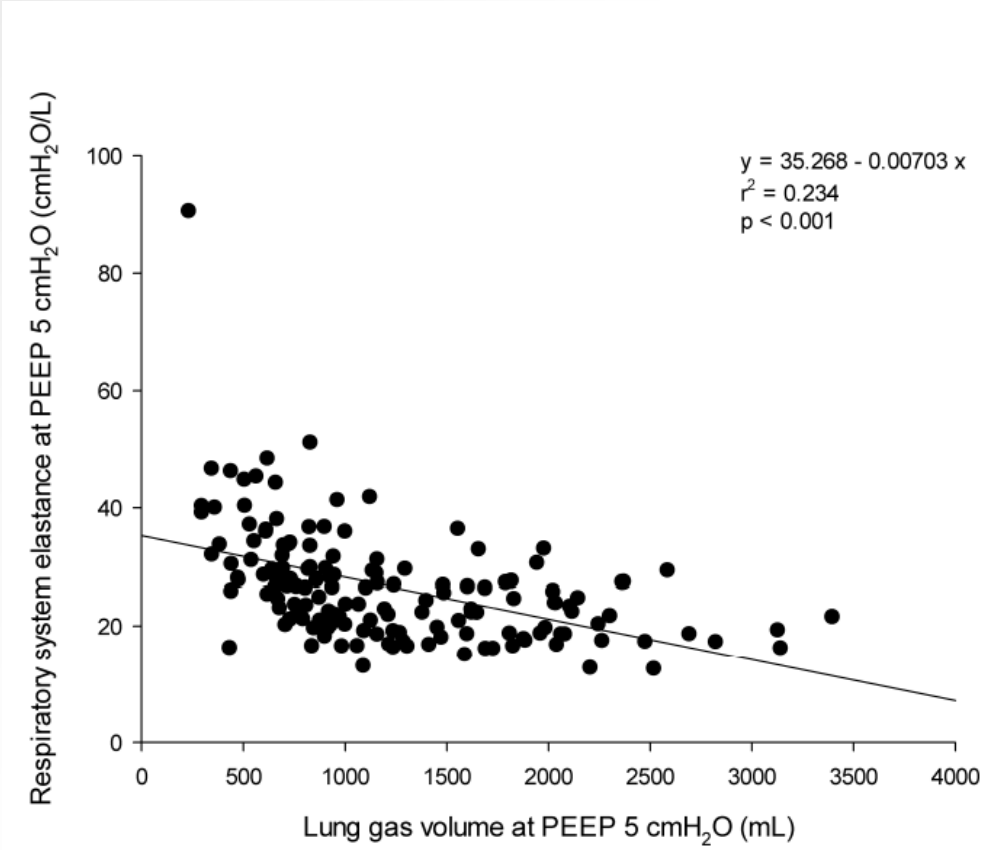
VT/Crs = VT/[VT/(Pplat-PEEP)]

VT/Crs= Pplat-PEEP= ΔP



ΔP= Pplat-PEEP





Chiumello, Crit Care 2016

Νεότερα στο μηχανικό αερισμό
Driving Pressure

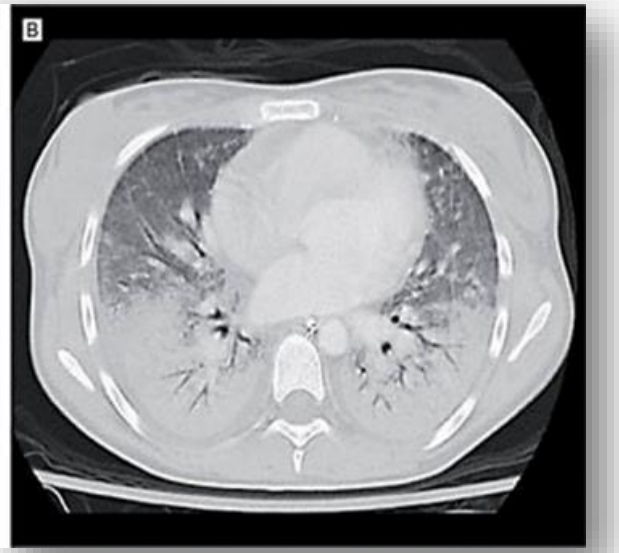
The NEW ENGLAND JOURNAL of MEDICINE

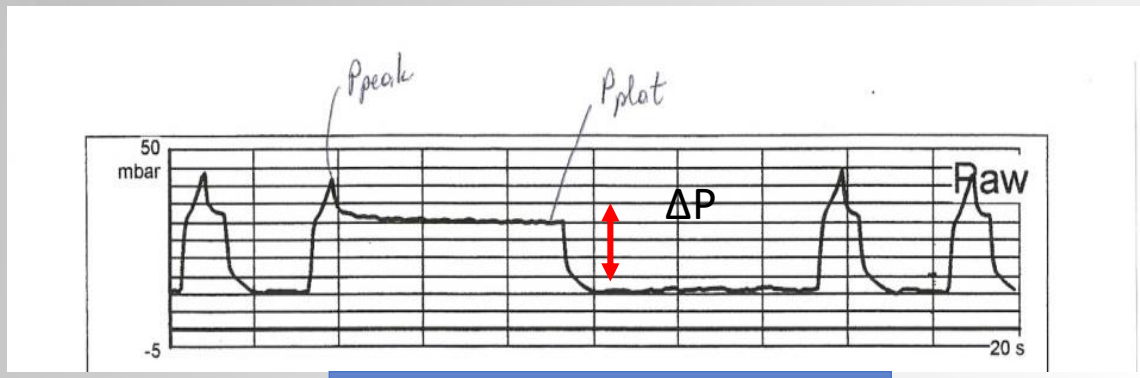
SPECIAL ARTICLE

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 372;8 NEJM.ORG FEBRUARY 19, 2015





ΔP= Pplat-PEEP

Lung protective ventilation

1. Pplat < 30cm H_2O
2. V_T = 6 mL/KgPbw
3. High PEEP

Driving Pressure

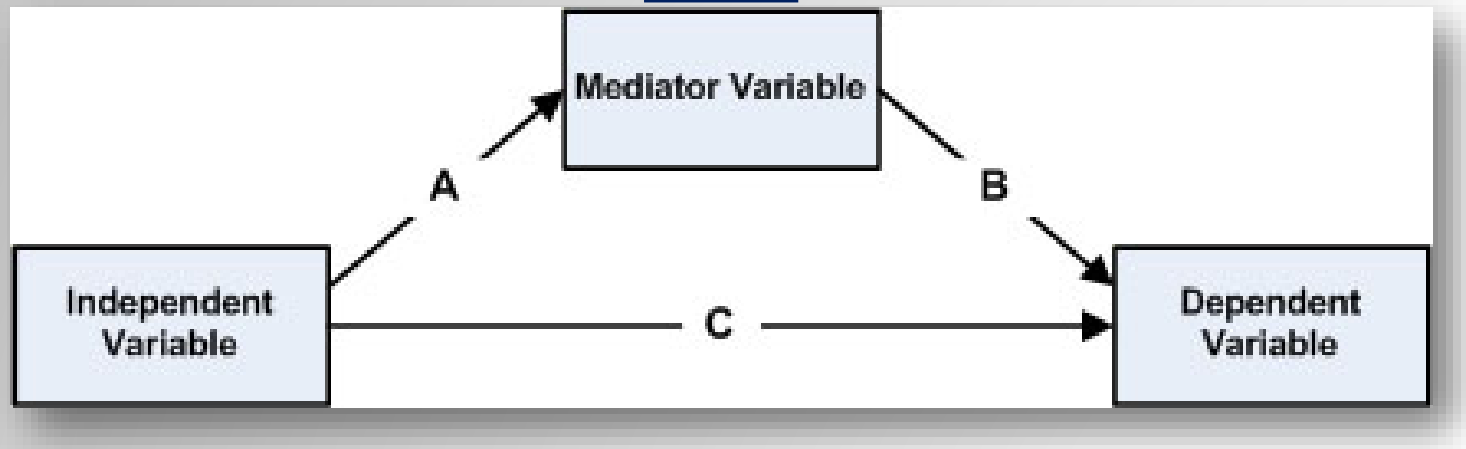
Lower vs. Higher V_T-trials ¶ :	Years of recruitment
Amato et al.[1] §	*1991-1995*
Stewart et al.[2]	*1995-1996*
Brochard et al.[3]	*1994-1996*
Brower et al.[4]	*1994-1996*
ARDSnet$_{VT}$[5]	*1996-1999*

Higher vs. Lower PEEP-trials ‖ :	
ARDSnet$_{PEEP}$[6]	*1999-2002*
EXPRESS[7]	*2002-2005*
LOVS[8]	*2000-2006*
Talmor et al.[9]	*2004-2007*

N ENGL J MED 372;8 NEJM.ORG FEBRUARY 19, 2015

Mediation analysis

ΔP

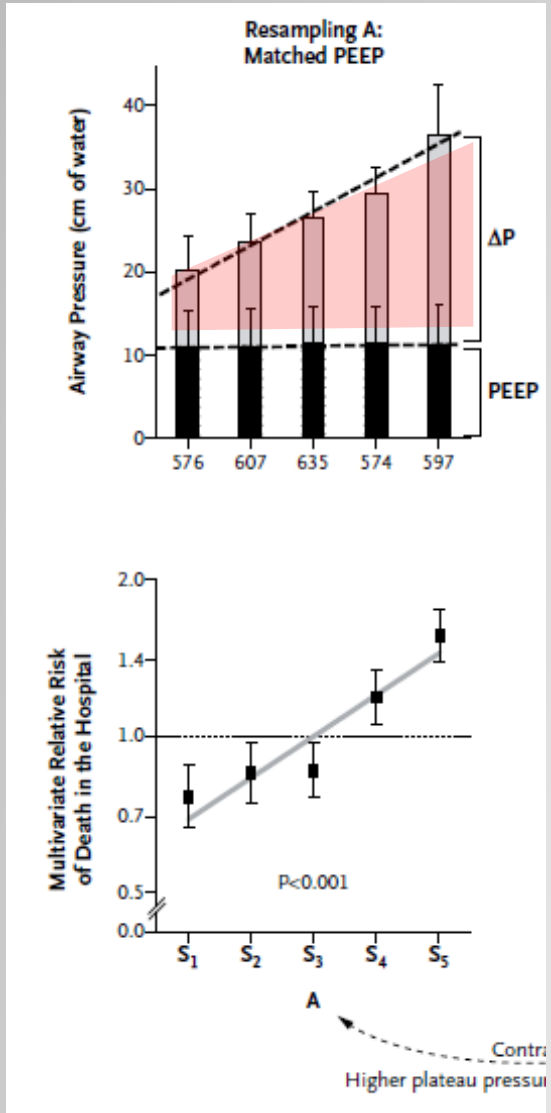


VT
Pplat
PEEP

Outcome

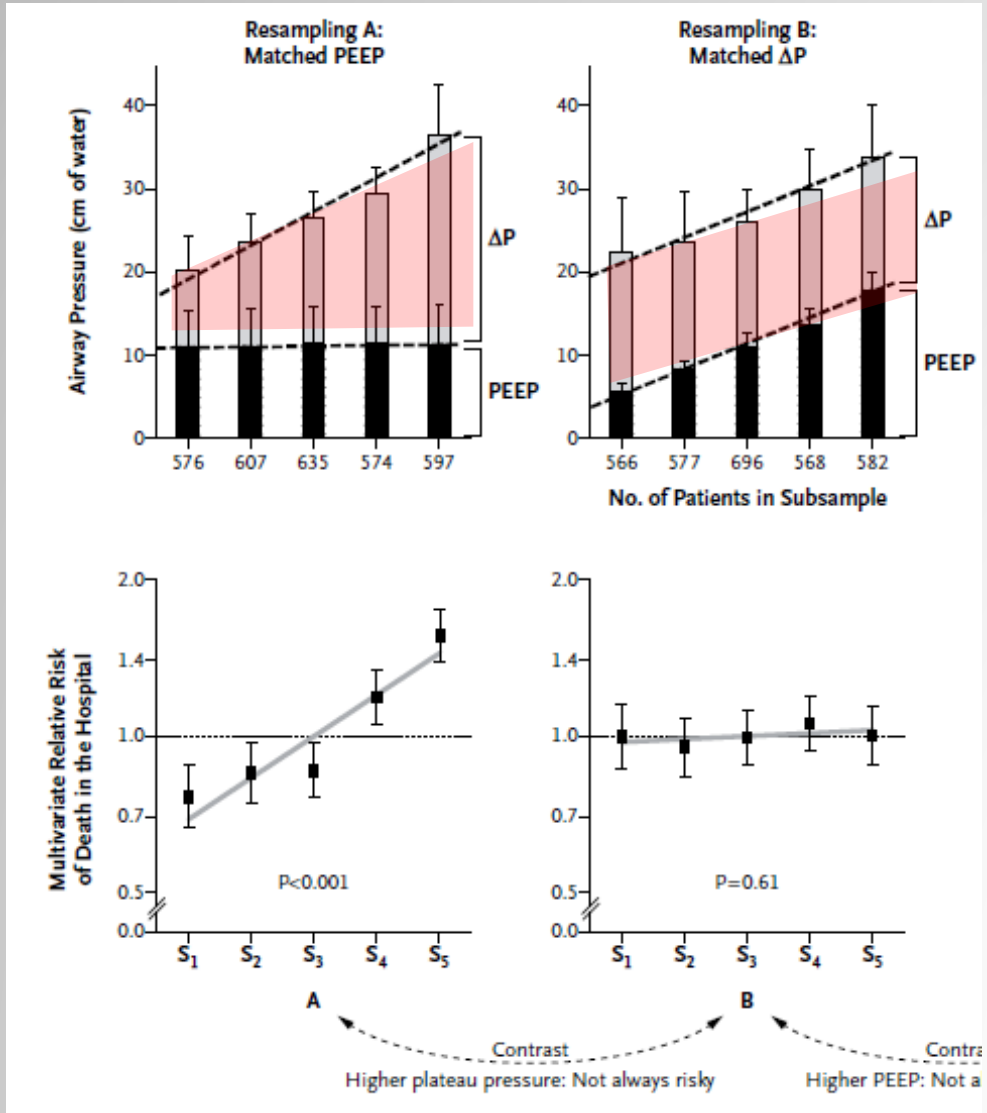
- Μελέτησαν κατά πόσον οι μεταβολές στην οδηγό πίεση απότοκες των μεταβολών στις ρυθμίσεις του αναπνευστήρα συσχετίζονται με την έκβαση

Driving pressure and survival in ARDS



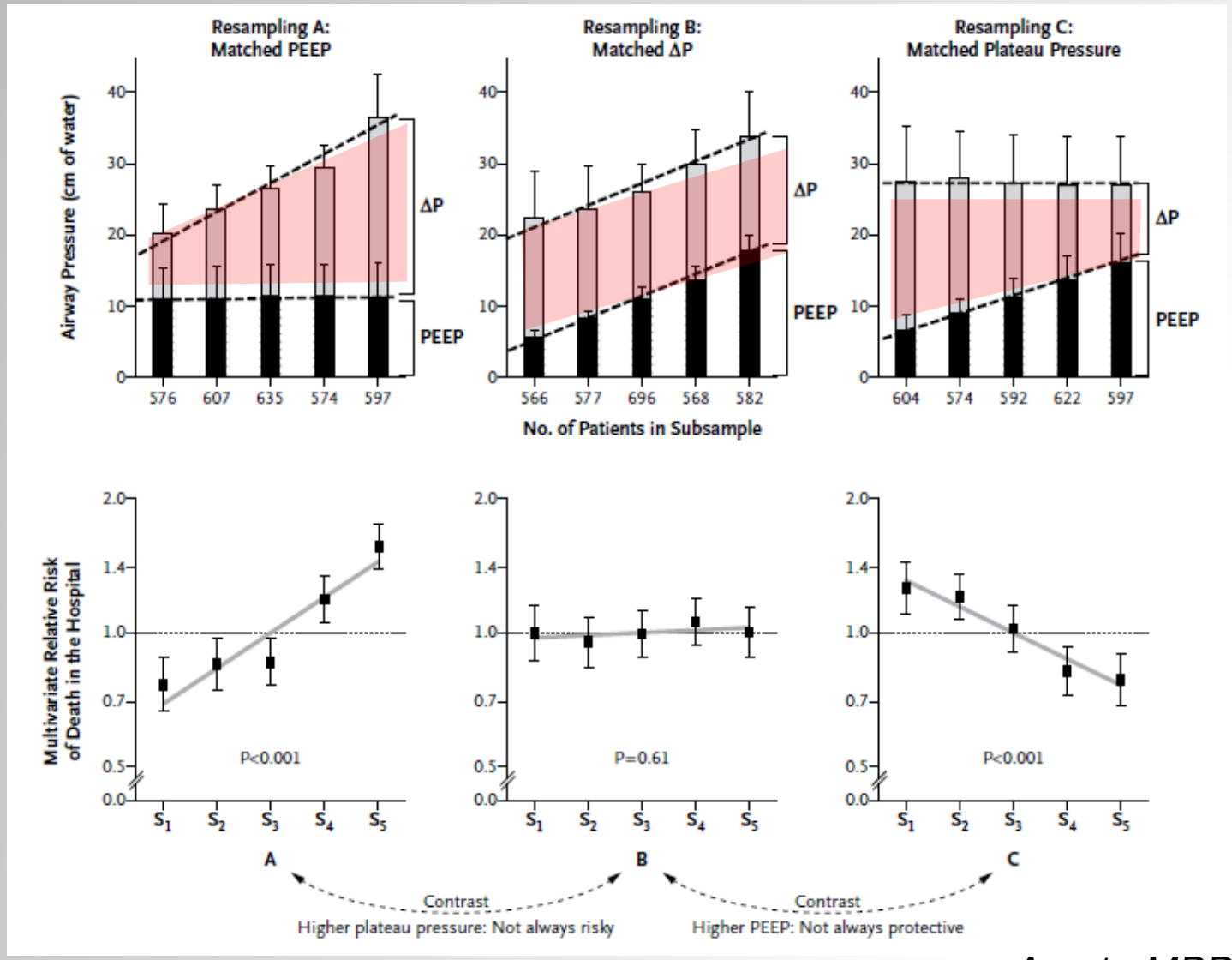
Amato MBP, et al. N Engl J Med 2015;372

Driving pressure and survival in ARDS

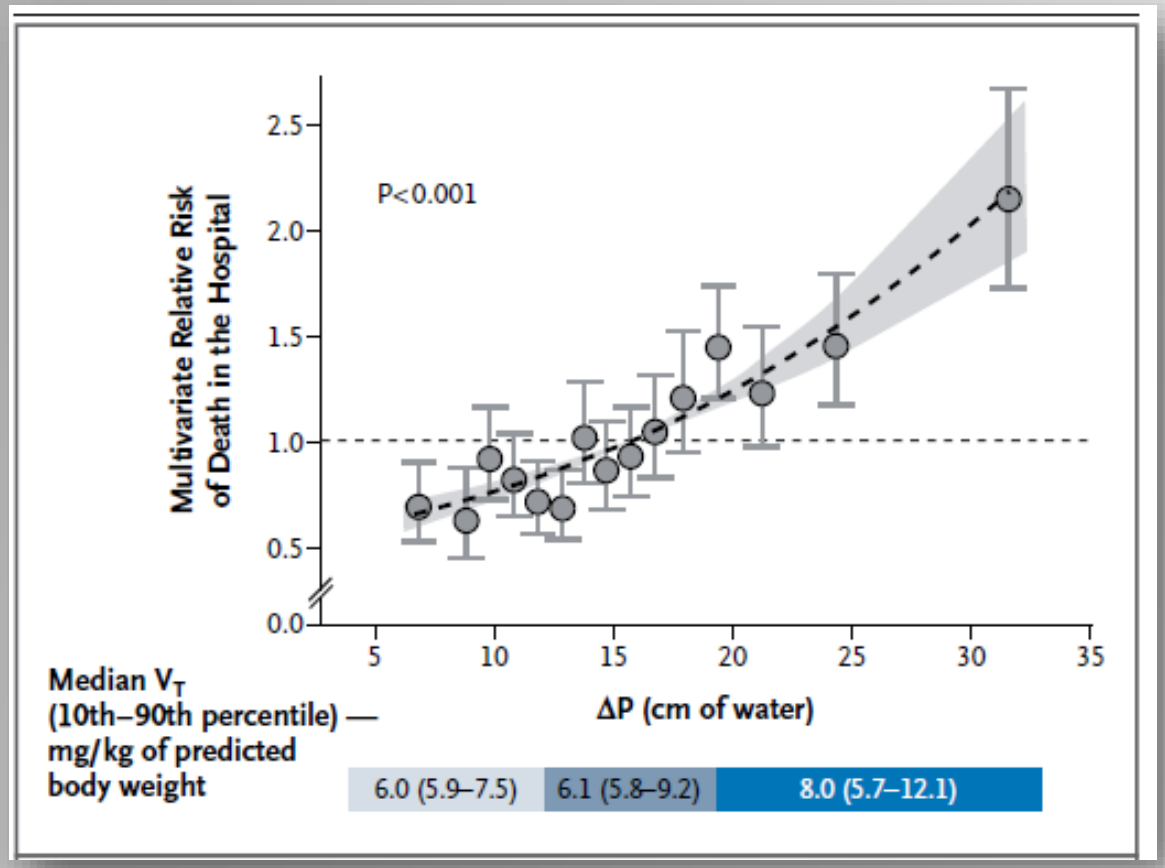


Amato MBP, et al. N Engl J Med 2015;372

Driving pressure and survival in ARDS



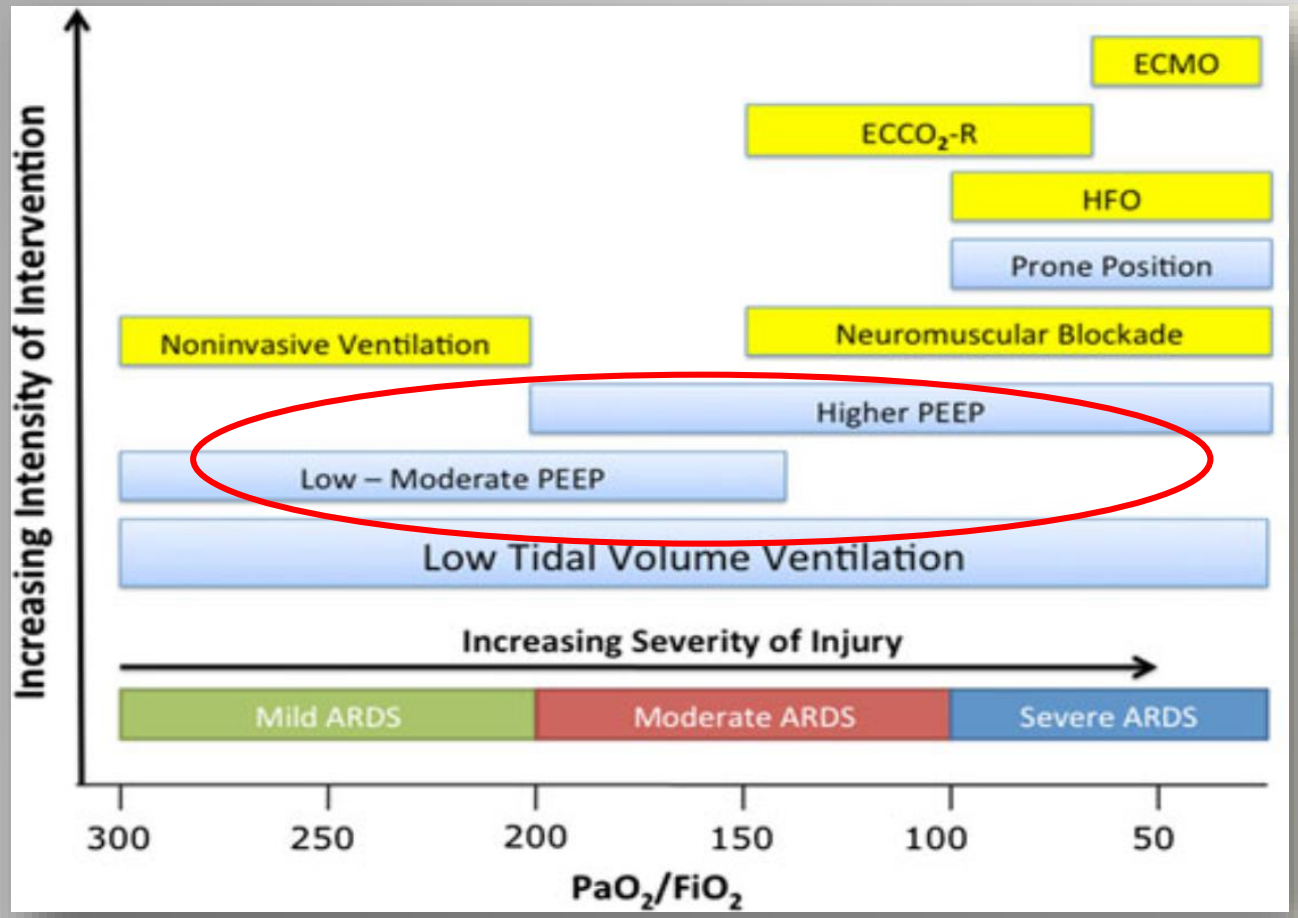
Amato MBP, et al. N Engl J Med 2015;372



- Η εξαρτημένη μεταβλητή ΔP σχετίζεται ισχυρά και ανεξάρτητα με την επιβίωση.
- Μείωση του Vt ή αύξηση της PEEP έχουν επίδραση στην επιβίωση μόνο εάν σχετίζονται με μείωση της ΔP

Amato et al, N Engl J Med 2015

ARDS: Lung protective ventilation



Long-Simmering Questions For the Bedside

- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*

The ARDS definition Task Force: JAMA 2012

Marini J. Crit Care 2015

Επιλογή της PEEP

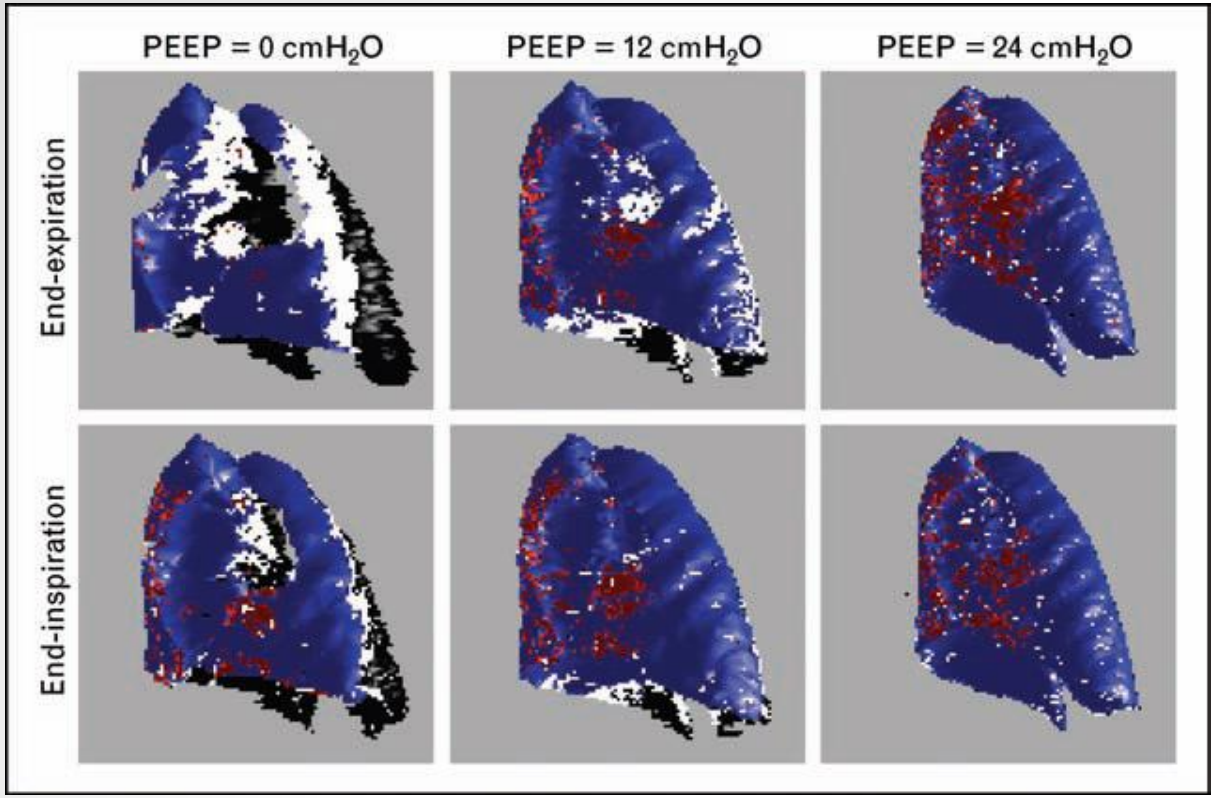
Δυνητική στρατευσιμότητα του πνεύμονα
Αποφυγή υπερδιάτασης

Ανομοιογένεια

Table 1. Settings for Positive End-Expiratory Pressure (PEEP), According to the Required Fraction of Inspired Oxygen (F_IO_2).*

F_IO_2	PEEP
0.3	5
0.4	5–8
0.5	8–10
0.6	10
0.7	10–14
0.8	14
0.9	14–18
1.0	18–24

* Settings are from the ARDSNet trial.[19] The required F_IO_2 is the lowest value that maintains arterial oxyhemoglobin saturation above 90%. After the corresponding level of PEEP is selected, arterial oxyhemoglobin saturation and plateau airway pressure should be monitored in the patient.



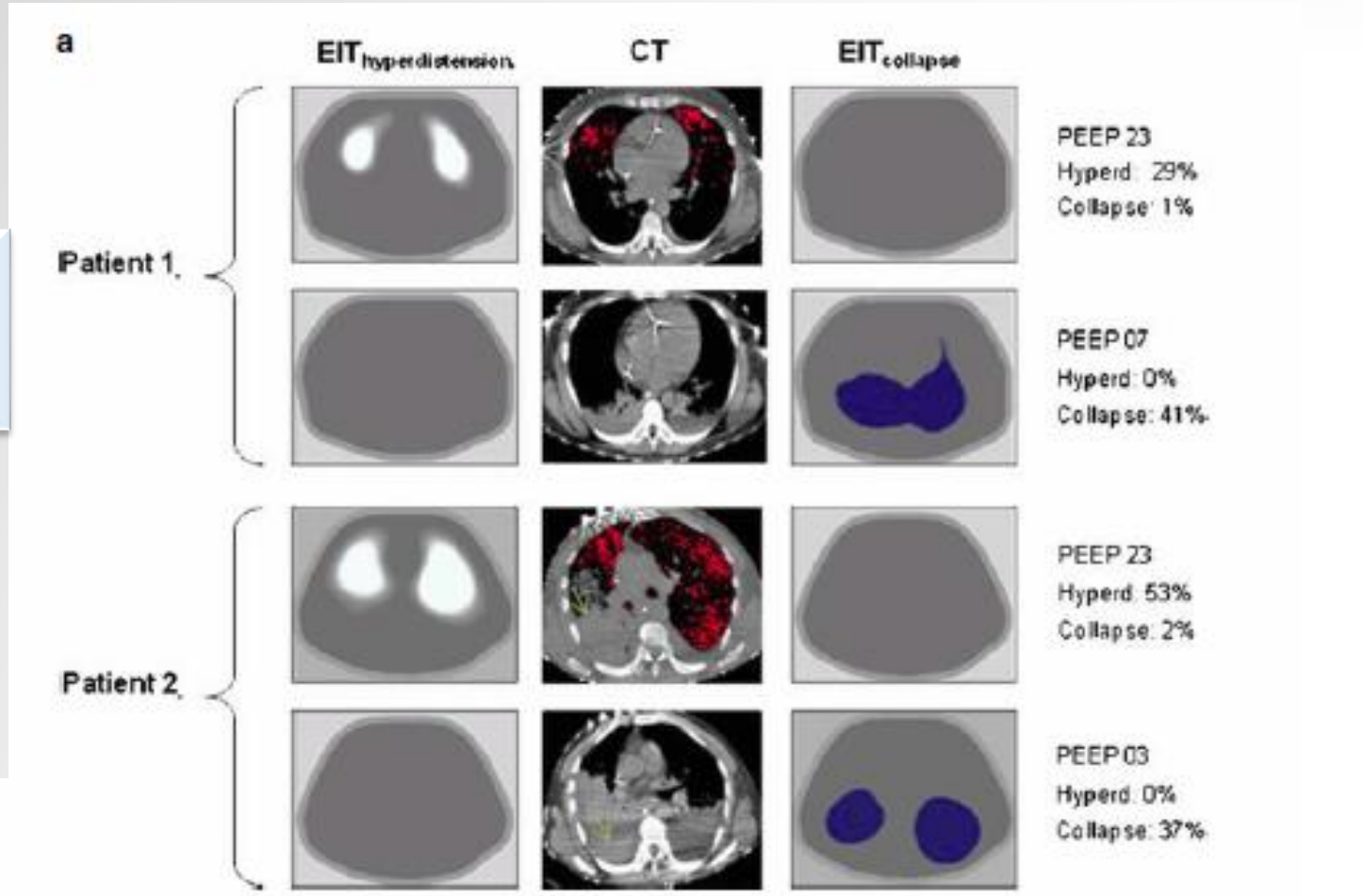
Pelosi Curr Opin Crit Care 2011

Επιλογή της PEEP
Electrical Impedance Tomography

$$\text{Impedance (Z)} = \frac{\text{Voltage (V)}}{\text{Current (I)}}$$

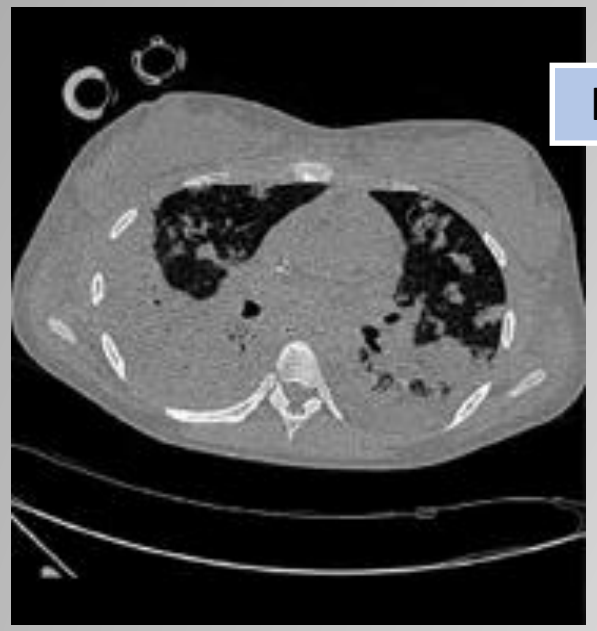
Δυνητική στρατευσιμότητα του πνεύμονα

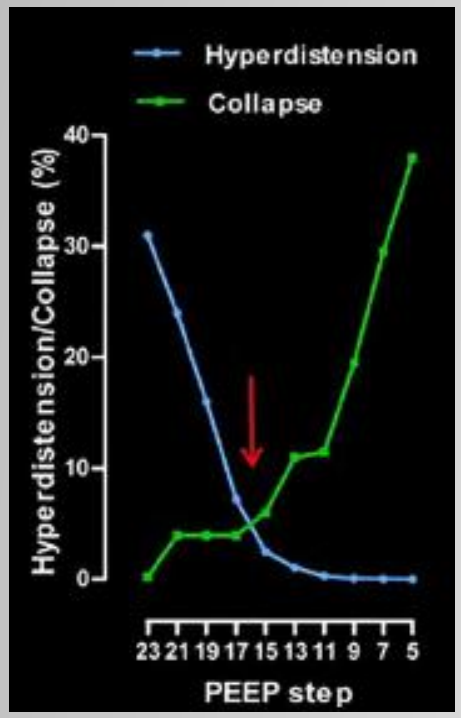
Αποφυγή υπερδιάτασης



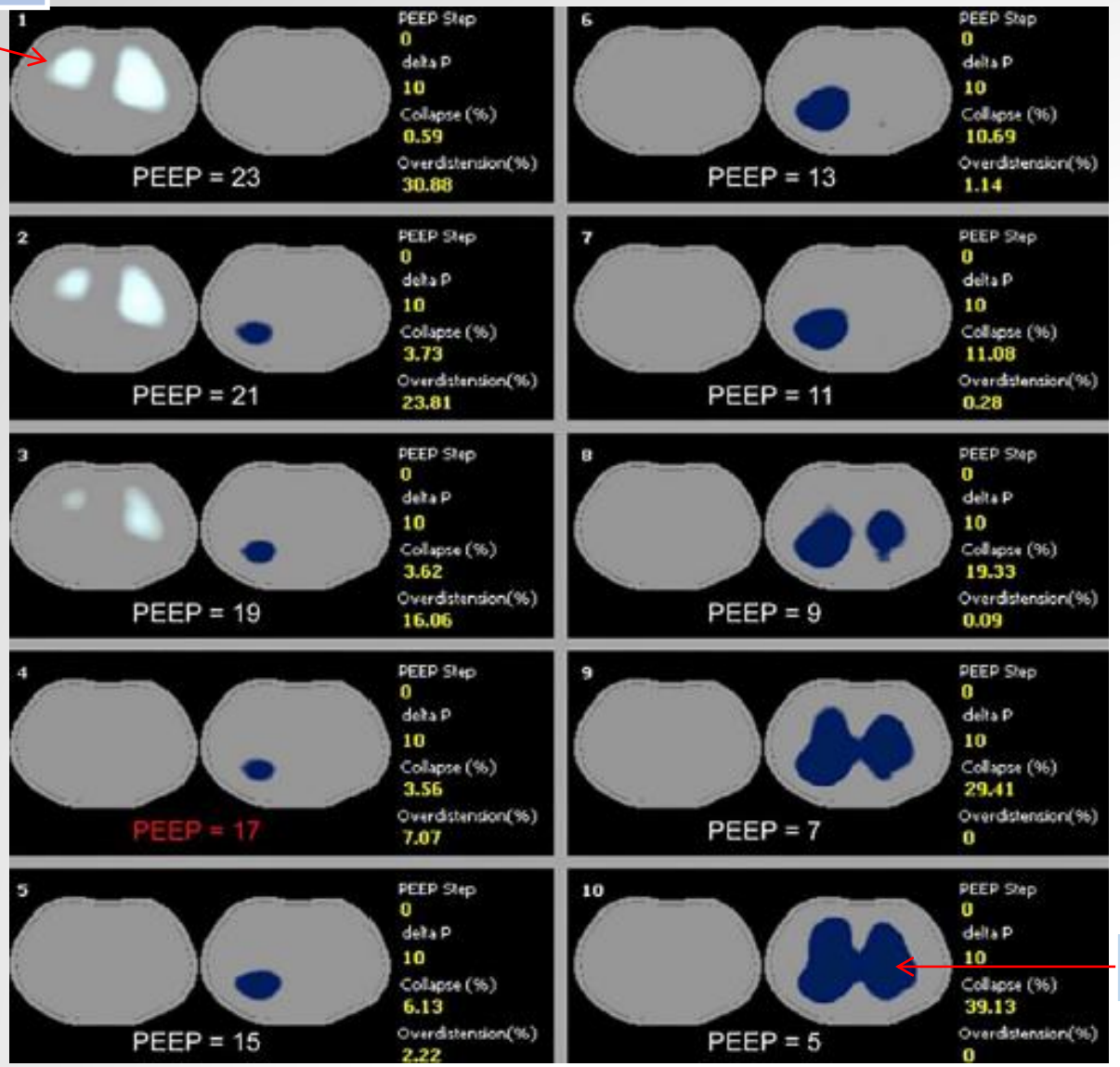
Bedside estimation of recruitable alveolar collapse and hyperdistension by electrical impedance tomography

Costa et al, Intens Care Mes 2009; 35





hyperdistension



Collapsed

Επιλογή της PEEP στο ARDS

Δυνητική στρατευσιμότητα του πνεύμονα

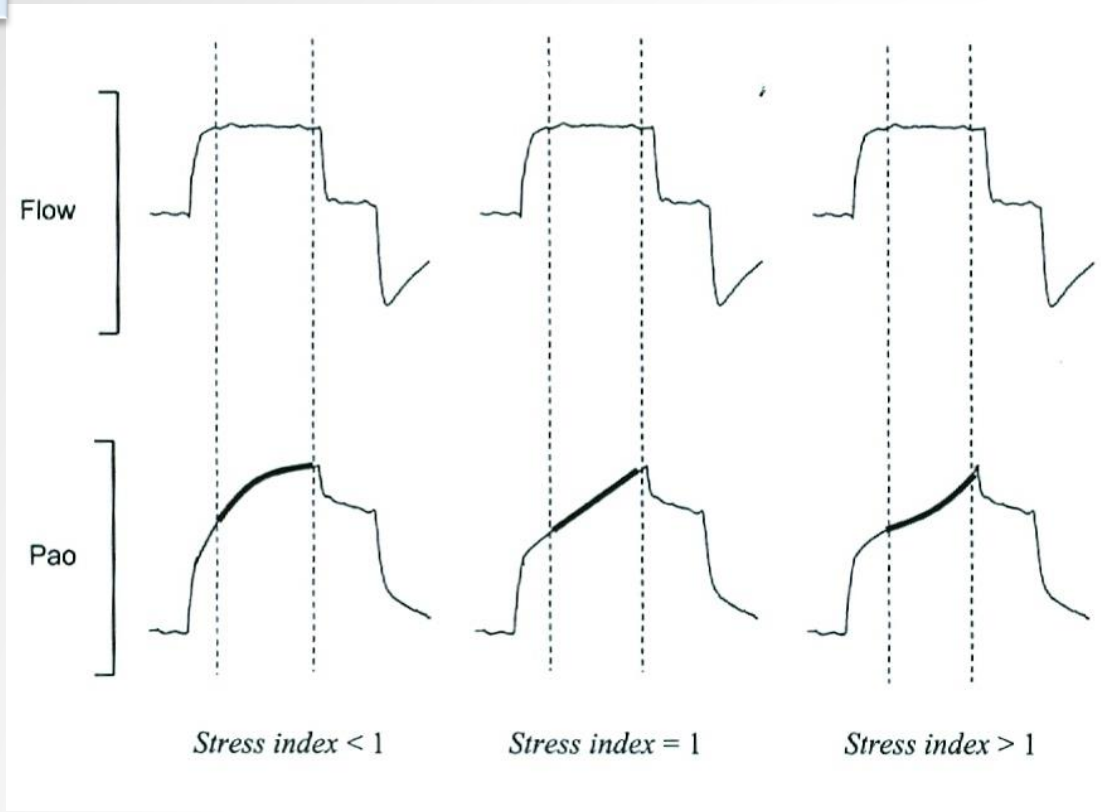
Αποφυγή υπερδιάτασης

Αύξηση του νεκρού χώρου

V_ExPaCO_2/40 >10L/min

~ Vd/Vt=50%

Stress Index

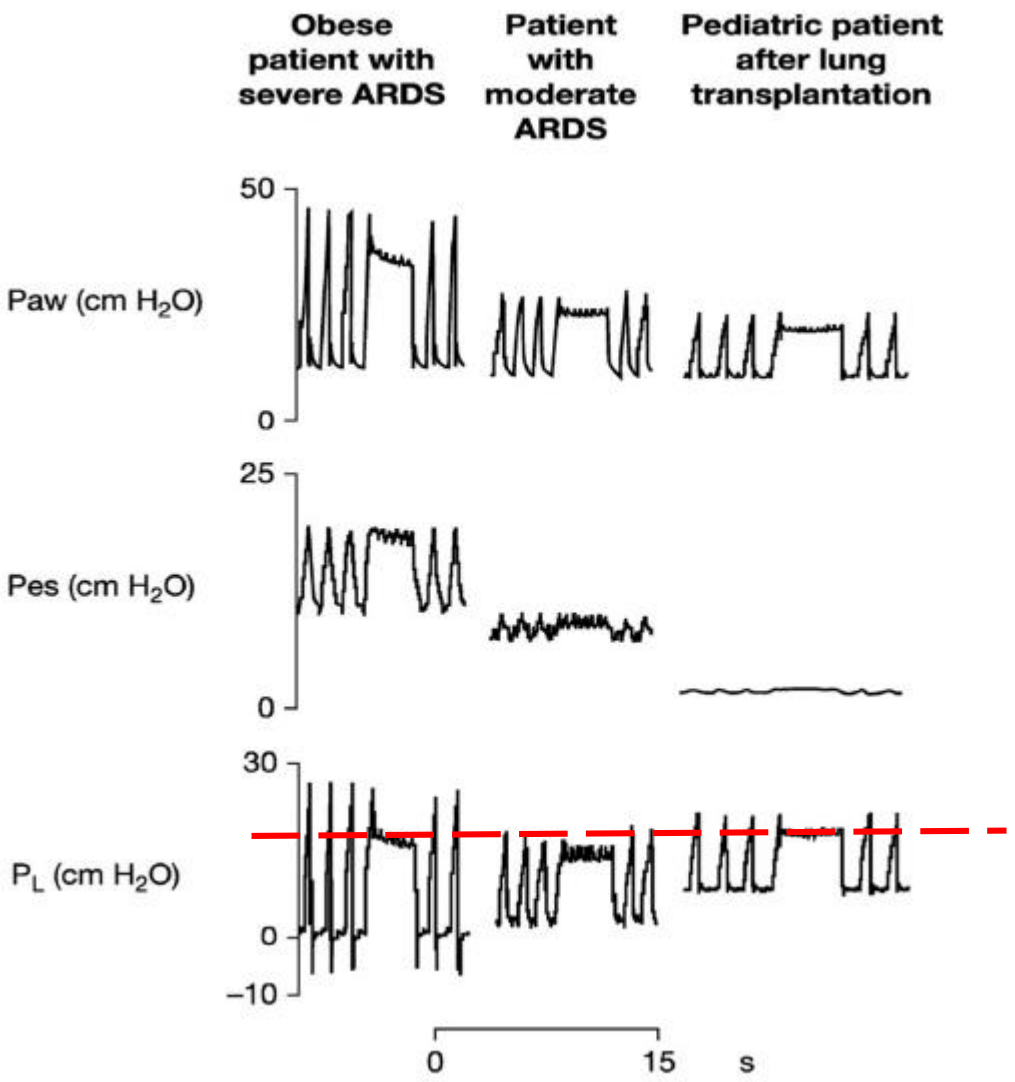


Ranieri AJRCCM 1994

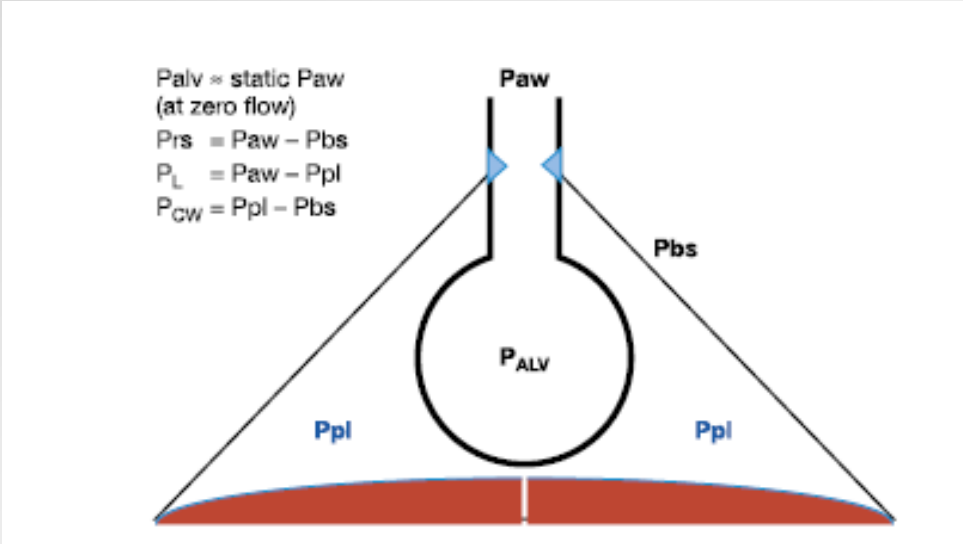
Grasso CCM 2004

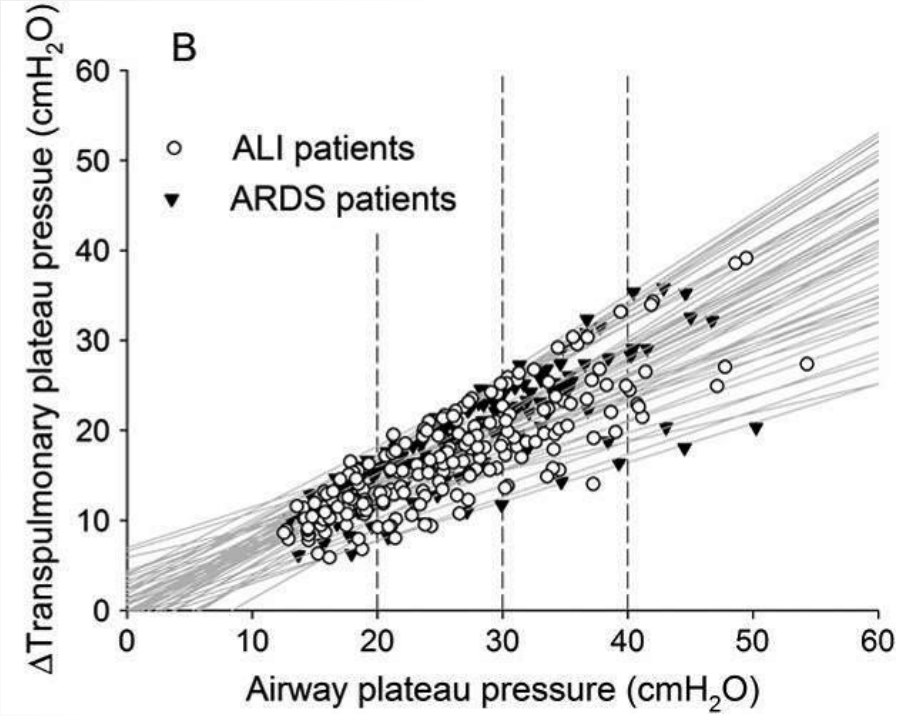
Επιλογή της PEEP στο ARDS

Chest wall mechanics!! PTP= Paw-Pes



Akoumianaki AJRCCM 2014



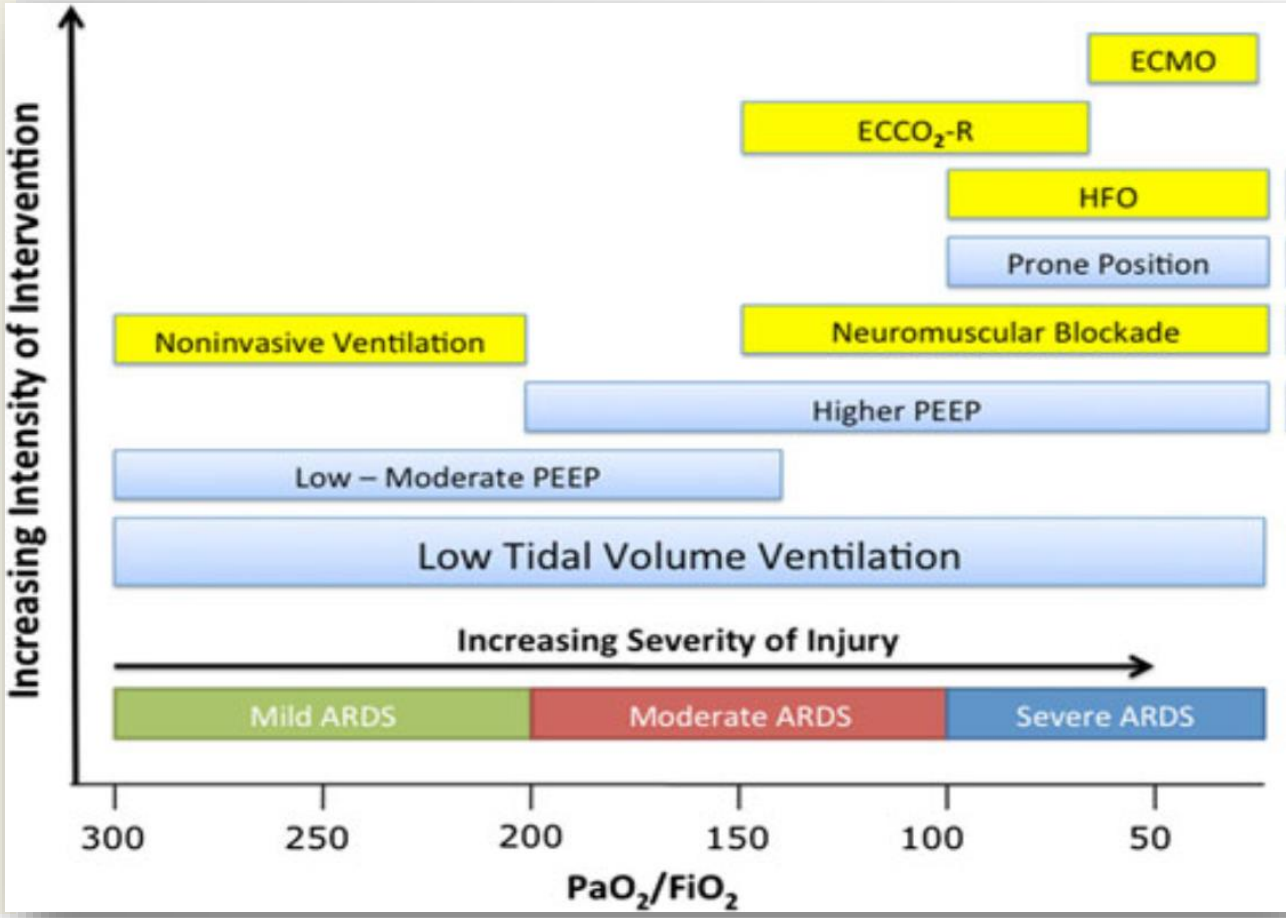


Chiumello et al AJRCCM 2008

ARDS: Lung protective ventilation

Long-Simmering Questions For the Bedside

- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*



Marini J. Crit Care 2015

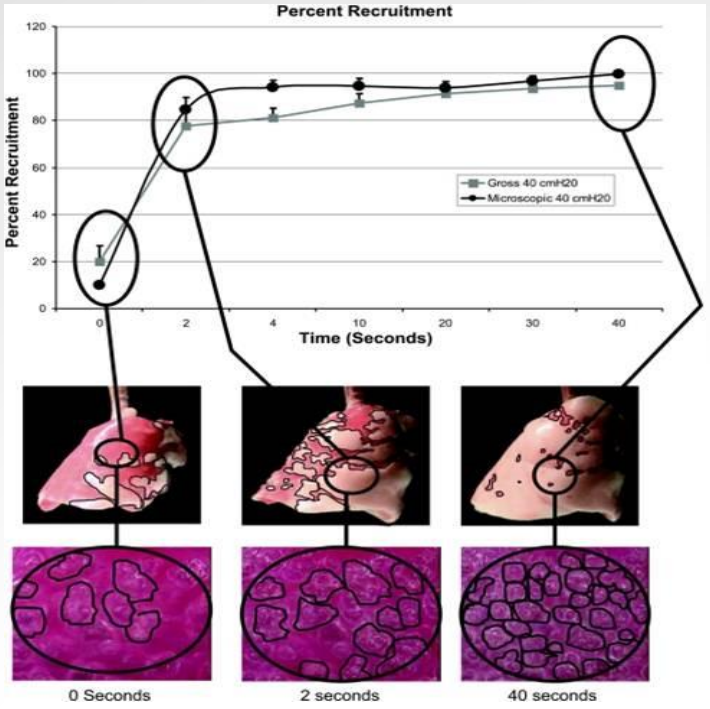
The ARDS definition Task Force: JAMA 2012

ARDS: Lung protective ventilation

Χειρισμοί στράτευσης (Recruitment maneuvers)

RMs

Δυναμική διαδικασία διάνοιξης ασταθών και κλειστών κυψελίδων μέσω της σκόπιμης εφαρμογής παροδικής αύξησης της διαπνευμονικής πίεσης



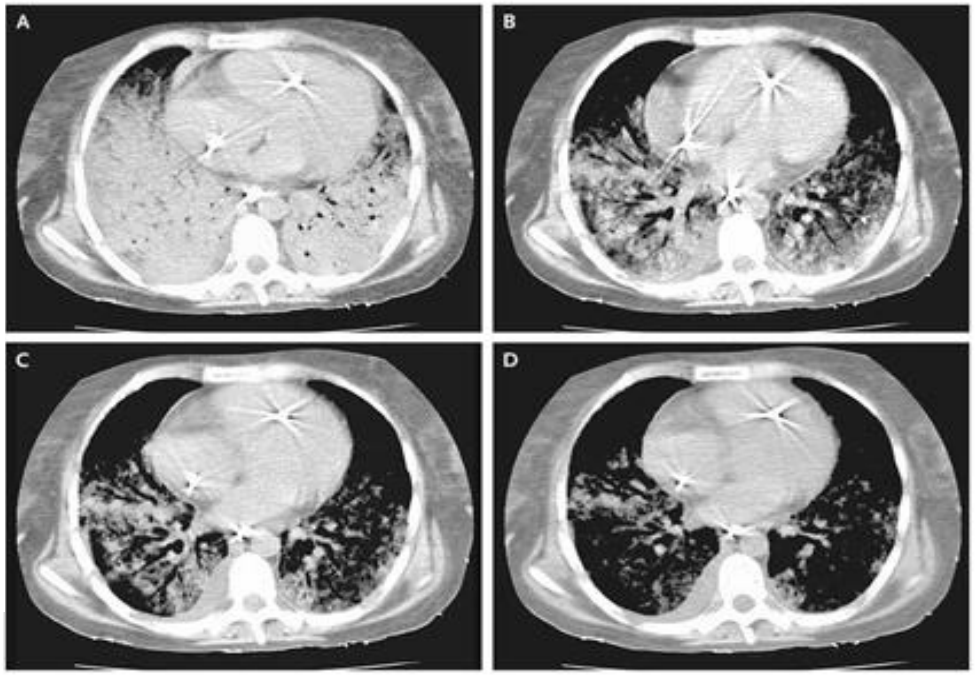
CONFERENCE REPORTS AND EXPERT PANEL

CrossMark

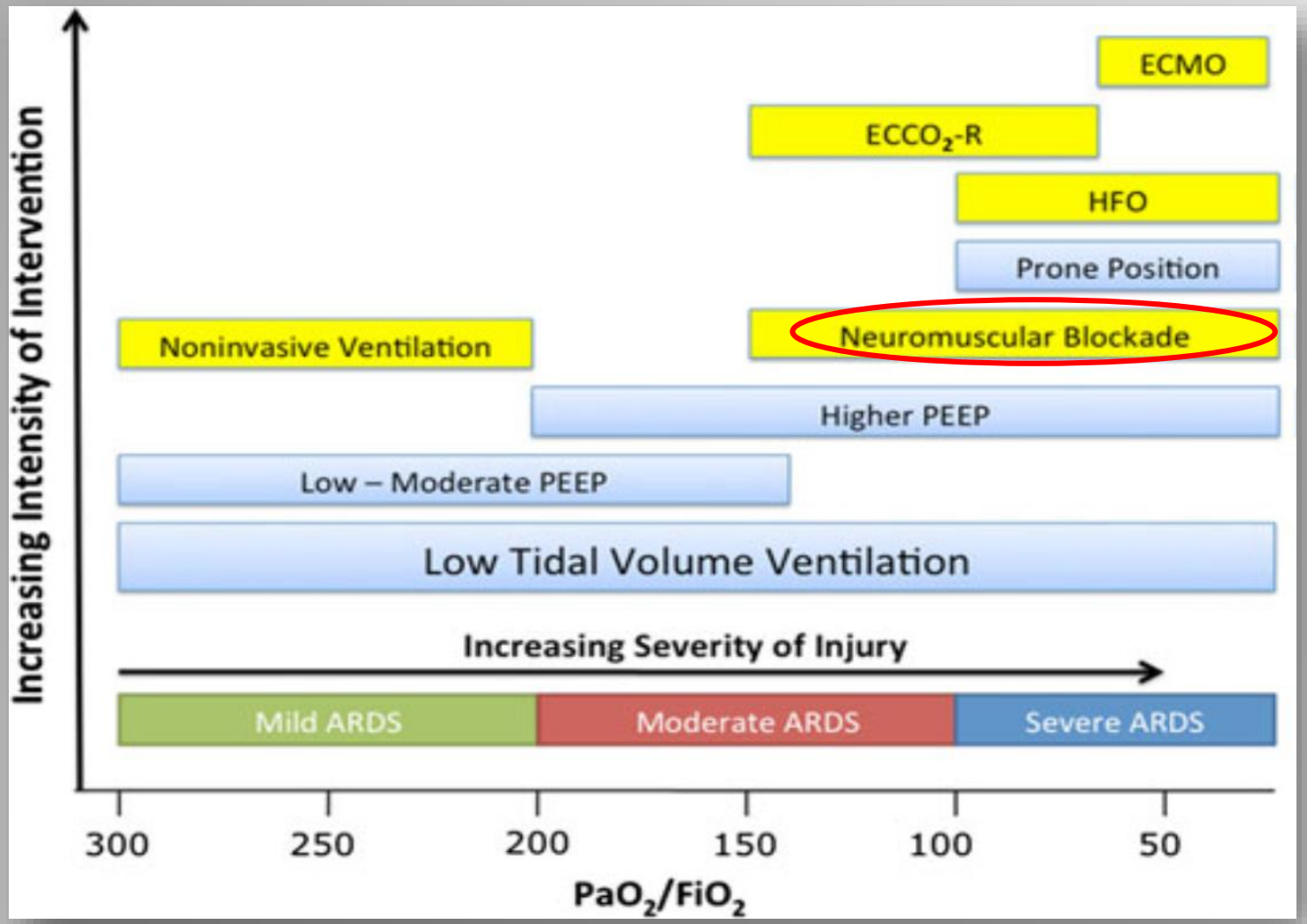
Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016

Andrew Rhodes[1*] Laura E. Evans[2] Waleed Alhazzani[3] Mitchell M. Levy[4] Massimo Antonelli[5] Ricard Ferrer[6]

4. **We suggest using recruitment maneuvers in adult patients with sepsis-induced, severe ARDS (weak recommendation, moderate quality of evidence).**



ARDS: Lung protective ventilation



The ARDS definition Task Force: JAMA 2012

Φάρμακα: Neuromuscular blockers in early ARDS

Βασικά θεραπευτικά εργαλεία

Φάρμακα: Neuromuscular blockers in early ARDS

Πολυκεντρική, διπλή τυφλή μελέτη με 340 ασθενείς με βαρύ πρωιμο ARDS (PaO_2/FiO_2 < 150 mm Hg)

Cisatracurium besylate (178) or placebo (162) for 48 h

Mortality at 28 days:

23.7% cisatracurium besylate

33.3% placebo (P=0.05)

ICU- acquired paresis not significantly different

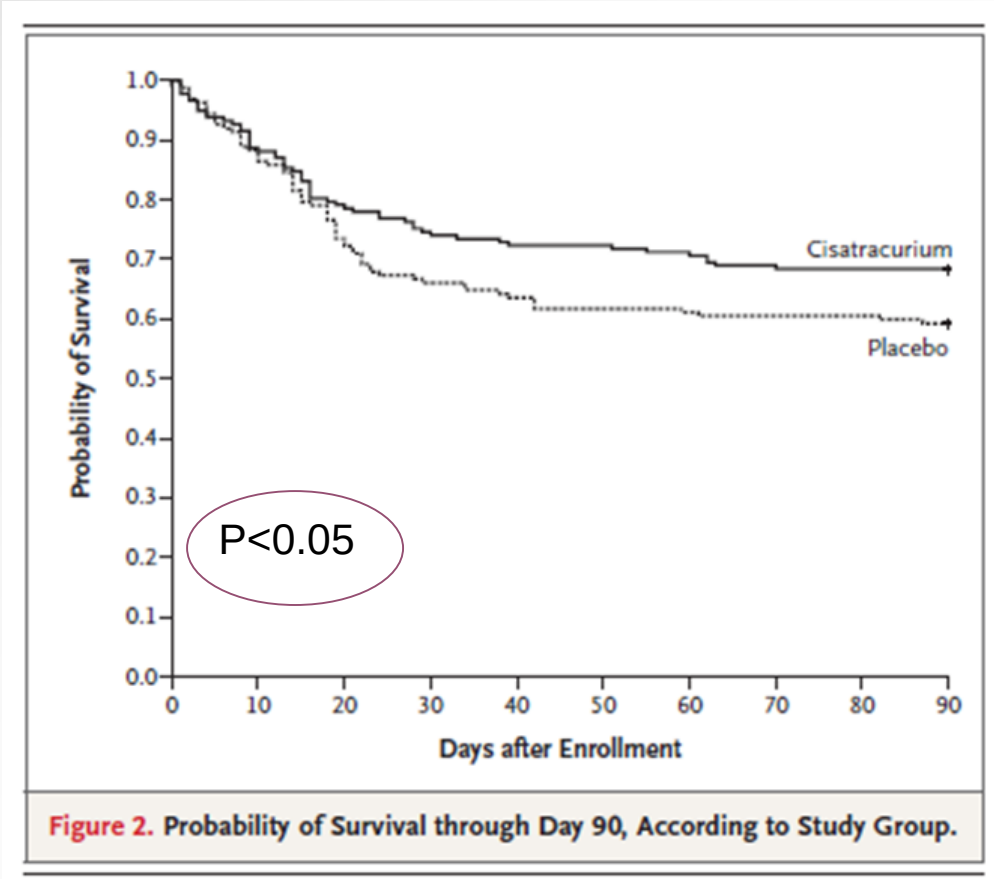


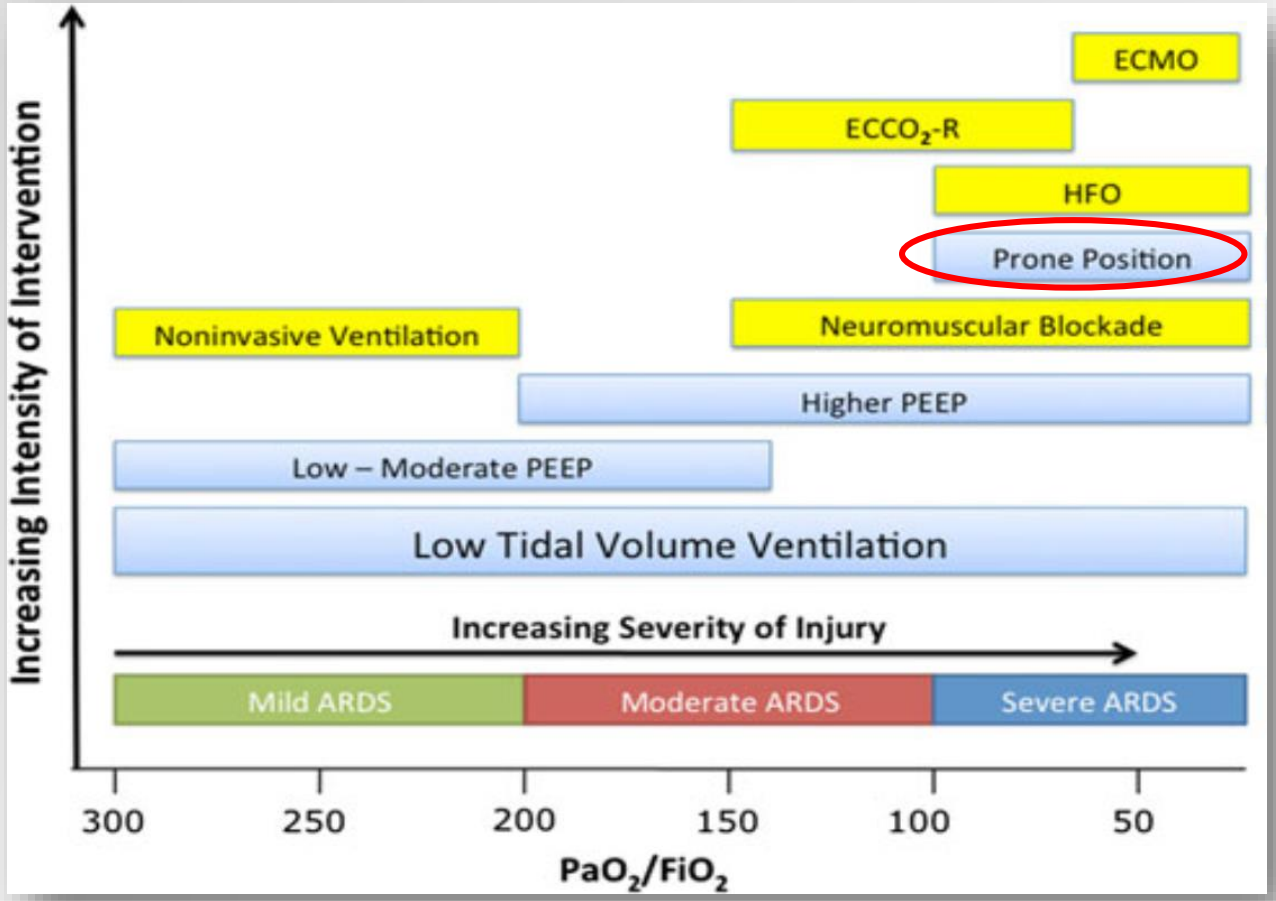
Figure 2. Probability of Survival through Day 90, According to Study Group.

Papazian et al NEJM 2010

ARDS: Lung protective ventilation

Long-Simmering Questions For the Bedside

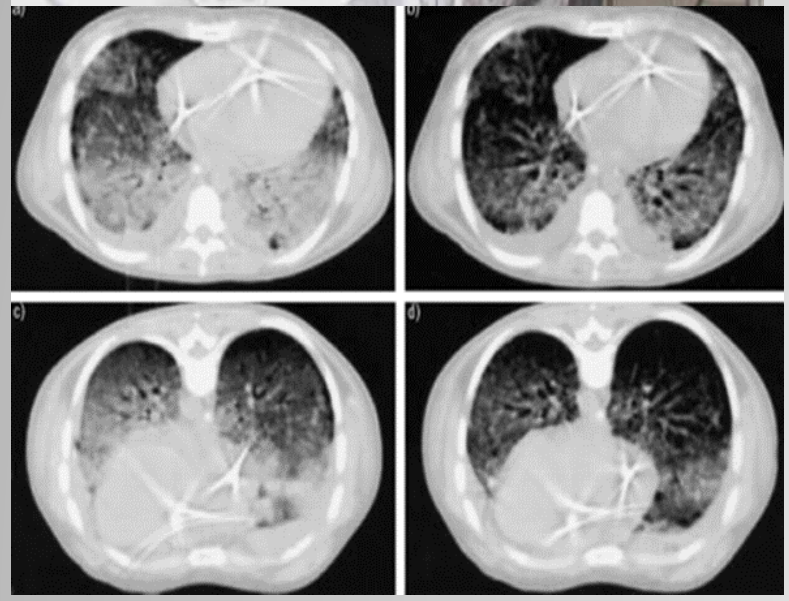
- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*



Marini J. Crit Care 2015

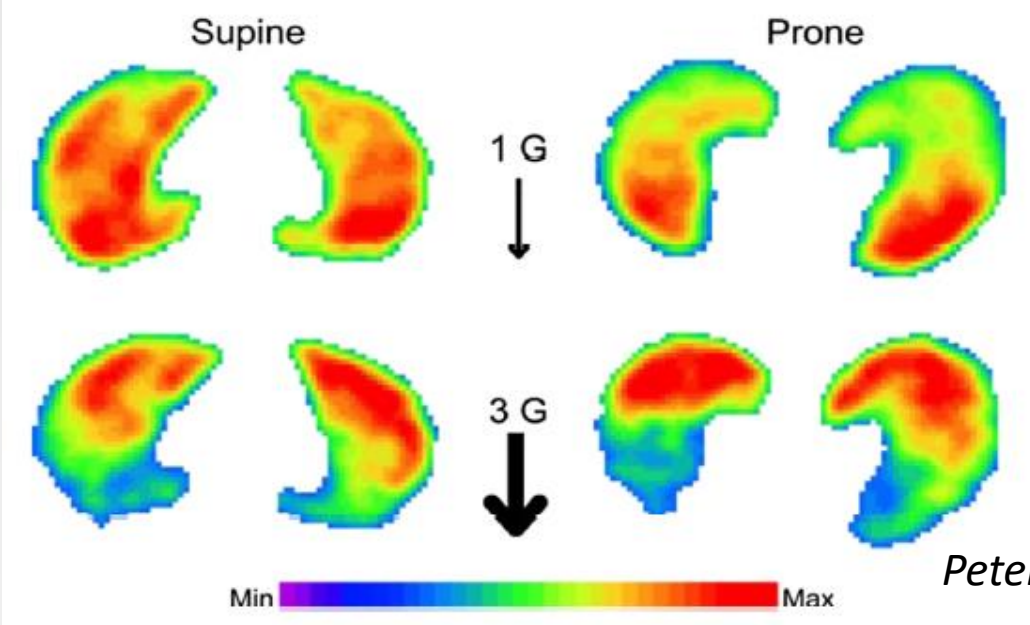
The ARDS definition Task Force: JAMA 2012

Μηχανικός αερισμός στο ARDS: Πρηνής Θέση



65-75% βελτίωση της οξυγόνωσης λόγω:

- ✓Ομοιογενέστερης κατανομής αερισμού-αιμάτωσης
- ✓Μείωσης των περιοχών με πνευμονικό οίδημα και ατελεκτασία
- ✓Αποφόρτιση από το βάρος της καρδιάς
- ✓Παροχέτευση των εκκρίσεων



Petersson, JAP 2006

The NEW ENGLAND JOURNAL of MEDICINE

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

Prone Positioning in Severe Acute Respiratory Distress Syndrome

Claude Guérin, M.D., Ph.D., Jean Reignier, M.D., Ph.D., Jean-Christophe Richard, M.D., Ph.D., Pascal Beuret, M.D., Arnaud Gacouin, M.D., Thierry Boulain, M.D., Emmanuelle Mercier, M.D., Michel Badet, M.D., Alain Mercat, M.D., Ph.D., Olivier Baudin, M.D., Marc Clavel, M.D., Delphine Chatellier, M.D., Samir Jaber, M.D., Ph.D., Sylvène Rosselli, M.D., Jordi Mancebo, M.D., Ph.D., Michel Sirodot, M.D., Gilles Hilbert, M.D., Ph.D., Christian Bengler, M.D., Jack Richecoeur, M.D., Marc Gainnier, M.D., Ph.D., Frédérique Bayle, M.D., Gael Bourdin, M.D., Véronique Leray, M.D., Raphaele Girard, M.D., Loredana Baboi, Ph.D., and Louis Ayzac, M.D. for the PROSEVA Study Group*

- 26 ICUs, 456 pts
- ARDS σύμφωνα με τα κριτήρια του AECCC 1994
- Μηχ. αερισμος < 36 h
- Βαρύ ARDS (PaO_2/FiO_2< 150 mm Hg)
- FiO2 > 0,60
- PEEP > 5 cm H_2O
- VT: 6 mL/Kg
- Prone positioning >17 h

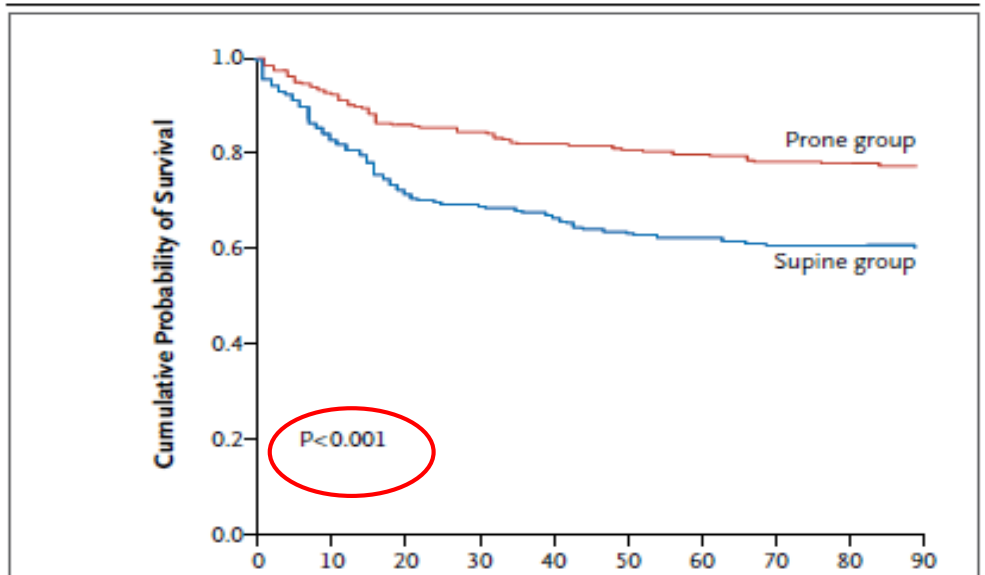
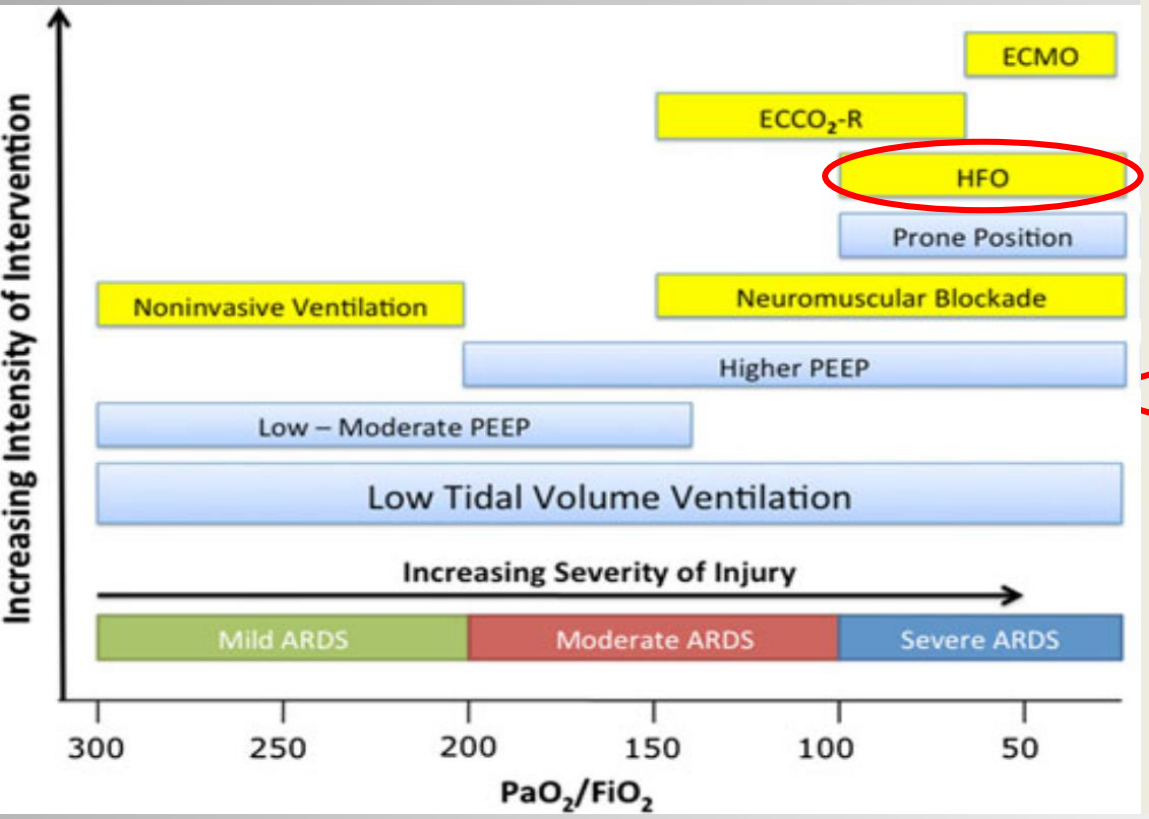


Figure 2. Kaplan–Meier Plot of the Probability of Survival from Randomization to Day 90.

ARDS: Lung protective ventilation

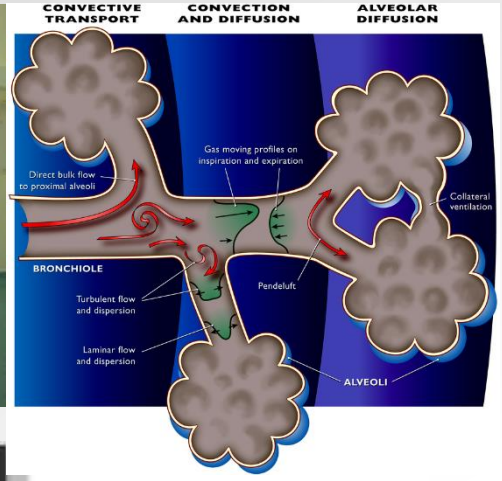


Long-Simmering Questions For the Bedside

- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*

Marini J. Crit Care 2015

Βασικά θεραπευτικά εργαλεία



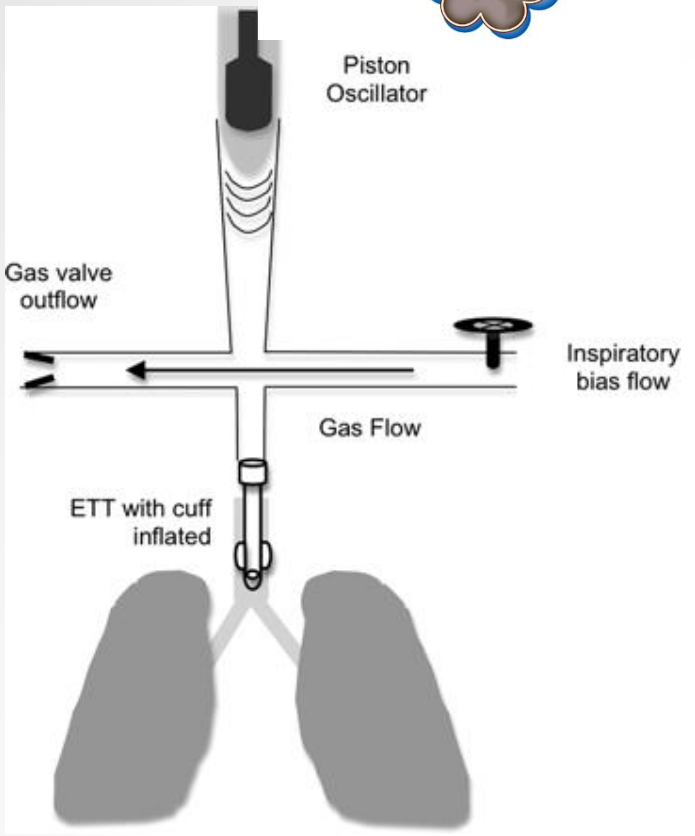
High frequency oscillation-HFO

↓↓ VT (1-3 mL/Kg),

↑↑↑ f (3-9 Hz),

σταθερή μέση πίεση αεραγωγών (mPaw)

** η εκπνοή είναι ενεργητική



- Αποφυγή υπερδιάτασης
- Αποφυγή ατελεκτασιών
- Ικανοποιητική ανταλλαγή αερίων

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 28, 2013 VOL. 368 NO. 9

High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome

Niall D. Ferguson, M.D., Deborah J. Cook, M.D., Gordon H. Guyatt, M.D., Sangeeta Mehta, M.D., Lori Hand, R.R.T., Peggy Austin, C.C.R.A., Qi Zhou, Ph.D., Andrea Matte, R.R.T., Stephen D. Walter, Ph.D., Francois Lamontagne, M.D., John T. Granton, M.D., Yaseen M. Arabi, M.D., Alejandro C. Arroliga, M.D., Thomas E. Stewart, M.D., Arthur S. Slutsky, M.D., and Maureen O. Meade, M.D., for the OSCILLATE Trial Investigators and the Canadian Critical Care Trials Group*

Outcome	HFOV Group (N = 275)	Control Group (N = 273)	Relative Risk (95% CI)	P Value
Death in hospital — no. (%)	129 (47)	96 (35)	1.33 (1.09–1.64)	0.005
Death in intensive care unit — no. (%)	123 (45)	84 (31)	1.45 (1.17–1.81)	0.001
Death before day 28 — no. (%)	111 (40)	78 (29)	1.41 (1.12–1.79)	0.004
New barotrauma — no./total no. (%)*	46/256 (18)	34/259 (13)	1.37 (0.91–2.06)	0.13
New tracheostomy — no./total no. (%)†	59/273 (22)	66/267 (25)	0.87 (0.64–1.19)	0.39
Refractory hypoxemia — no. (%)	19 (7)	38 (14)	0.50 (0.29–0.84)	0.007
Death after refractory hypoxemia — no./total no. (%)	15/19 (79)	25/38 (66)	1.20 (0.87–1.66)	0.31
Refractory acidosis — no. (%)	9 (3)	8 (3)	1.12 (0.44–2.85)	0.82
Refractory barotrauma — no. (%)	2 (<1)	2 (<1)	0.99 (0.14–7.00)	0.99
Use of mechanical ventilation, among survivors — days				0.59
Median	11	10		
Interquartile range	7–19	6–18		
Stay in intensive care, among survivors — days				0.93
Median	15	14		
Interquartile range	9–25	9–26		
Length of hospitalization, among survivors — days				0.74
Median	30	25		
Interquartile range	16–45	15–41		

Multicenter, Randomized, Controlled trial

39 ICUs

Moderate to severe ARDS

HFOV or Controlled ventilation (with low V_T, high PEEP)

548 Pts (1200)

In conclusion, in adults with moderate-to-severe ARDS, the early application of HFOV targeting lung recruitment — as compared with a ventilation strategy that uses low tidal volume and high PEEP and that permits HFOV only in cases of refractory hypoxemia — does not reduce mortality and may be harmful.

ARDS: Lung protective ventilation

Intensive Care Med (2017) 43:256–258
DOI 10.1007/s00134-016-4483-4

EDITORIAL

Ventilation-induced lung injury exists in spontaneously breathing patients with acute respiratory failure: We are not sure

Luciano Gattinoni*

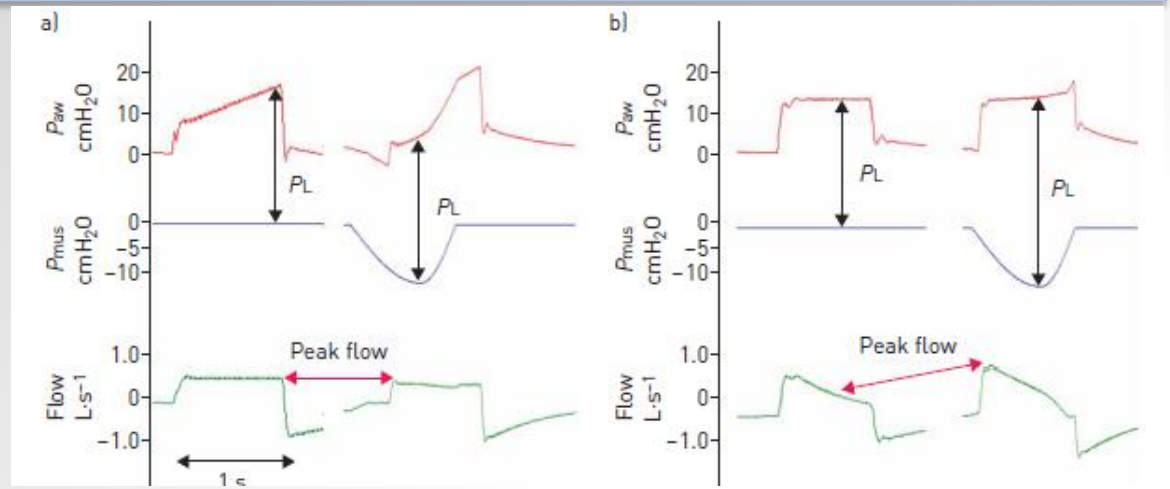
Long-Simmering Questions For the Bedside

- Which Tidal Volume?
- Which PEEP?
- Recruitment Maneuvers?
- Proning?
- High Frequency?
- Patient or Physician Control?
  - Encourage Spontaneous Breathing or not?
- Steroids?
- Extra-Pulmonary Gas Exchange?
- *ETC…*

Marini J. Crit Care 2015

Μηχανικός αερισμός στο ARDS: Spontaneous breathing

Spontaneous breathing

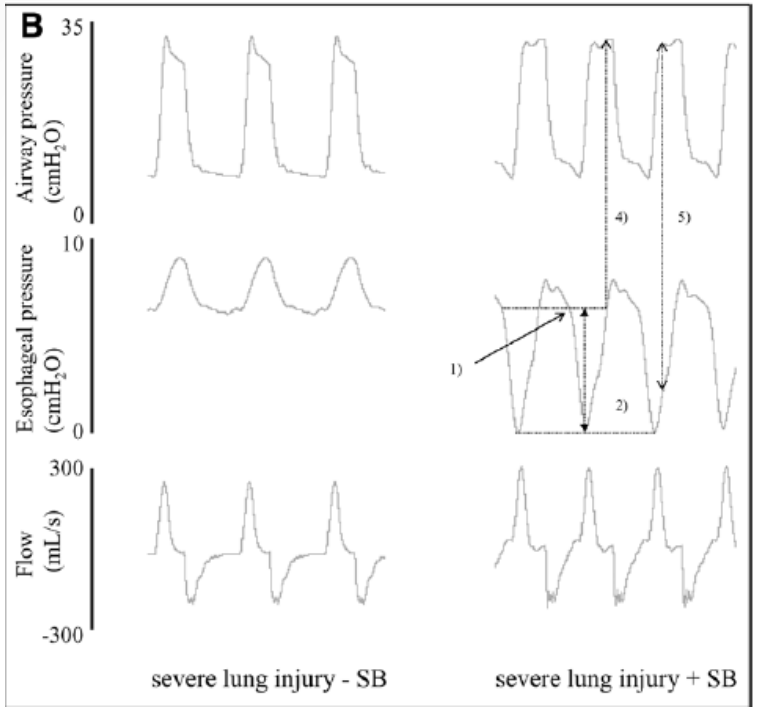


- **Βελτιώνει την οξυγόνωση.** ***Carvalho, JAP 2011***
- **Ευοδώνει την στράτευση πνευμονικού όγκου ιδίως στις υποκείμενες περιοχές**
- **Αυξάνει τον αερισμό των υποκείμενων περιοχών.** ***Putensen, AJRCCM 1999***
- **Αποτρέπει την ατροφία των αναπνευστικών μυών** ***Levine NEJM 2008***

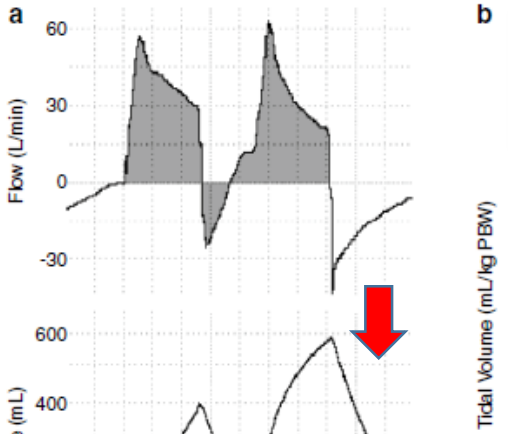
Μπορεί να προκαλέσει VILI

Stress (P_L)

Strain



Gama de Abreu, Cur Opin Cri Care 2014
Yoshiba et al, AJRCCM in Press



Spontaneous breathing
Asynchronies during mechanical ventilation

Beitler, ICM 2016

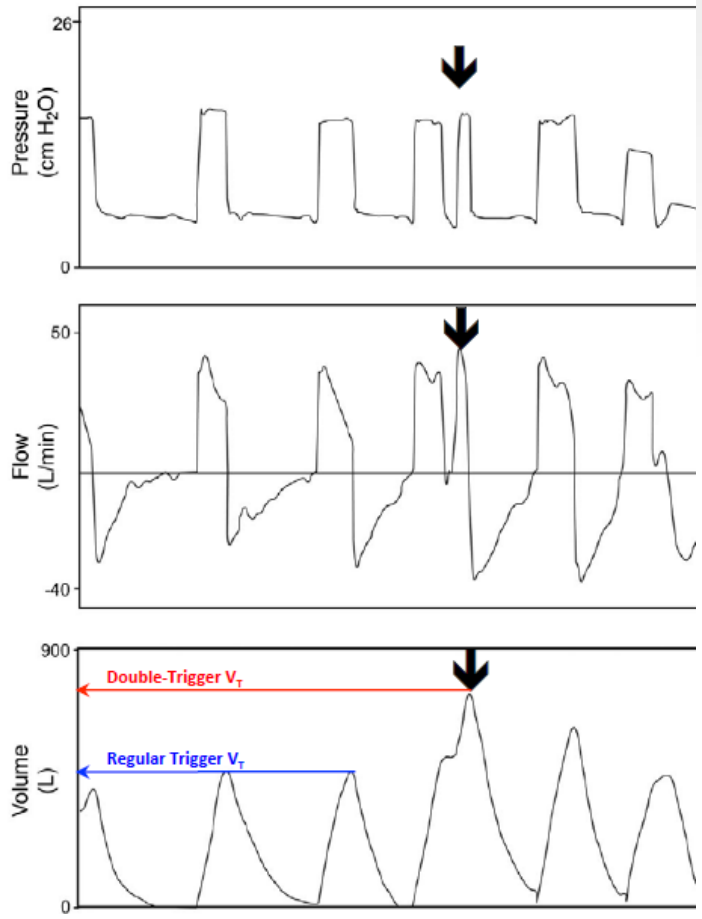
Intensive Care Med (2015) 41:633–641
DOI 10.1007/s00134-015-3692-6

ORIGINAL

Lluís Blanch
Ana Villagra
Bernat Sales
Jaume Montanya
Umberto Lucangelo
Manel Luján

Asynchronies during mechanical ventilation are associated with mortality

AJRCCM Articles in Press. Published on 27-October-2016 as 10

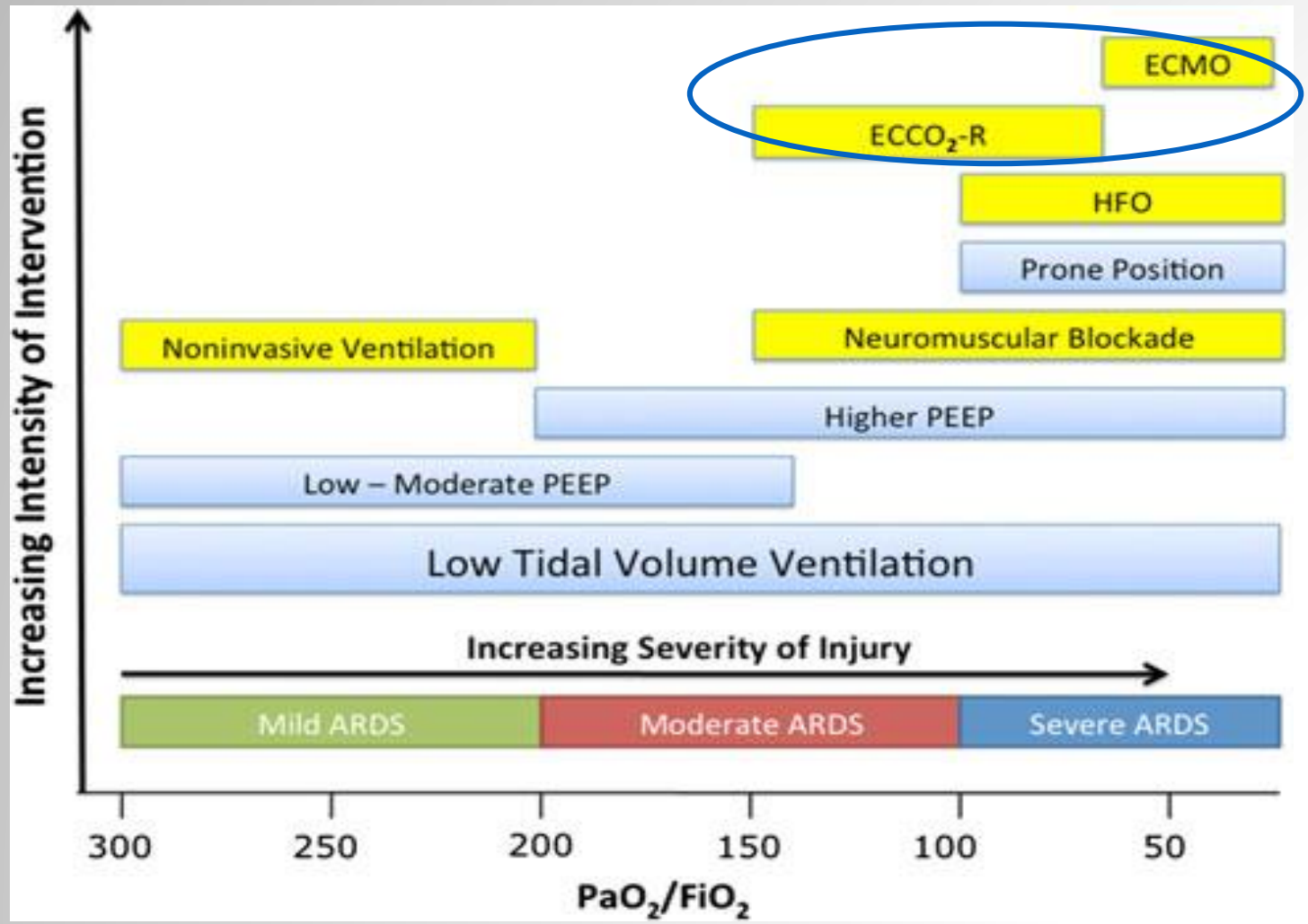


Yoshiba et al, AJRCCM in Press

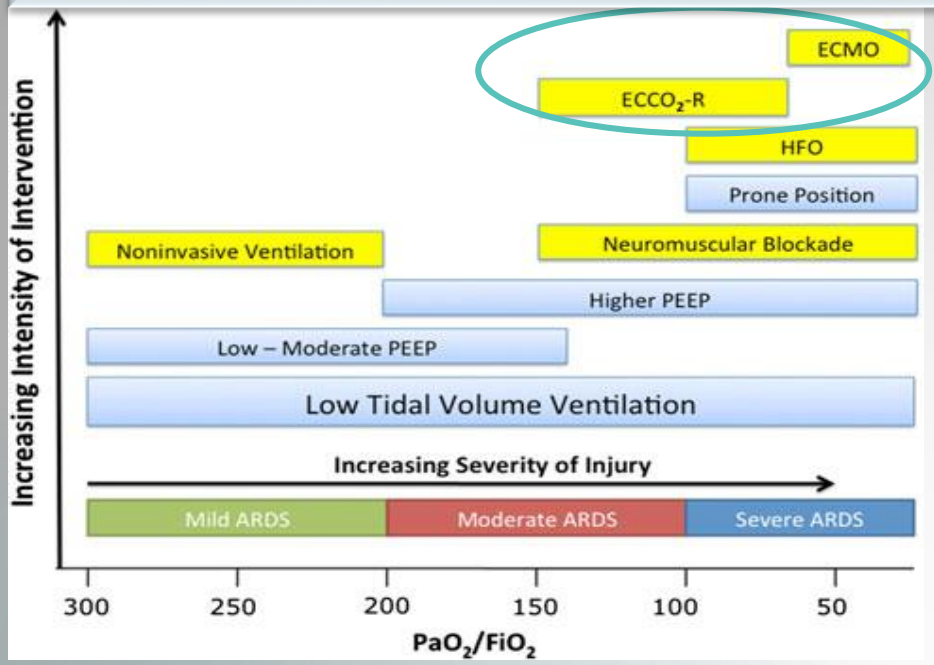
Table 2 Relationship between AI and duration of MV, reintubation, tracheostomy, and ICU and hospital mortality by comparing patients AI ≤ 10 vs AI > 10 %

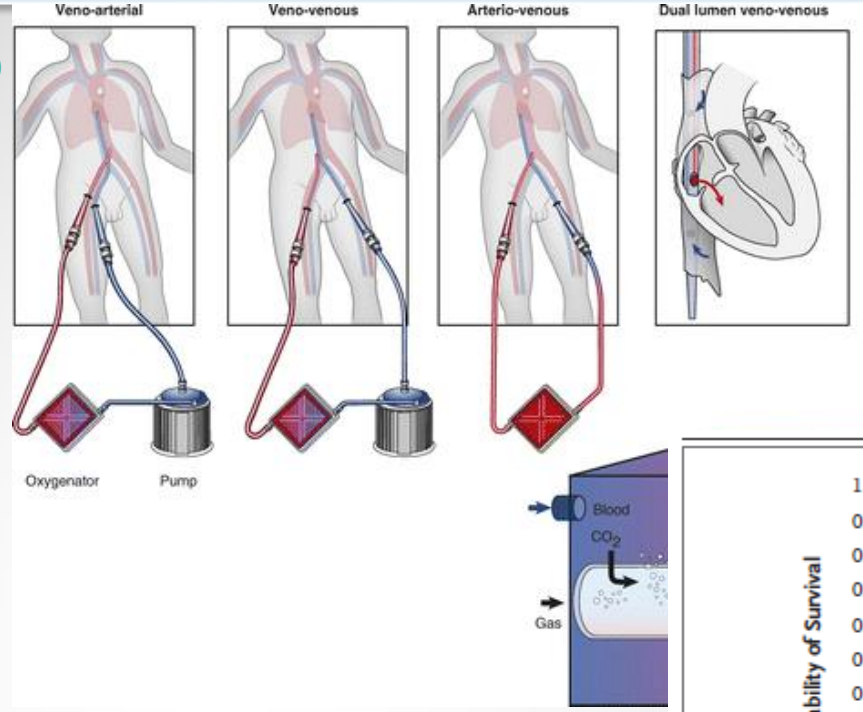
	AI ≤ 10 % ($n = 44$)	AI > 10 % ($n = 6$)	p value
Length of MV (days)	6 [5.0; 15.0]	16 [9.7; 20.0]	0.061
Reintubation	9 (20 %)	0 (0 %)	0.57
Tracheostomy	14 (32 %)	2 (33 %)	0.999
ICU mortality	6 (14 %)	4 (67 %)	0.011*
Hospital mortality	10 (23 %)	4 (67 %)	0.044*

ARDS: The Berlin definition criteria



Extra-corporeal Membrane Oxygenation (ECMO) and/or CO_2 Removal (ECCO2-R)





International Clinical Trial
249 ασθενείς με πολύ βαρύ ARDS
124: ECMO
125: συντηρητική αγωγή

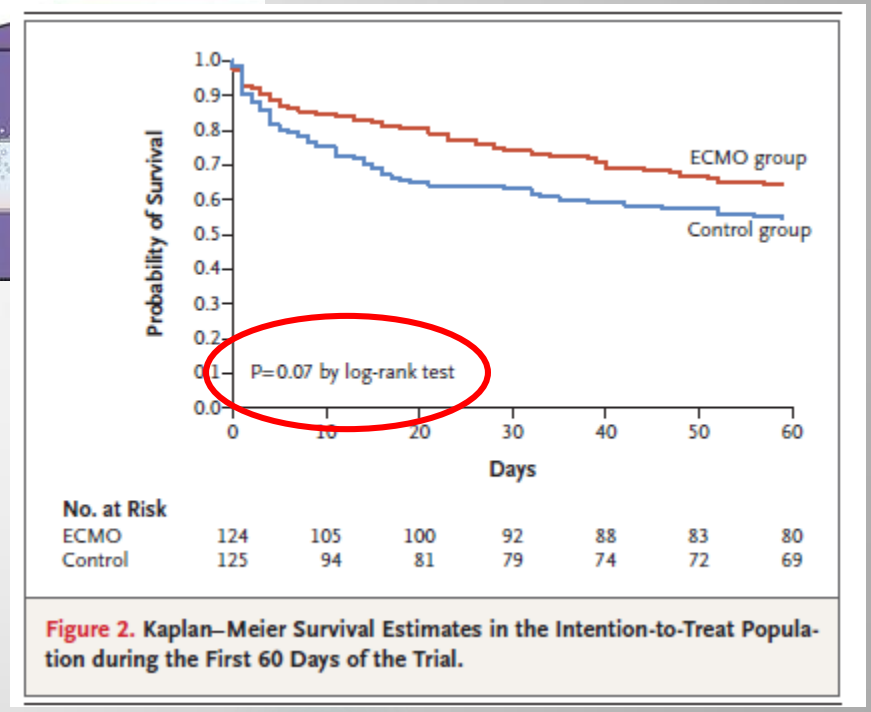
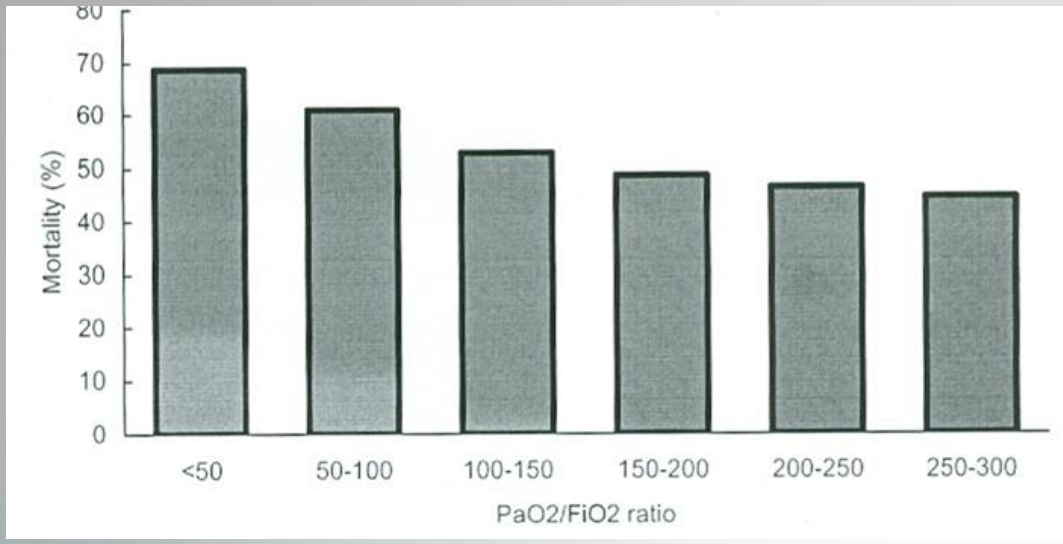
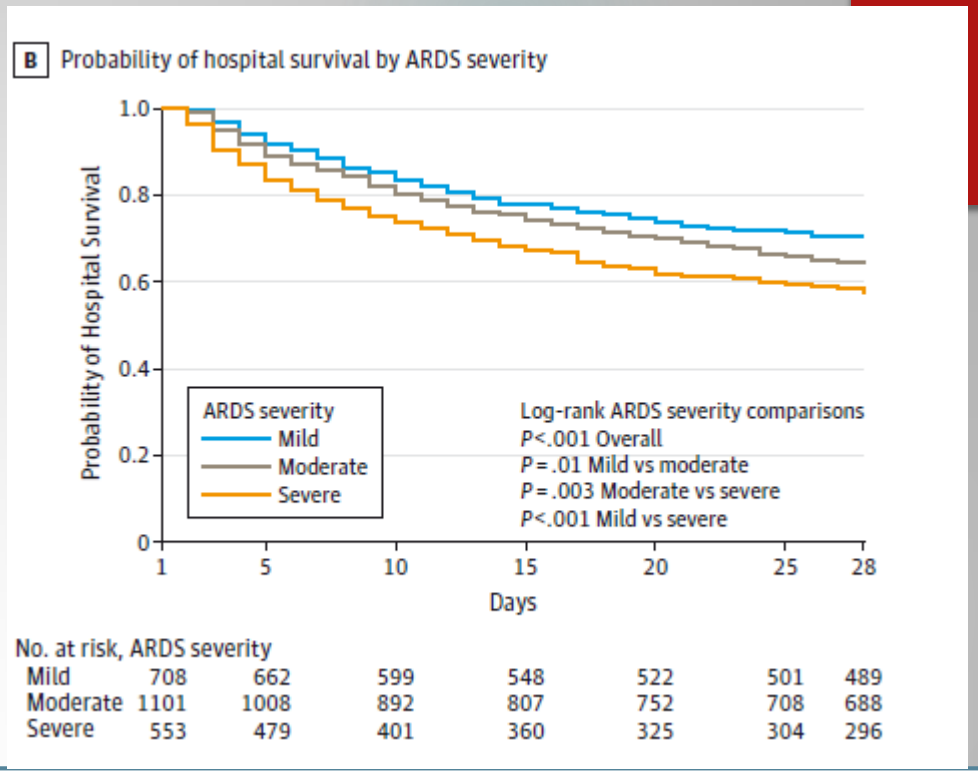


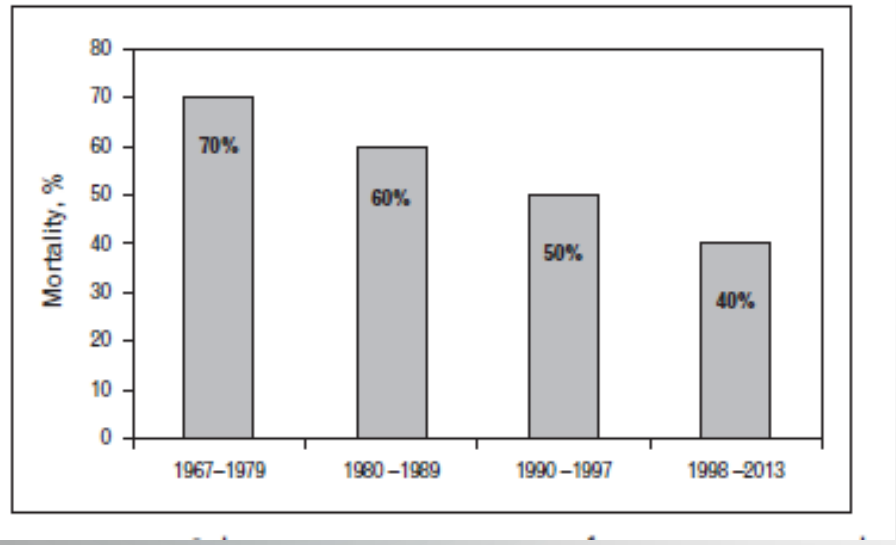
Figure 2. Kaplan–Meier Survival Estimates in the Intention-to-Treat Population during the First 60 Days of the Trial.

Combes, NEJM 2018

Έκβαση







Villar Curr Opin Crit Care 2014

Η θνητότητα μάλλον μειώνεται τα τελευταία χρόνια λόγω:

Καλύτερων στρατηγικών μηχανικού αερισμού
Πρωιμότερης διάγνωσης-θεραπείας της σήψης

Επιβαρυντικοί παράγοντες

Χρονία ηπατική νόσος
Εξωπνευμονική οργανική ανεπάρκεια
Μεγάλη ηλικία

Πλήρης (??) αποκατάσταση πνευμονικής λειτουργίας σε 6-12 μήνες

Νεότερα στην Έκβαση

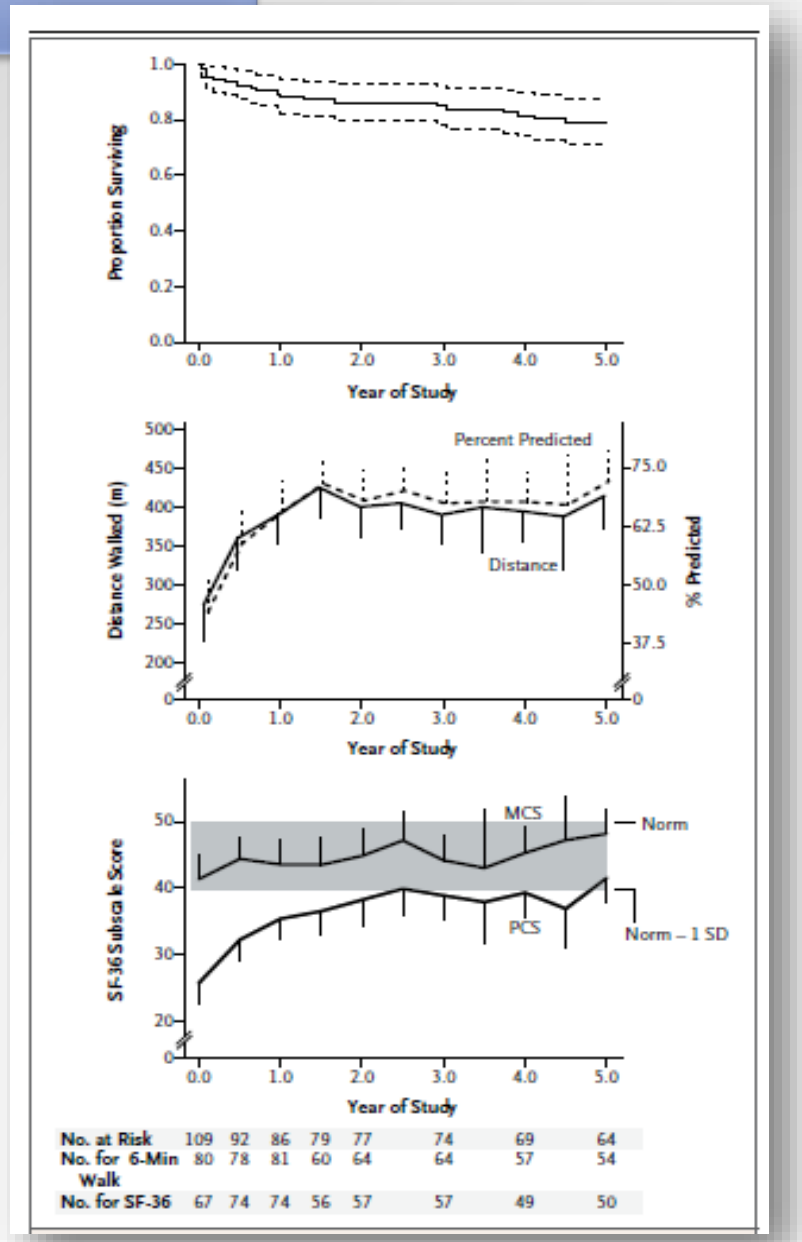
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 7, 2011 VOL. 364 NO. 14

Functional Disability 5 Years after Acute Respiratory Distress Syndrome

Margaret S. Herridge, M.D., M.P.H., Catherine M. Tansey, M.Sc., Andrea Matté, B.Sc., George Tomlinson, Ph.D., Natalia Diaz-Granados, M.Sc., Andrew Cooper, M.D., Cameron B. Guest, M.D., C. David Mazer, M.D., Sangeeta Mehta, M.D., Thomas E. Stewart, M.D., Paul Kudlow, B.Sc., Deborah Cook, M.D., Arthur S. Slutsky, M.D., and Angela M. Cheung, M.D., Ph.D., for the Canadian Critical Care Trials Group

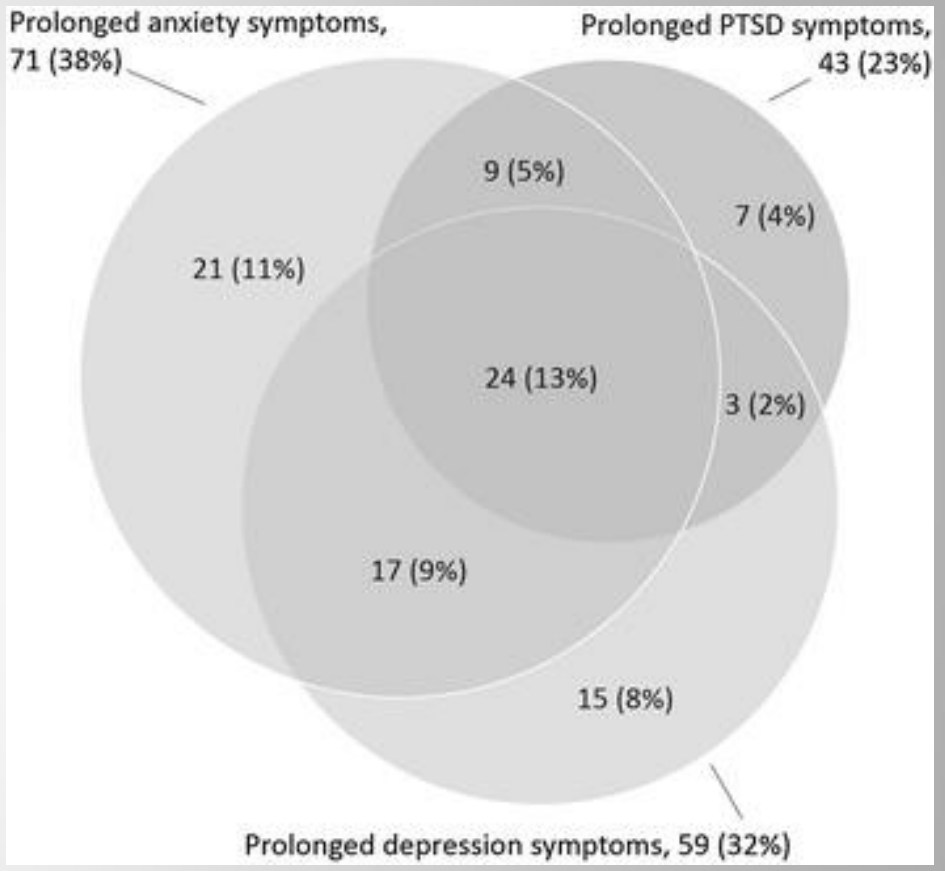
- Toronto Study
- 4 ΜΕΘ
- 109 ασθενείς με ARDS που επεβίωσαν
- Εκτιμήθηκαν 3, 6, 12 μήνες, 2,3,4,5 έτη
- Φυσική κατάσταση: 6MWD
- Πνευματική κατάσταση
- Ποιότητα ζωής: SF-36



Νεότερα στην Έκβαση

January 2018, Volume 44, Issue 1, pp 38–47

- 13 medical and surgical intensive care units in four hospitals,
- follow-up at 3, 6, 12, 24, 36, 48, and 60 months post-ARDS
- Anxiety
- depression,
- posttraumatic stress disorder (PTSD)



Intensive Care Med (2016) 42:772–774
DOI 10.1007/s00134-016-4280-0

EDITORIAL

What's new in ARDS: can we prevent it?

Roy G. Brower[1] and Massimo Antonelli[2*]

"an ounce of prevention is worth a pound of cure,"

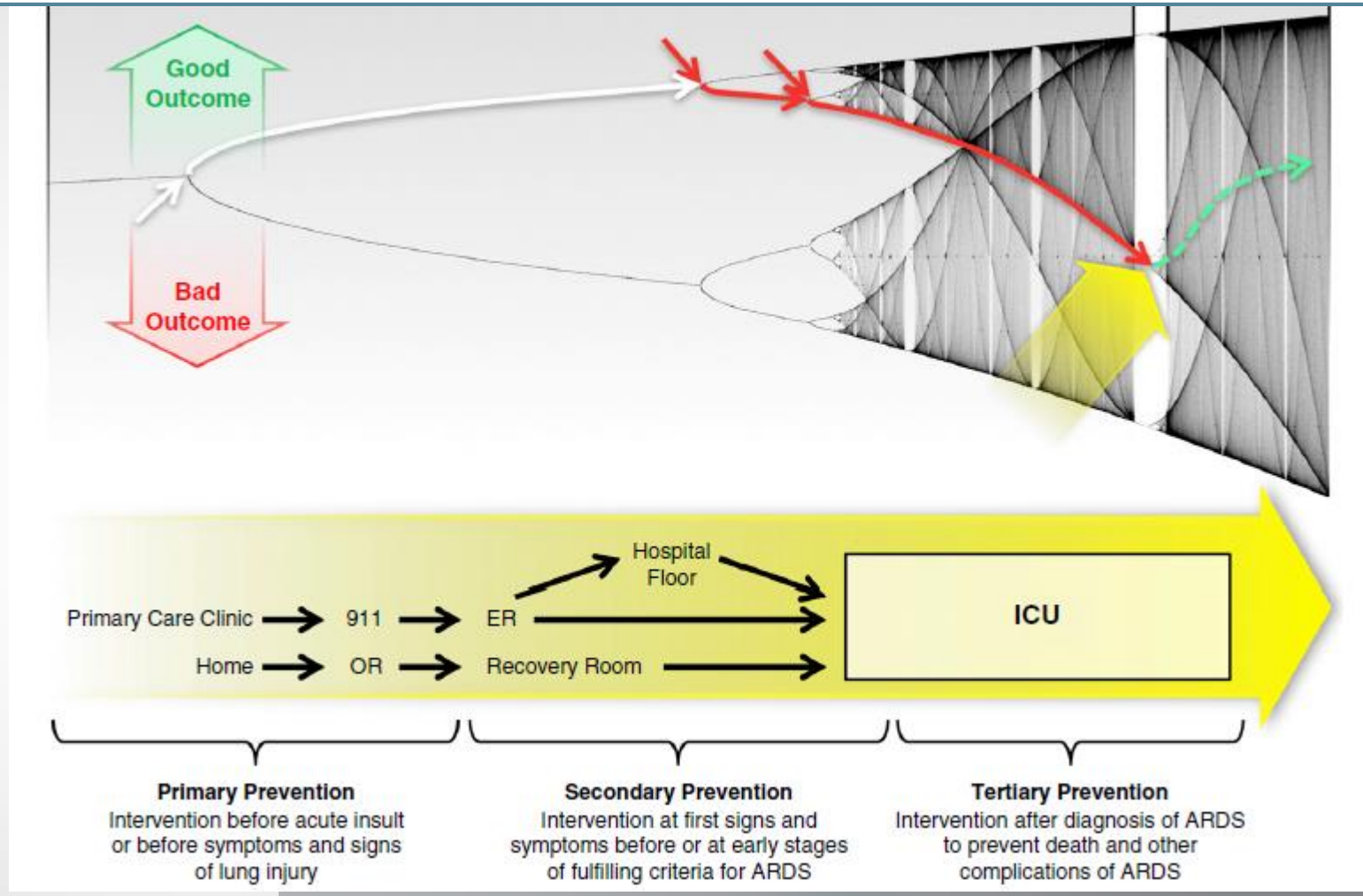
Πρόληψη ανάπτυξης η εξέλιξης ARDS

Η διαταραχή που προκαλεί η βαριά νόσος στη φυσιολογική ομοιόσταση έχει κοινά χαρακτηριστικά με τα πολύπλοκα φυσικά συστήματα όπως η ατμόσφαιρα, τα οικονομικά συστήματα, τα κοινωνικά κινήματα…….

Η θεωρία του χάους

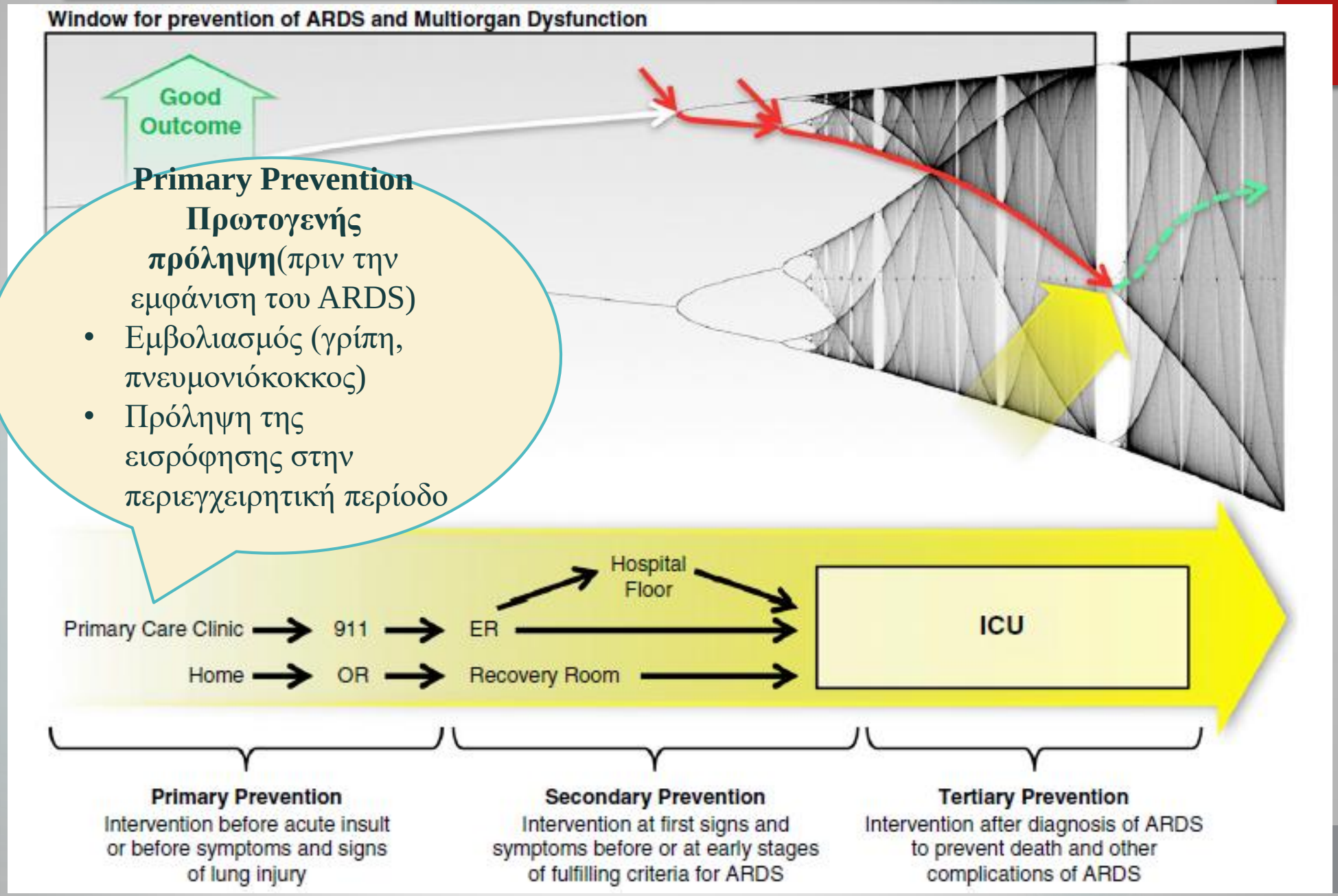
Τα μη γραμμικά δυναμικά συστήματα είναι εξαιρετικά ευαίσθητα στις αρχικές μεταβολές!

Μικρές διαφορές στις αρχικές συνθήκες θα αποδώσουν πολύ διαφορετικά αποτελέσματα μακροπρόθεσμα

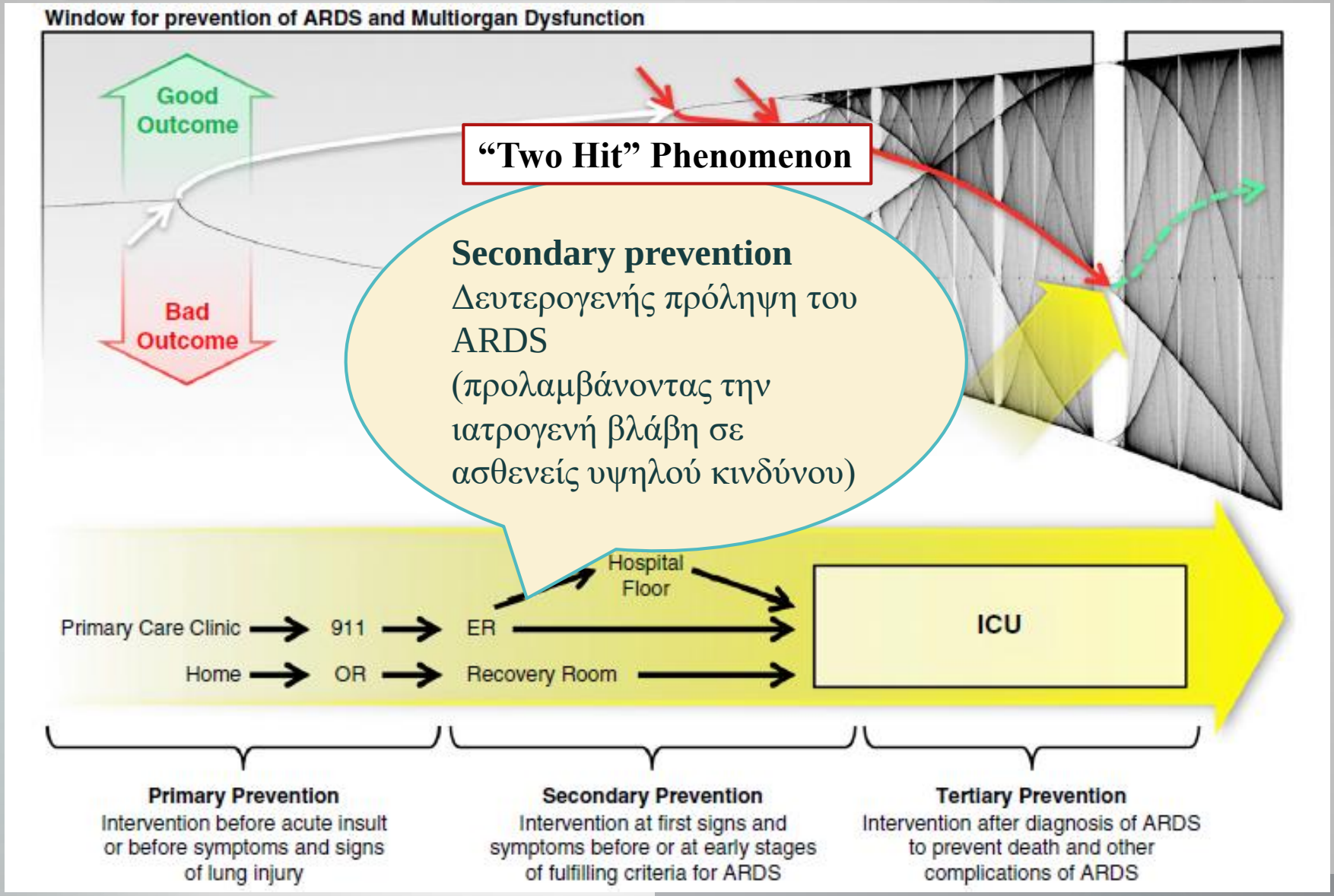


Yadav, AMRCCM 2017

Πρόληψη ανάπτυξης η εξέλιξης ARDS



Πρόληψη ανάπτυξης η εξέλιξης ARDS

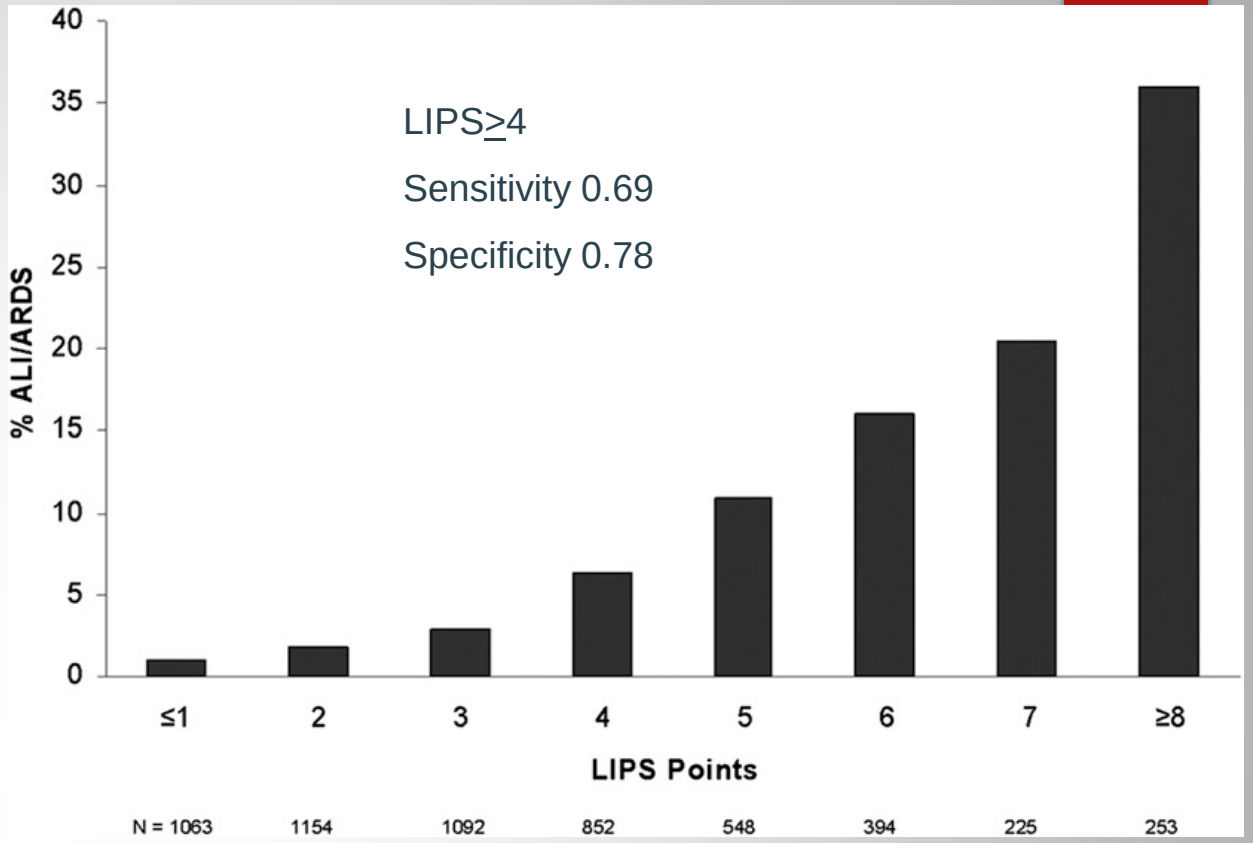


Πρόληψη-Ασθενείς υψηλού Κινδύνου

TABLE 2 Calculation of the Lung Injury Prediction Score (LIPS)

Characteristic	Points Awarded
Predisposing conditions	
Shock	2
Aspiration	2
Sepsis	1
Pneumonia	1.5
High-risk surgery[a]	
Orthopedic spine	1
Acute abdomen	2
Cardiac	2.5
Aortic vascular	3.5
High-risk trauma	
Traumatic brain injury	2
Smoke inhalation	2
Near drowning	2
Lung contusion	1.5
Multiple fractures	1.5
Risk modifiers	
Alcohol abuse	1
Obesity (BMI > 30 kg/m²)	1
Hypoalbuminemia (albumin < 3.5 g/dL)	1
Chemotherapy	1
Fio_2 > 0.35 (> 4 L/min)	2
Tachypnea (respirations > 30/min)	1.5
Spo_2 < 95%	1
Acidosis (pH < 7.35)	1.5
Diabetes mellitus with sepsis	−1

Adapted with permission from Gajic et al.[12] Spo_2 = oxygen saturation as measured by pulse oximetry.
[a]Add 1.5 points if emergency surgery.



Gajic Am J Respir Crit Care Med, 2011

Πρόληψη-Ασθενείς υψηλού Κινδύνου

Πρόληψη- Πρώιμη διάγνωση, Early ALI (EALI)

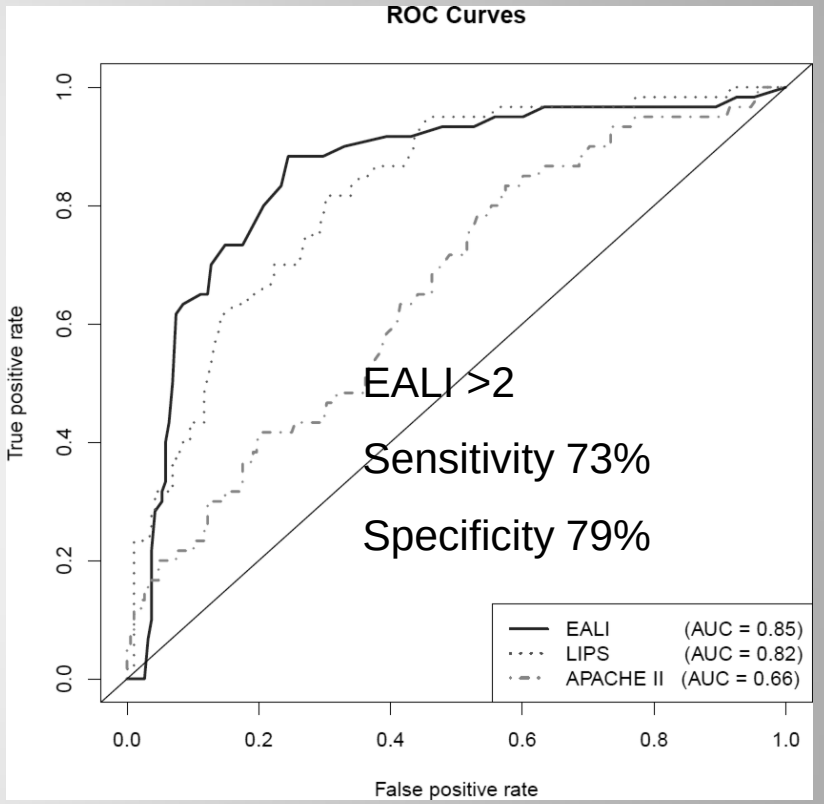
32.341 CxR, 5,545 Pathologic,

256 αμφοτεροπλευρα διηθήματα

62 (25%) ALI

Risk Factor		Odds Ratio	95% CI	p
Supplemental oxygen				
≤ 2 L/min	1 p	Reference		
> 2–6 L/min	2 p	5.2	1.8–15	0.002
> 6 L/min	1 p	33.7	12–93	< 0.0001
Respiratory rate ≥ 30 breaths/min	1 p	2.9	1.4–6.2	0.006
Immune suppression		2.5	1.2–5.5	0.02

Variables selected by backward stepwise regression (significance ≤ 0.05) of significant variables on univariable analysis (respiratory rate, oxygen requirement, immune suppression, heart rate, abnormal temperature, do not intubate status, positive sputum culture, and shock).



Levitt, Crit Care Med 2013

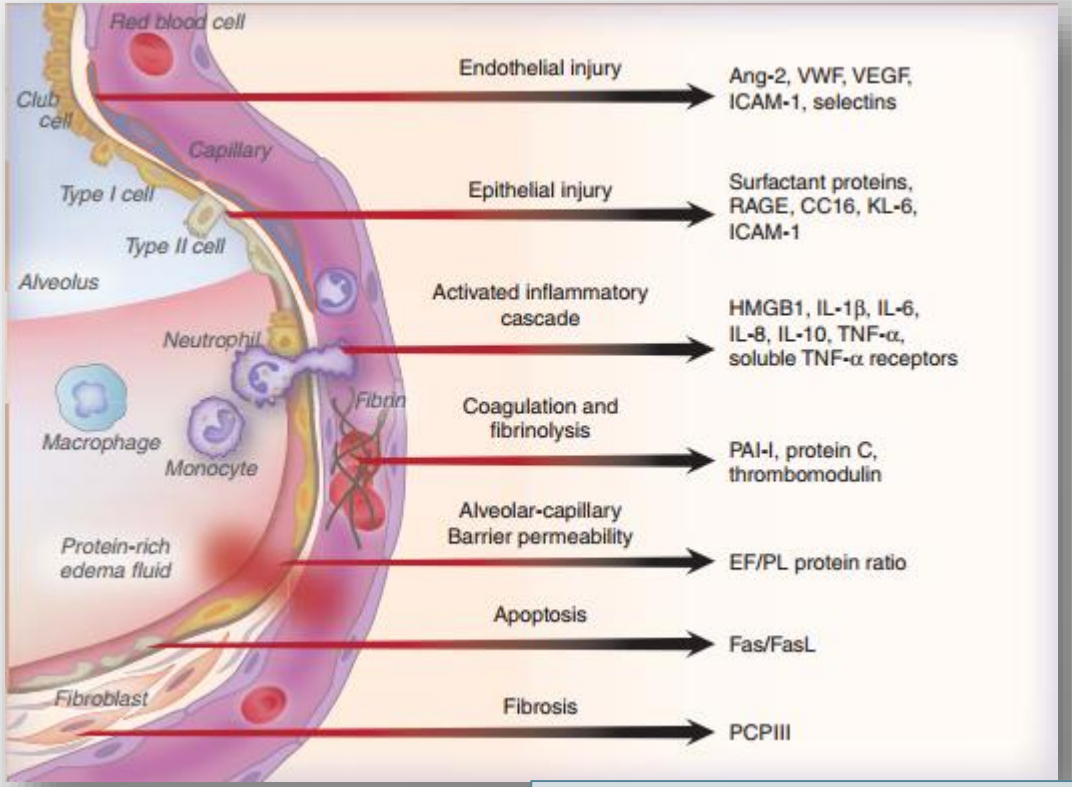
Πρόληψη-Πρώιμη αναγνώριση

Genetic predisposition
Γενετική προδιάθεση
Συγκεκριμένα γονίδια

- **Biomarkers**
- 20 βιοδείκτες διάγνωσης
- 19 βιοδείκτες πρόγνωσης

Table 1 Specific markers with a predictive value for development and/or outcome of ARDS

Biological compartment and markers	Cell injury/inflammation
Plasma	
RAGE	Epithelium
Ang-2	Endothelium
SP-D	Epithelium
IL-8	Acute inflammation
BALF	
Fas, Fas ligand	Epithelium
PCP I	Fibroproliferation
PCP III	Fibroproliferation
Exhaled air	
Octane	Lipid peroxidation
Acetaldehyde	Bacterial metabolism, inflammation
3-methylheptane	Lipid peroxidation



Walter, Expert Rev Respir Med 2014

Πρόληψη –Πρώιμη θεραπεία

"Two Hit" Phenomenon

Patient at Risk
(1st hit)

- Pneumonia
- Toxic inhalation
- Pancreatitis
- Aspiration
- Trauma
- Sepsis
- Shock
- Alcohol
- Tobacco
- High risk surgery
- Preexisting lung disease
- Radiation
- Chemotherapy

Patients at Risk

Early recognition

~~Biomarkers~~

~~Genetic predisposition~~

Preventive Measures

Low tidal volume

Restrictive transfusion

Sepsis management

Conservative fluid management

ARDS

De Haro, Annals Intens Care 2013

Intensive Care Med (2016) 42:772–774
DOI 10.1007/s00134-016-4280-0

EDITORIAL

What's new in ARDS: can we prevent it?

Roy G. Brower[1] and Massimo Antonelli[2*]

Crit Care Med. 2014 January ; 42(1): . doi:10.1097/CCM.0b013e318298a6db.

The Role of Potentially Preventable Hospital Exposures in the Development of Acute Respiratory Distress Syndrome: A Population-Based Study

Adil H. Ahmed, MBBS, John M. Litell, DO, Michael Malinchoc, MS, Rahul Kashyap, MBBS, Henry J. Schiller, MD, Sonal R Pannu, MBBS, Balwinder Singh, MBBS, Guangxi Li, MD, and Ognjen Gajic, MD, MSc

Preventive Measures

- **Low tidal volume**
- Restrictive transfusion
- Sepsis management
- Conservative fluid management

414 ασθενείς στη διάρκεια 10 ετών

Selected Exposures in ARDS Cases and Controls [a]

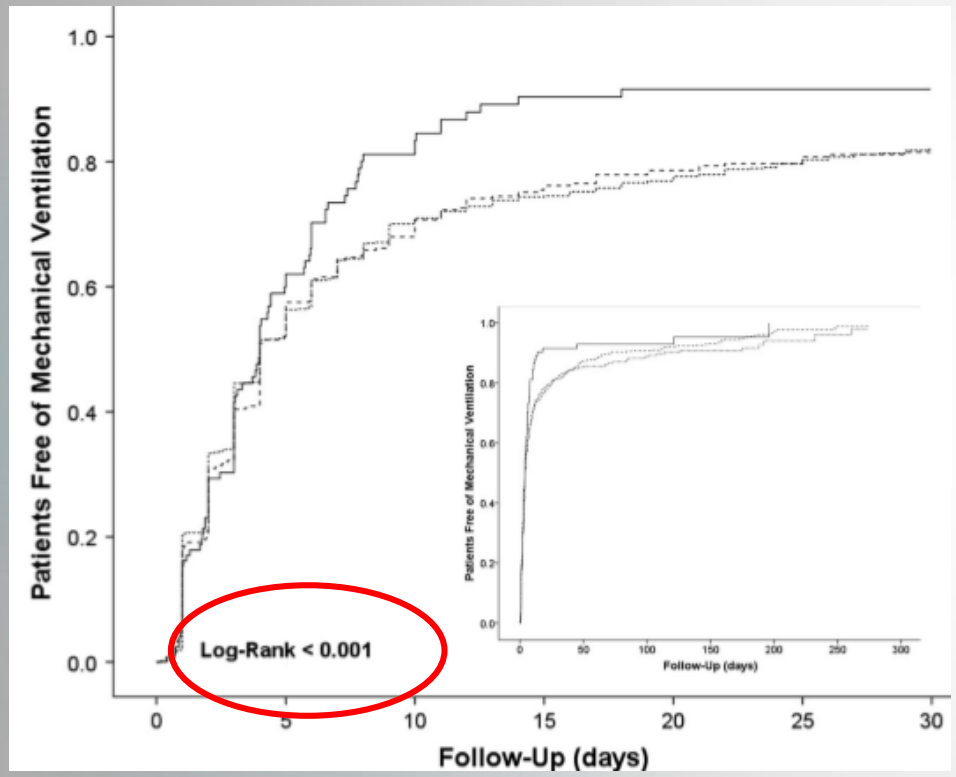
Exposures	Cases and controls after removing 2001 -2002 (N=308 pair)	Cases and controls after adjusting for baseline characteristics
	OR (95% CI) P value [b]	OR (95% CI) P value [b]
Any adverse events	4.7 (3.0-7.6) P<0.001	6.5 (4.1-10.4) P<0.001
Inadequate empiric antimicrobial	2.5 (1.3-4.7) P = 0.006	3.6 (2.0-6.7) P<0.001
Aspiration	34.0 (4.7-248.4) P <0.001	52.0 (7.1-383.2) P<0.001
Red blood cells [c]	1.4 (1.2-1.6) P <0.001	1.4 (1.2-1.5) P<0.001
Fresh frozen plasma [c]	1.4 (1.2-1.6) P <0.001	1.4 (1.2-1.6) P<0.001
Platelets [c]	2.9 (1.6-5.5) P <0.001	2.0 (1.4-2.9) P<0.001
TV -PBW [d]	1.3 (0.82-2.2) P 0.25	2.1 (1.1-4.1) P = 0.025

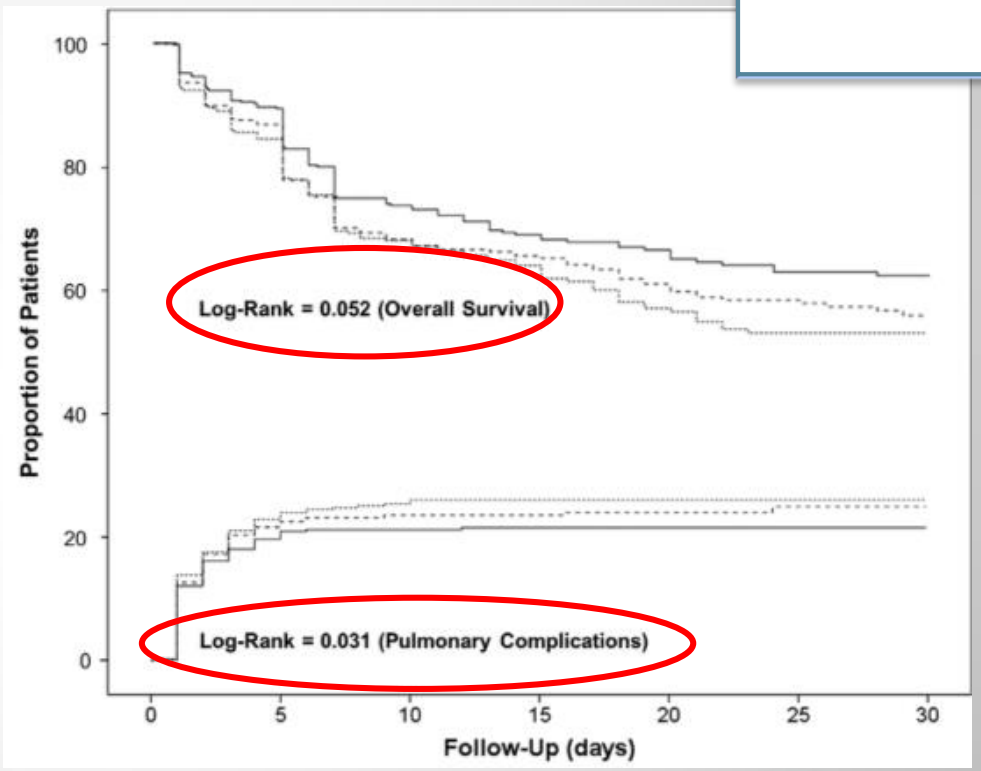
Abbreviations: ARDS, acute respiratory distress syndrome; OR, odds ratio; PBW, predicted body weight; TV, tidal volume

Αναπνεόμενος όγκος σε ασθενείς χωρίς ARDS

7 μελέτες (2,184 ασθενείς)
Ημέρες εκτός μηχ. Αερισμού
Δόση και διάρκεια καταστολής και μυοχάλασης
3 Ομάδες:
VT: < 6 mL/Kg PBW
VT: 6-10 mL/Kg PBW
VT: > 10 mL/Kg PBW

A Meta-analysis: Seven investigations (2,184pts)



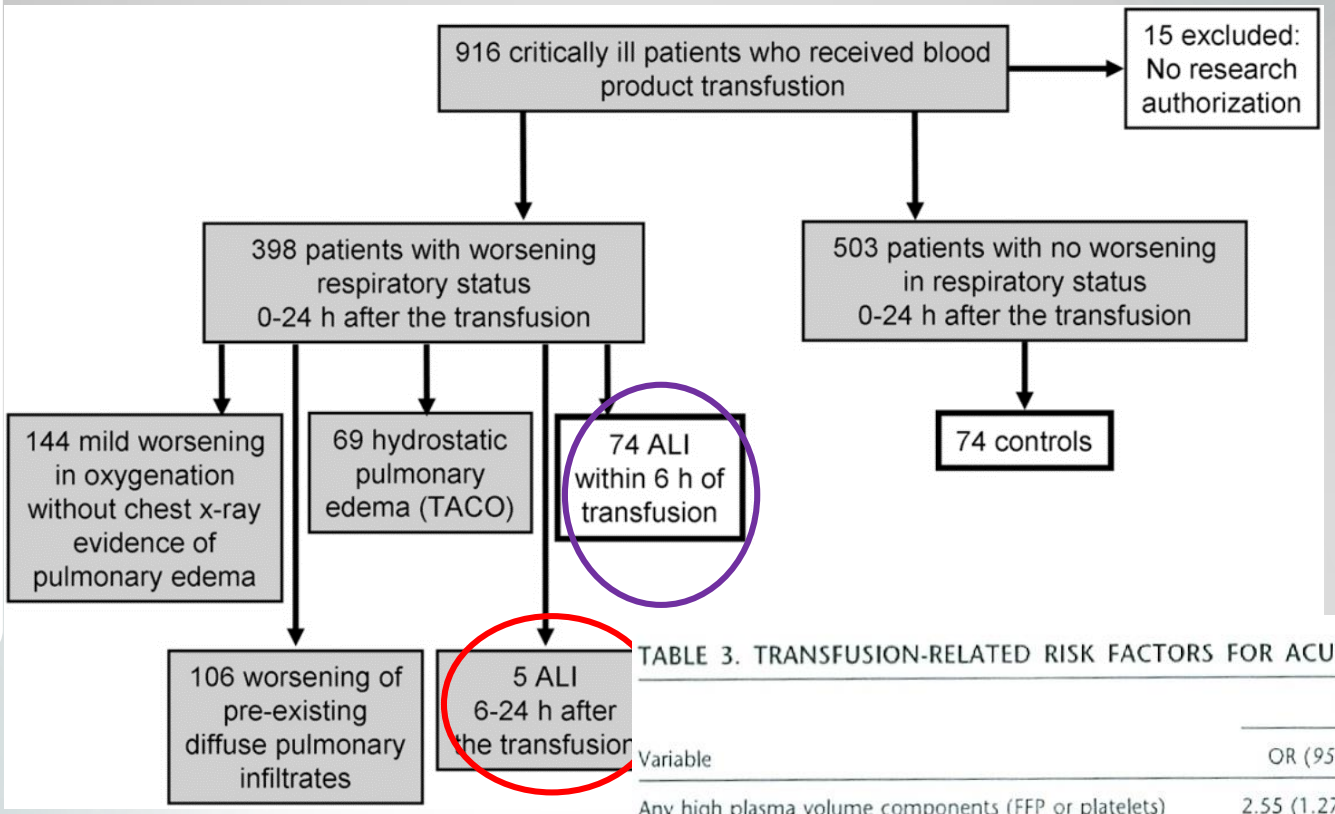


Serpa Neto, ICM 2014, CCM 2015

Περιορισμός των μεταγγίσεων

Preventive Measures

- Low tidal volume
- **Restrictive transfusion**
- Sepsis management
- Conservative fluid management



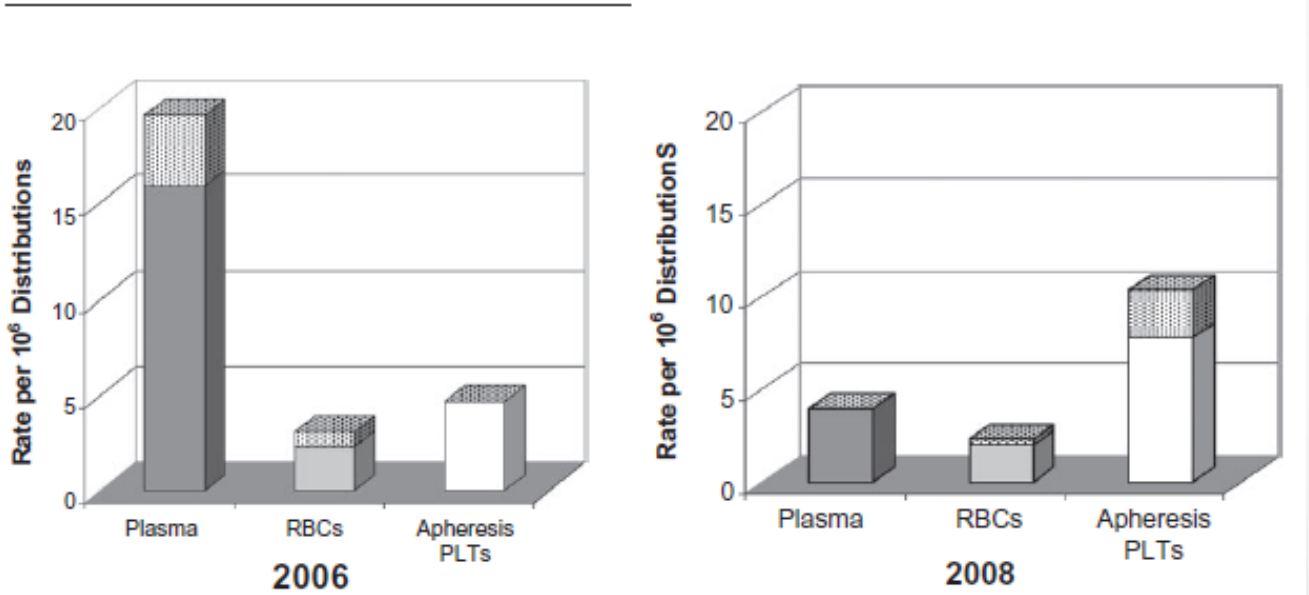
Gajic AJRCCM 2007

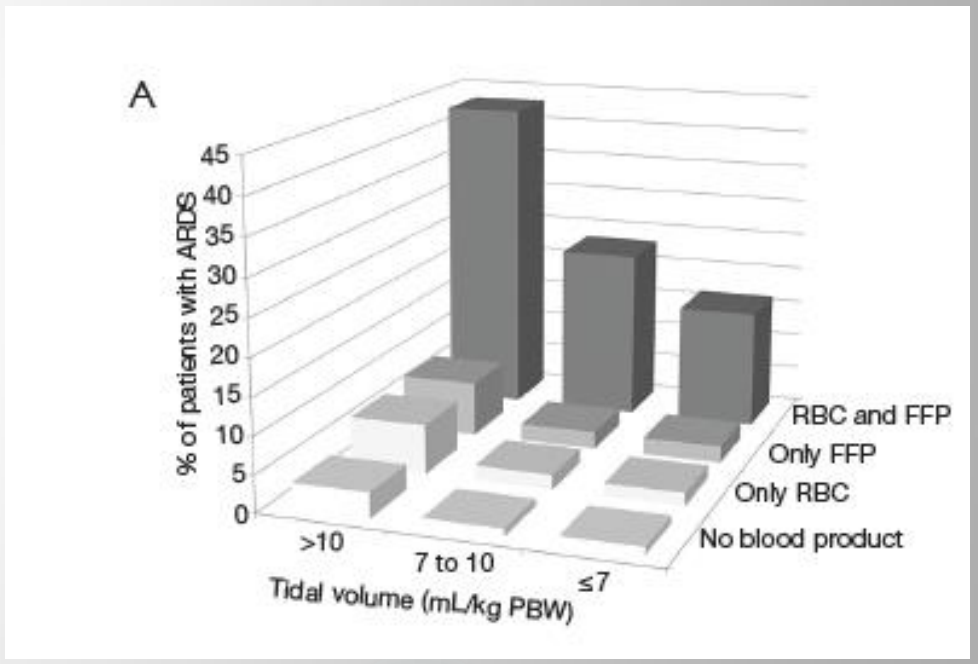
TABLE 3. TRANSFUSION-RELATED RISK FACTORS FOR ACUTE LUNG INJURY

	Unadjusted*		Adjusted†	
Variable	OR (95% CI)	P Value	OR (95% CI)	P Value
Any high plasma volume components (FFP or platelets)	2.55 (1.27–5.11)	0.009	2.78 (1.21–6.38)	0.016
Number of units	1.09 (0.99–1.20)	0.081	1.11 (0.99–1.25)	0.086
Number of units from female donors	1.30 (1.03–1.66)	0.029	1.51 (1.08–2.12)	0.016
Amount of plasma from male donors, L	1.55 (0.79–3.06)	0.202	1.60 (0.76–3.37)	0.215
Amount of plasma from female donors, L	3.23 (1.17–8.91)	0.024	5.09 (1.37–18.85)	0.015
Amount of plasma from female donors with at least one pregnancy, L	4.41 (1.00–19.55)	0.050	9.48 (1.38–65.35)	0.022
Number of pregnancies among donors	1.11 (1.00–1.22)	0.047	1.19 (1.05–1.34)	0.007
Number of HLA class I^{+} units	1.81 (0.97–3.38)	0.061	1.70 (0.94–3.09)	0.098
Number of HLA class II^{-} units	1.93 (0.88–4.28)	0.103	3.08 (1.15–8.25)	0.025
Number of GIF^{+} units	4.19 (1.22–14.32)	0.023	4.85 (1.32–17.86)	0.018
Mean LysoPC 16:0** (per 10-mol/L increase)	1.16 (1.04–1.30)	0.011	1.16 (1.02–1.32)	0.022
Mean LysoPC 18:0** (per 10-mol/L increase)	1.58 (1.10–2.26)	0.013	1.61 (1.08–2.38)	0.018

Περιορισμός των μεταγγίσεων

17 μελέτες, 3659 ασθενείς στην περιεγχειρητική περίοδο
ARDS: 7,2% σε ασθενείς που έλαβαν εστω και μια μετάγγιση
ARDS: 2,5% χωρίς μετάγγιση





Eder, Tranf Pract 2010

Serpa Neto An Transl Med 2018

Πρόληψη –Πρώιμη θεραπεία

Έγκαιρη αντιμετώπιση της σήψης

Προοπτική μελέτη
160 ασθενείς με σηπτικό shock, χωρίς πνευμονική βλάβη

71 (44%) ανέπτυξαν ALI, 5h μετά την έναρξη του shock

Preventive Measures

- Low tidal volume
- Restrictive transfusion
- **Sepsis management**
- Conservative fluid management

Table 2. Risk factors for development of ALI in patients with septic shock: multiple logistic regression analysis

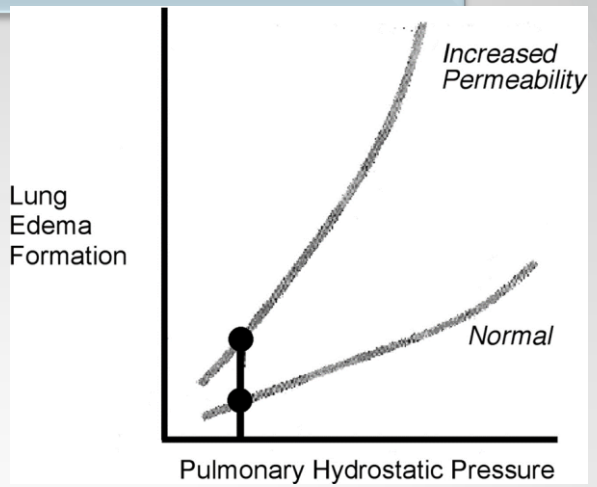
Πρώιμη θεραπεία	Odds Ratio	95% CI	*p* Value
Delayed goal-directed resuscitation	3.55	1.52–8.63	.004
Delayed antibiotics	2.39	1.06–5.59	.039
Respiratory rate (per sb)	2.03	1.38–3.08	<.001
Chemotherapy	6.47	1.99–24.9	.003
Chronic alcohol use	2.09	.88–5.10	.098
Transfusion	2.75	1.22–6.37	.016
Aspiration	3.48	1.22–10.78	.024
Diabetes mellitus	.44	.17–1.07	.076

Iscimen, Crit Care Med 2008

Συντηρητική χορήγηση υγρών

Preventive Measures

- Low tidal volume
- Restrictive transfusion
- Sepsis management
- **Conservative fluid management**



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

1000 ALI pts for 7 days

Fluid Balance:

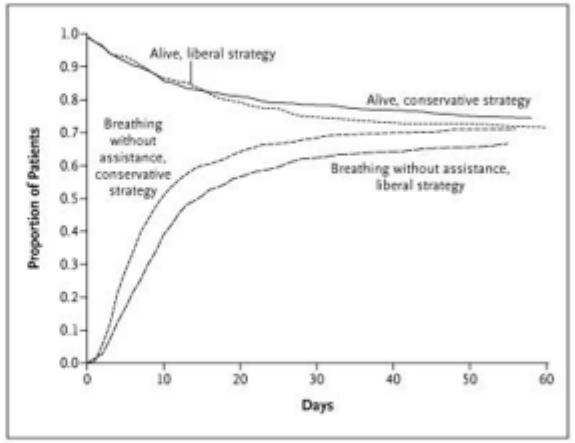
–136±491 mL vs 6992±502 mL P<0.001

Ventilator Free Days:

14.6±0.5 vs. 12.1±0.5, P<0.001

Mortality:

25.5% vs 28.4% p=0.30



The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. N Engl J Med 2006;354:2564-2575

The NEW ENGLAND JOURNAL of MEDICINE

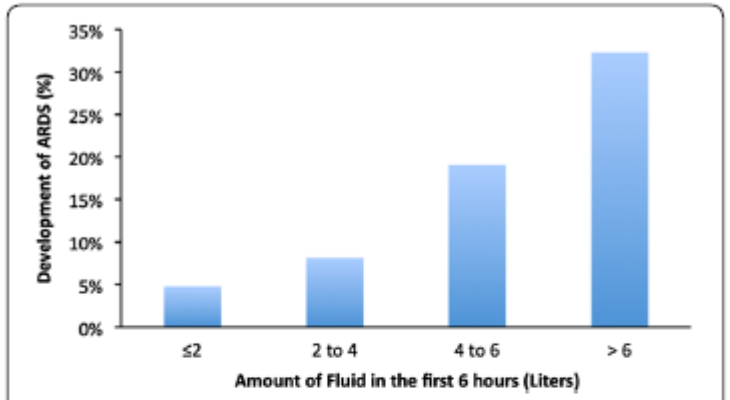


Fig. 2 Frequency of acute respiratory distress syndrome (ARDS) development according to amount of fluid administered during the first 6 h of hospital presentation

Table 4 Shock subgroup analysis: multivariable analysis of total volume in first 6 h and the development of ARDS

	Odds ratio (95% CI)	*p* value
Shock	1.05 (0.87–1.28)	0.60
No shock	1.21 (1.05–1.38)	0.01

The odds ratio indicates the increased odds of ARDS for a 1-l increase in volume of fluids administered

Seethala R, An Intens Care 2017

Το ARDS είναι ένα σύνδρομο, όχι μια νόσος
Δεν είναι όλοι οι ασθενείς με ARDS ίδιοι και άρα το ίδιο πιθανό να ευνοηθούν από μια συγκεκριμένη θεραπεία
Οι ασθενείς με ARDS μπορεί να έχουν διαφορετικούς παράγοντες κινδύνου, διαφορετικές συνοσηρότητες, διαφορετική παθοφυσιολογική εξέλιξη της νόσου

Intensive Care Med (2016) 42:756–767
DOI 10.1007/s00134-016-4331-6

CONFERENCE REPORTS AND EXPERT PANEL

Personalized medicine for ARDS: the 2035 research agenda

Jeremy R. Beitler[1*], Ewan C. Goligher[2], Matthieu Schmidt[3], Peter M. Spieth[4], Alberto Zanella[5], Ignacio Martin-Loeches[6], Carolyn S. Calfee[7], Alexandre B. Cavalcanti[8] and The ARDSne(x)t Investigators

The ARDSne(x)t research agenda for the next 20 years calls for bringing personalized medicine to ARDS, asking simultaneously both **whether** a treatment affords clinically meaningful benefit and **for whom**

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])