Acute Respiratory Distress Syndrome (ARDS)

B. Taylor Thompson MD

Massachusetts General Hospital and
Harvard Medical School

Outline

- Definition, epidemiology, and outcomes
- The need to treat injured lungs gently
- Problems with the conceptual model

The Lancet · Saturday 12 August 1967

ACUTE RESPIRATORY DISTRESS IN ADULTS

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

D. BOYD BIGELOW
M.D. Colorado
ASSISTANT IN MEDICINE AND AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE

THOMAS L. PETTY
M.D. Colorado
ASSISTANT PROFESSOR OF MEDICINE

BERNARD E. LEVINE
M.D. Michigan
AMERICAN THORACIC SOCIETY-NATIONAL TUBERCULOSIS ASSOCIATION FELLOW IN PULMONARY DISEASE*

From the Departments of Surgery and Medicine, University of Colorado Medical Center, Denver, Colorado, U.S.A.

Acute Respiratory Distress Syndrome (ARDS)

- First described by Ashbaugh and Petty 1967
  - 12 Patients with severe hypoxemia (dangerously low blood oxygen levels) and diffusely abnormal chest x-rays following a number of catastrophes (gun shot wounds, crush injuries, overwhelming pneumonia, pancreatitis, and drug overdose with aspiration)
- High concentrations of oxygen and pressures applied from artificial ventilation were needed for survival
- At post mortem, the lungs had features if infantile respiratory distress syndrome from premature delivery

ARDS

- ARDS is an inflammatory process that leads to injury of the lung lining cells (endothelium and epithelium)
- Injury begets increased permeability and leakage of protein-rich plasma into the lungs-> lungs stiffen and collapse
- White and red blood cells enter the lungs, release harmful products and amplify the injury
- Healing requires re-population of lung lining cells, active transport of liquid out of the lungs, and a surprisingly reversible fibrotic/scaring response

JAMA | 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

- 10% of ICU admissions and ~25% of all patients requiring mechanical ventilation have ARDS
- Half of the milder cases were not recognized by clinicians. In the severest cases 25% of cases of ARDS were not recognized as such by clinicians
- Mortality was 35% for the milder cases and 46% in the severe cases

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

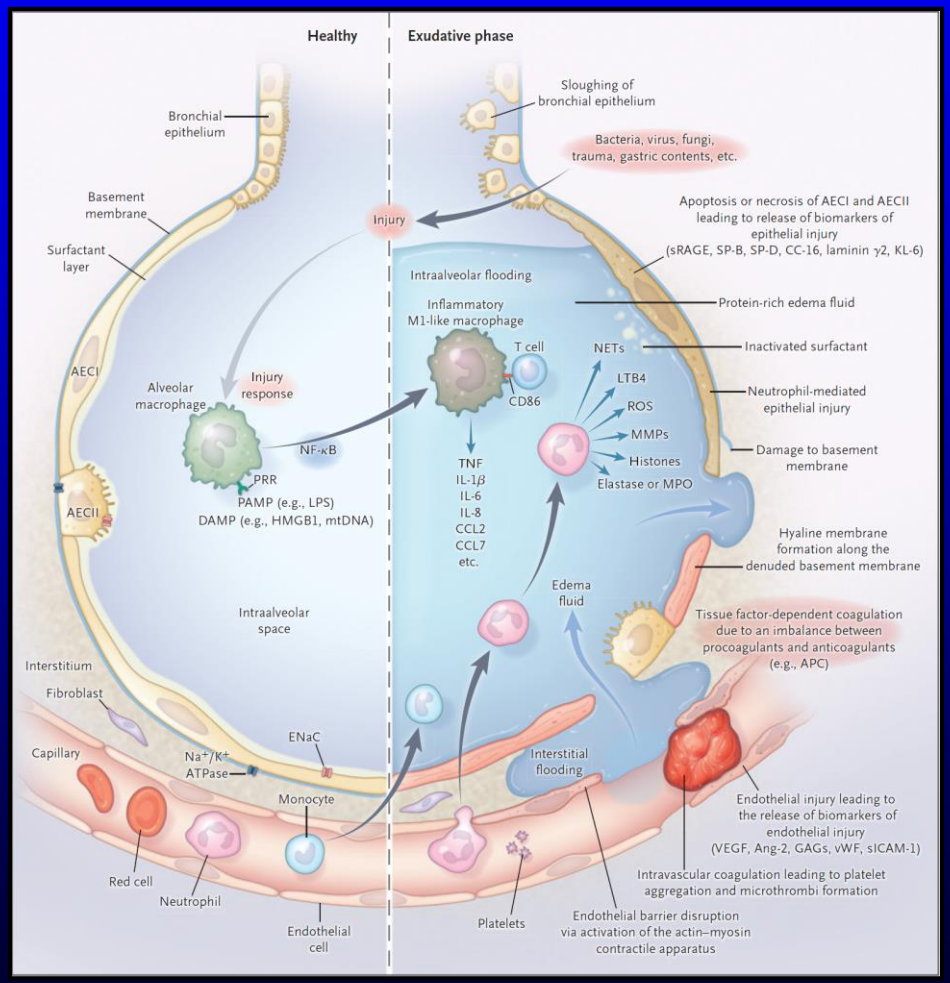
REVIEW ARTICLE

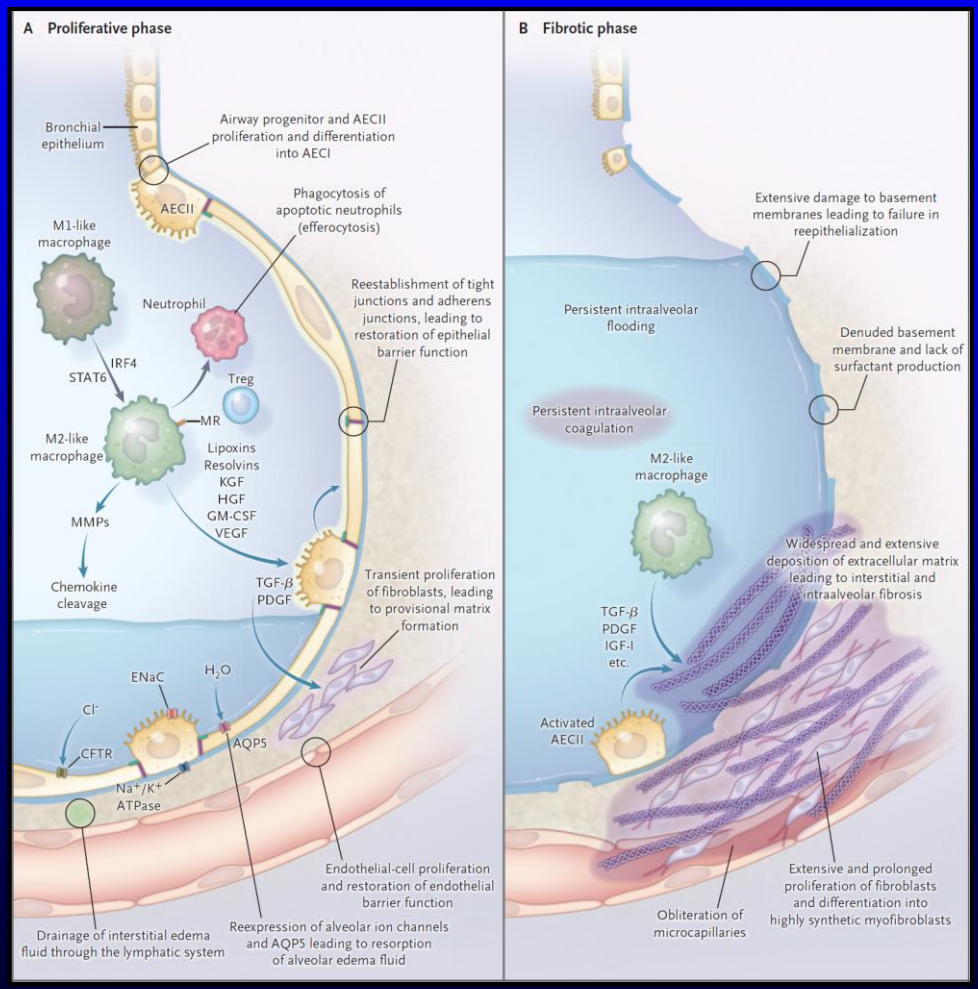
Jeffrey M. Drazen, M.D., *Editor*

N Engl J Med 2017;377:562-72.

Acute Respiratory Distress Syndrome

B. Taylor Thompson, M.D., Rachel C. Chambers, Ph.D., and Kathleen D. Liu, M.D., Ph.D.



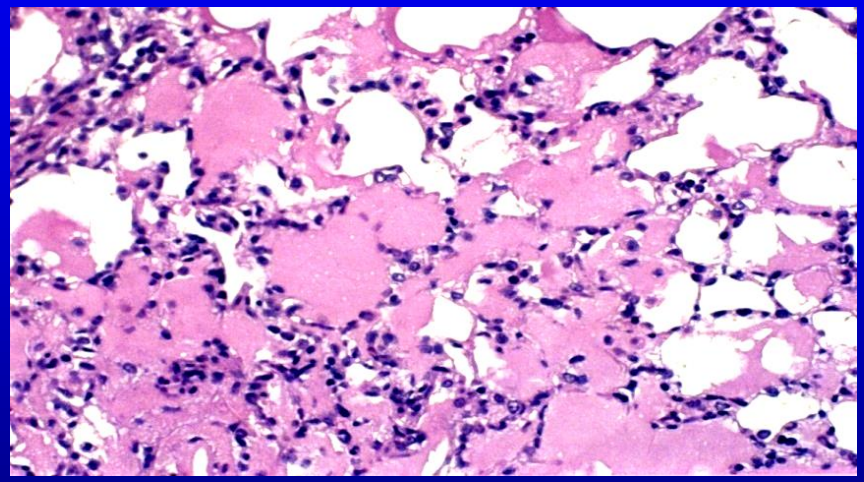


Prognostic ARDS Biomarkers

- **Inflammation** - IL-6, IL-8, sTNFRI, CRP
- **Disordered Coagulation** - Protein C, PAI-1
- **Endothelial injury** - Von Willebrand factor antigen
- **Myocardial Injury** – Troponin, BNP
- **Alveolar epithelium** - SP-D, sTNFRI, & RAGE
- **Adhesion molecule** - sICAM-1
- **Fibroblast proliferation** - PCPIII
- **Elastin breakdown product** - Desmosine (urine)
- **Nitric Oxide Levels** – exhaled NO

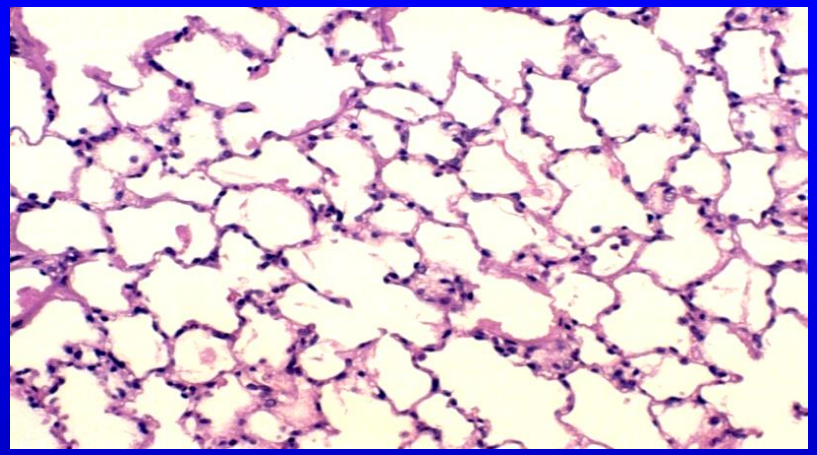
Ware , CCM 2014; Calfee, Lancet Resp Med 2014

ARDS

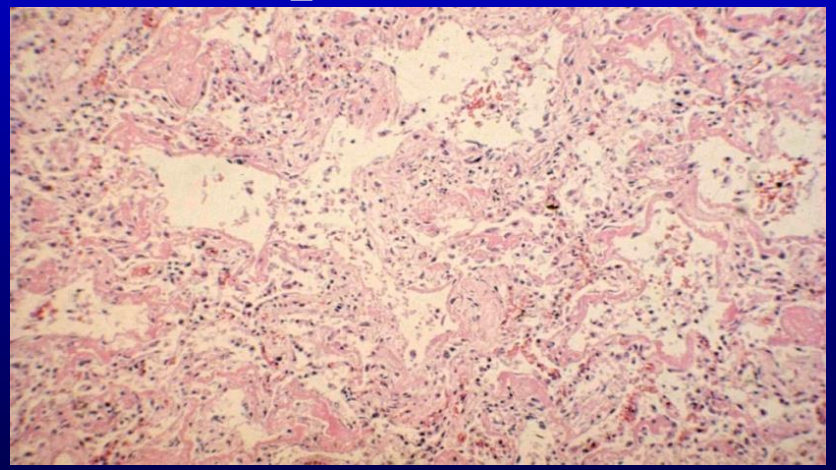


1. Intensity/nature of initial injury
2. Injurious ventilator settings
3. Over zealous fluid resuscitation
4. Genetics, subphenotype

Resolution



Fibroproliferation



Reviewed in Matthay JCI 2012; Thompson NEJM 2017

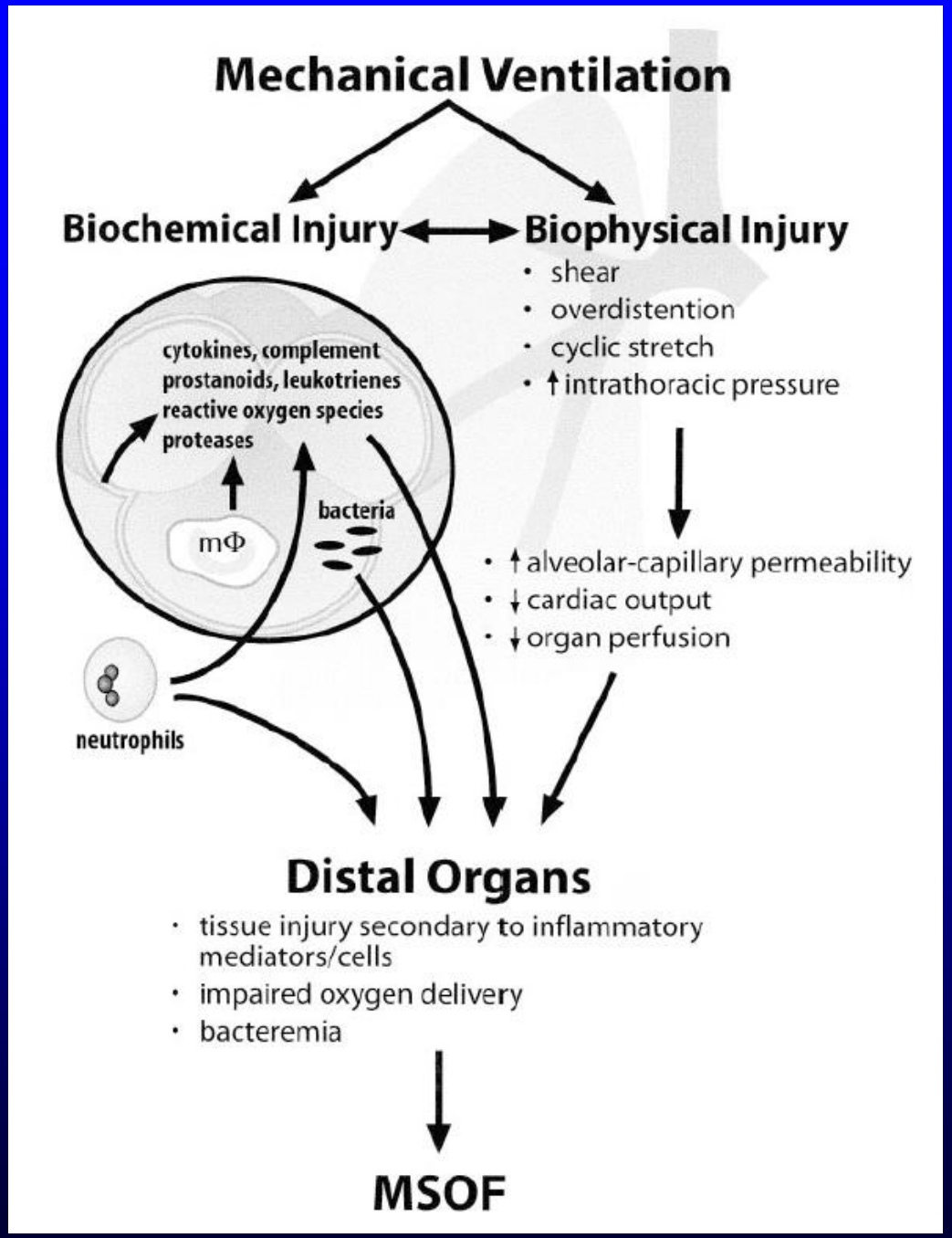
Cause of Death from ARDS

- Most patients can be supported on mechanical ventilation settings gentle enough to allow lung healing. For those that cannot, extracorporeal oxygen delivery and carbon dioxide removal (ECMO) can serve as a bridge to recovery

- During this time, the greatest threat to survival is the development of multisystem organ failure (MSOF). This will be discussed in the context of sepsis on Wednesday.

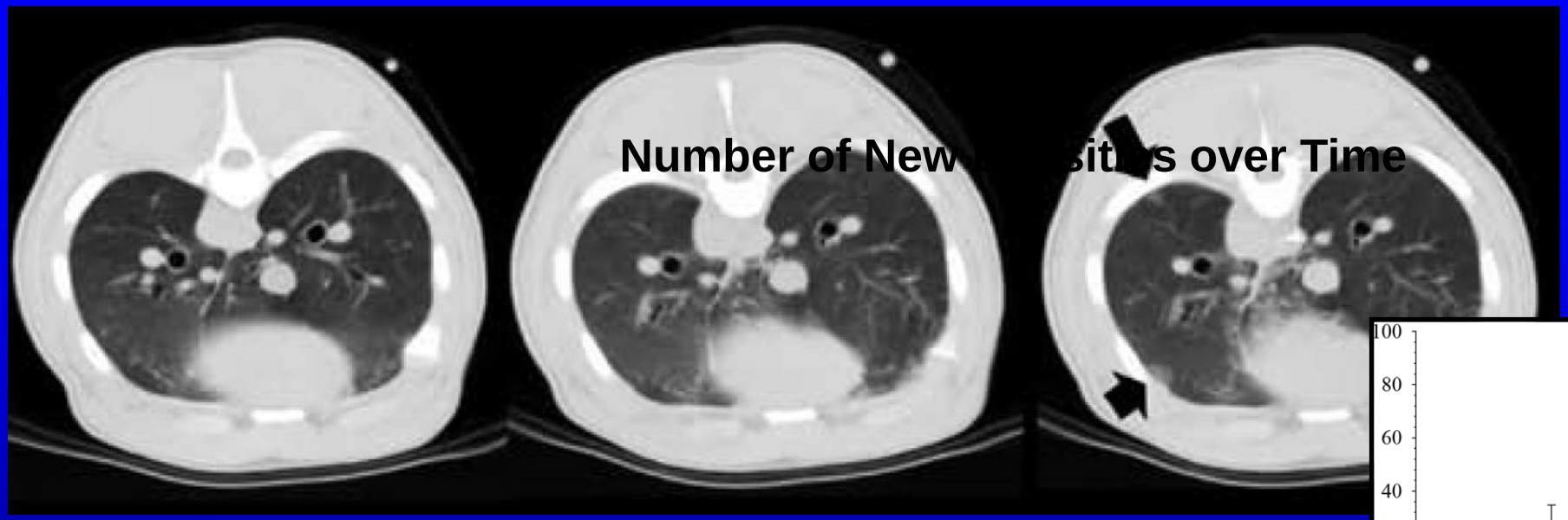
Outline

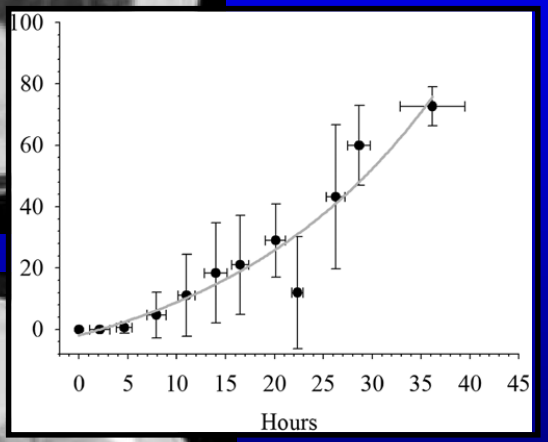
- Definition, epidemiology, and outcomes
- The need to treat injured lungs gently
- Problems with the conceptual model

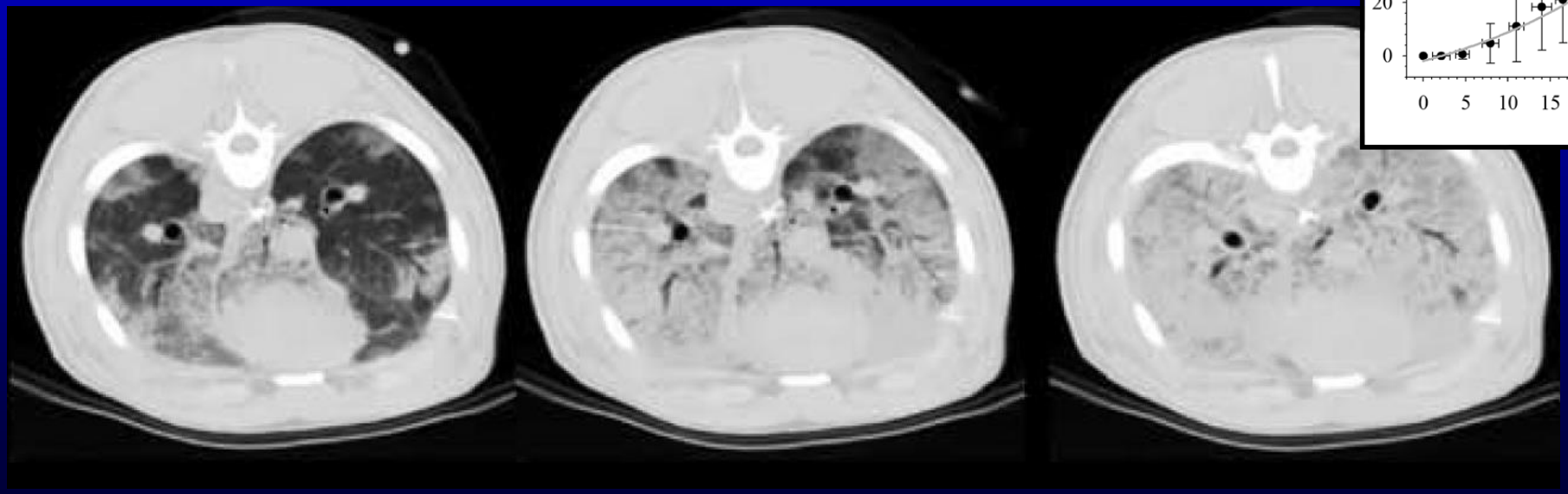


Slutsky AJRCCM 1998

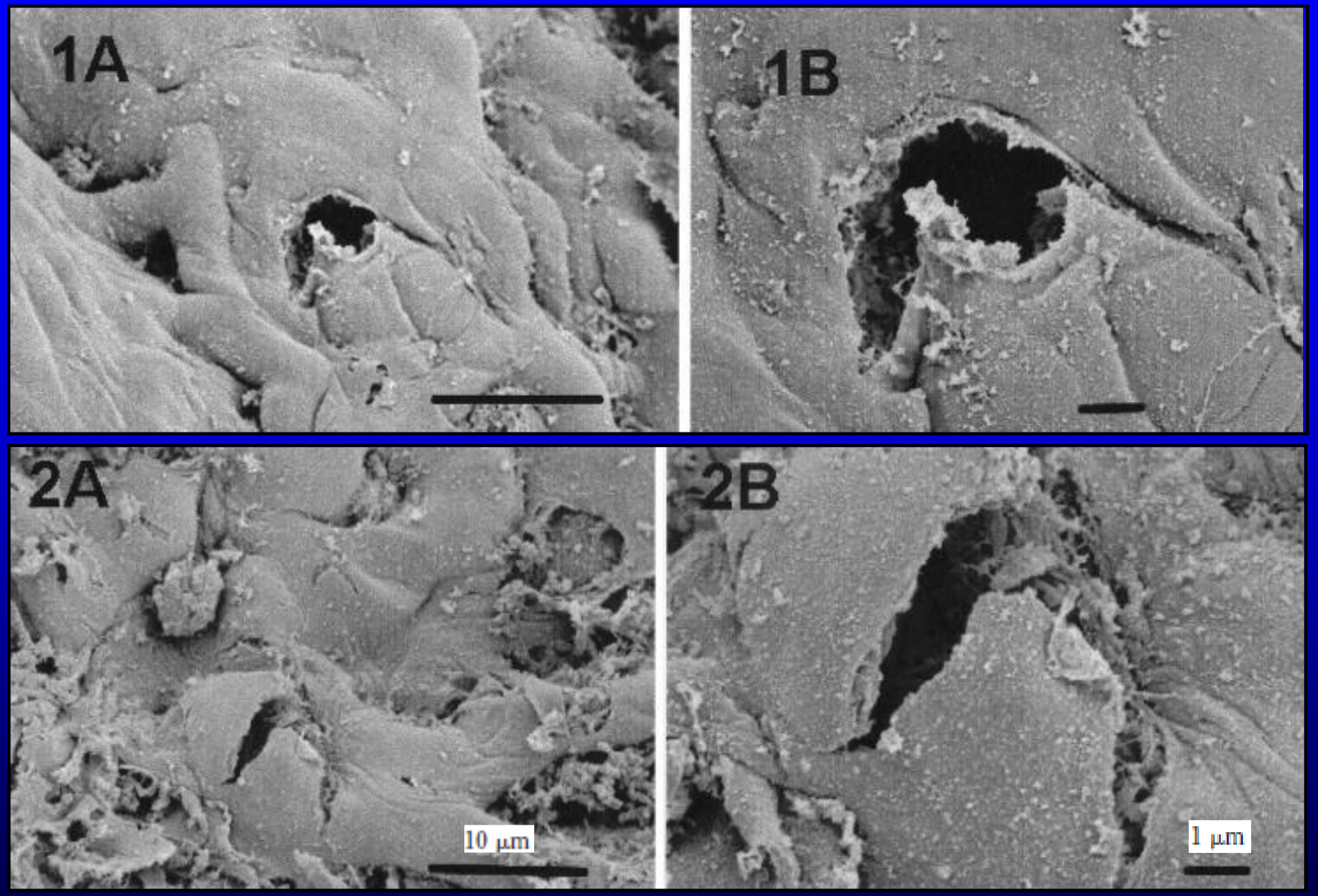
Lung Injury With Large Breaths Over ~36hrs







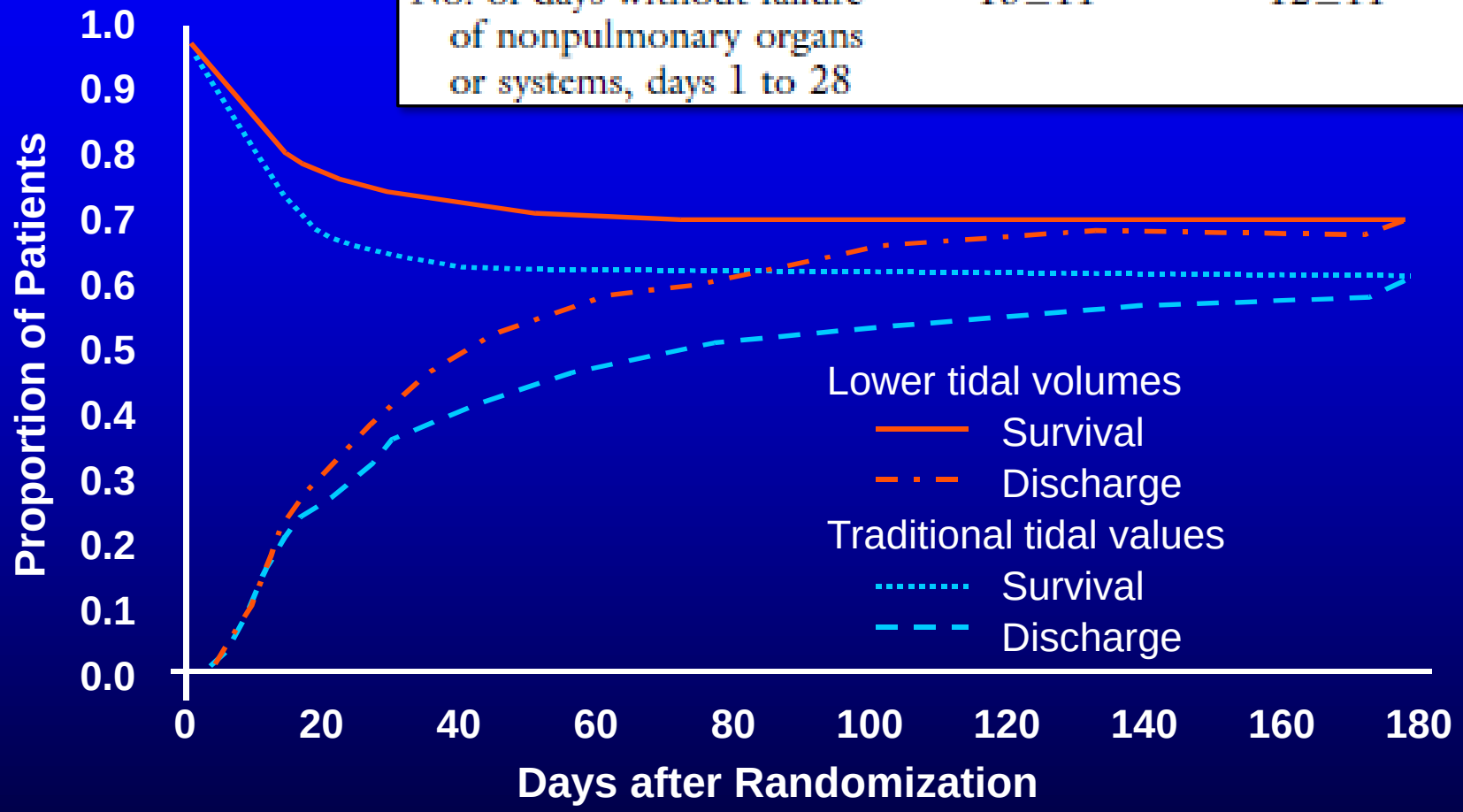
From Cressoni Crit Care Med 2015



From Cressoni Crit Care Med 2015

Improved survival with smaller breaths from the ventilator

No. of days without failure of nonpulmonary organs or systems, days 1 to 28	15±11	12±11	p= 0.006



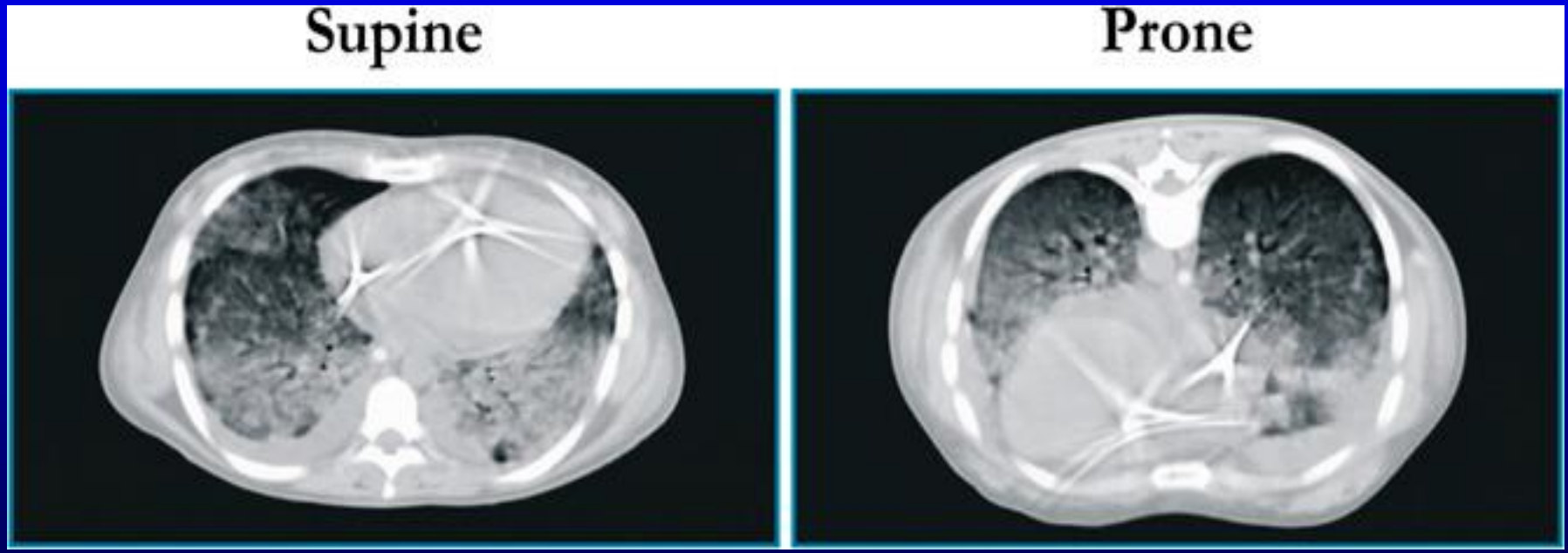
ARDS Net *N Engl J Med* 2000

Prone Position in Acute Respiratory Distress Syndrome

Rationale, Indications, and Limits

Luciano Gattinoni[1,2], Paolo Taccone[2], Eleonora Carlesso[1], and John J. Marini[3]

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 188 2013

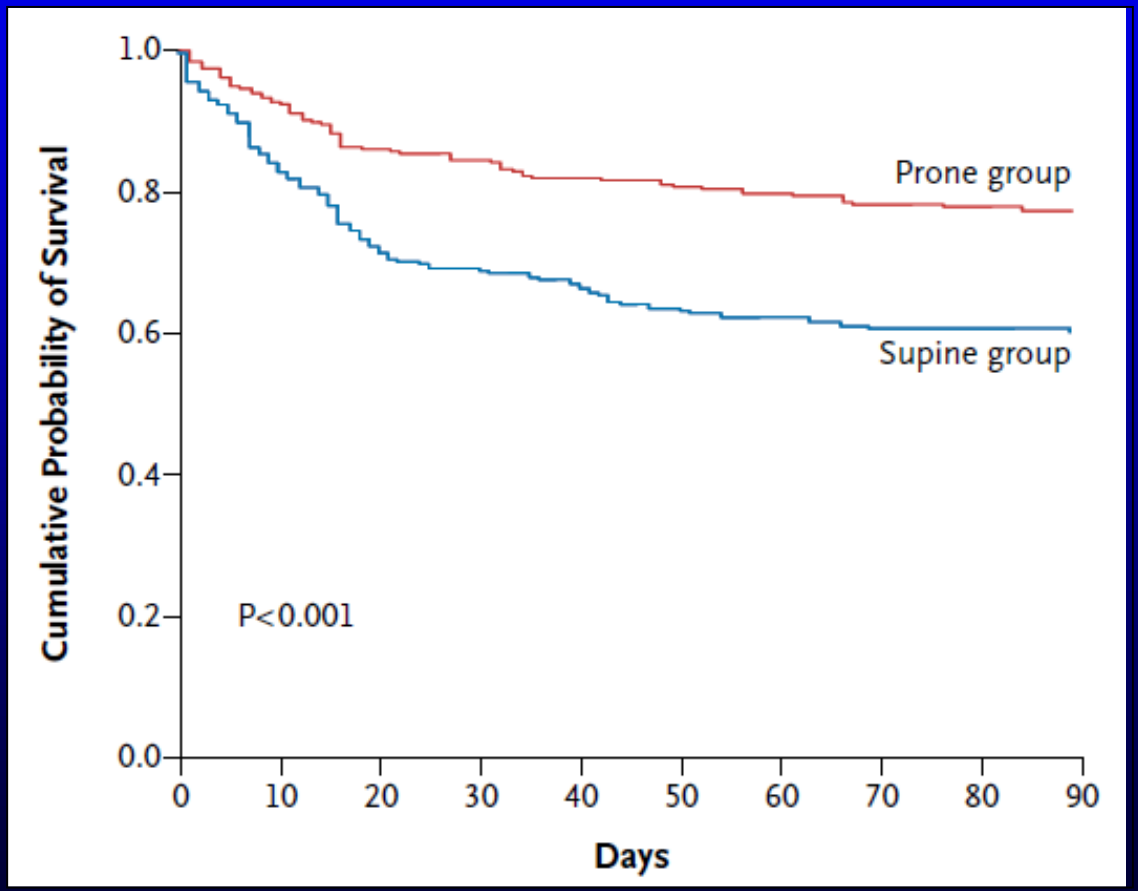


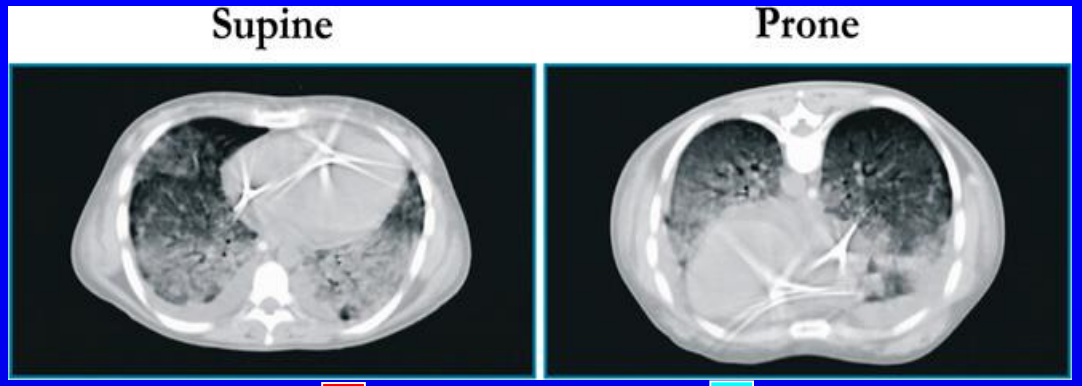
The NEW ENGLAND JOURNAL of MEDICINE

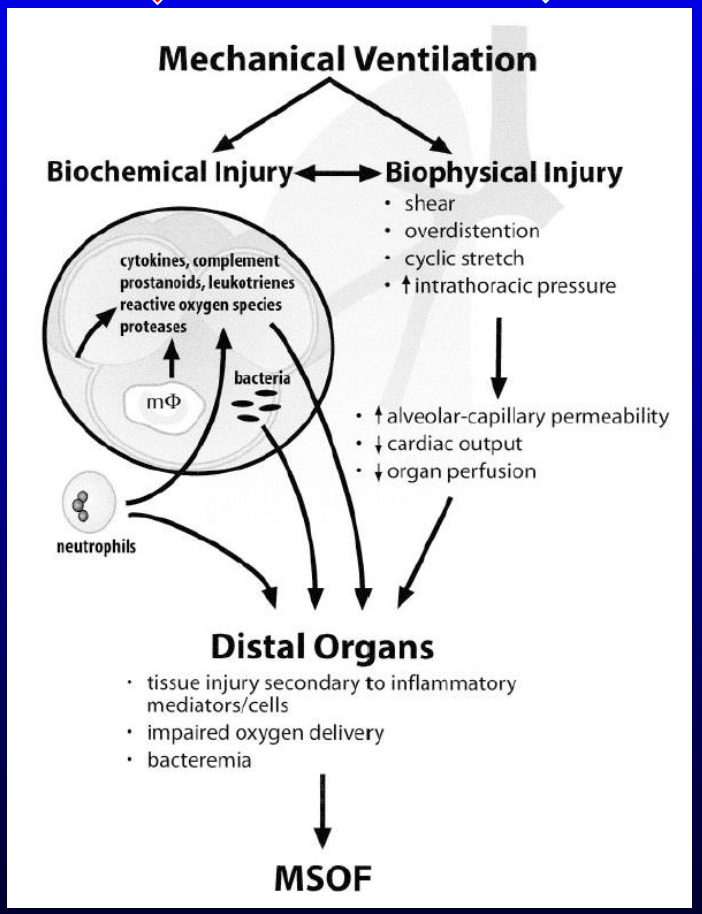
ORIGINAL ARTICLE

N Engl J Med 2013.

Prone Positioning in Severe Acute Respiratory Distress Syndrome



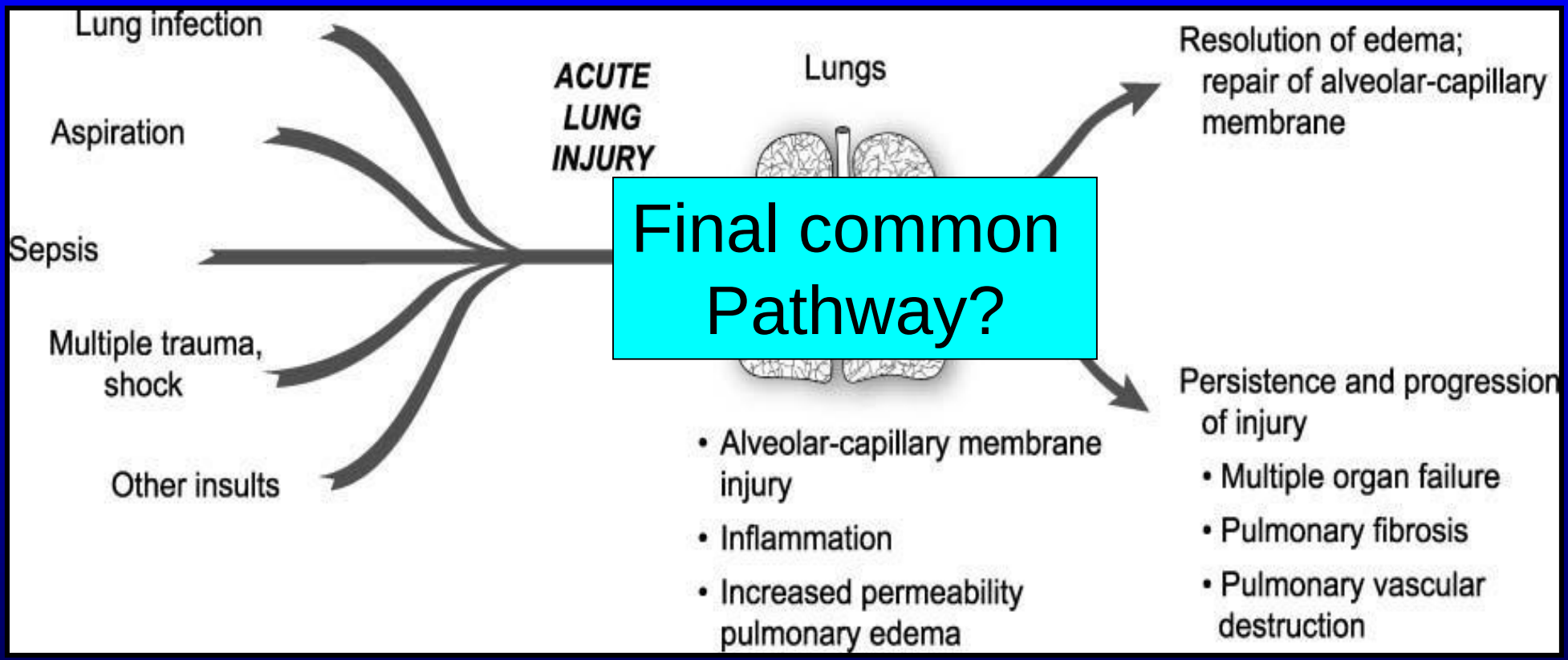

Supine
Prone


Mechanical Ventilation
Biochemical Injury
Biophysical Injury
• shear
• overdistention
• cyclic stretch
• ↑ intrathoracic pressure
cytokines, complement
prostanoids, leukotrienes
reactive oxygen species
proteases
bacteria
mΦ
neutrophils
• ↑ alveolar-capillary permeability
• ↓ cardiac output
• ↓ organ perfusion
Distal Organs
• tissue injury secondary to inflammatory mediators/cells
• impaired oxygen delivery
• bacteremia
MSOF

Outline

- Definition, epidemiology, and outcomes
- The need to treat injured lungs gently
- Problems with the conceptual model

Conceptual Model of ARDS: Diverse lung insults lead to a stereotypic "acute lung injury" response



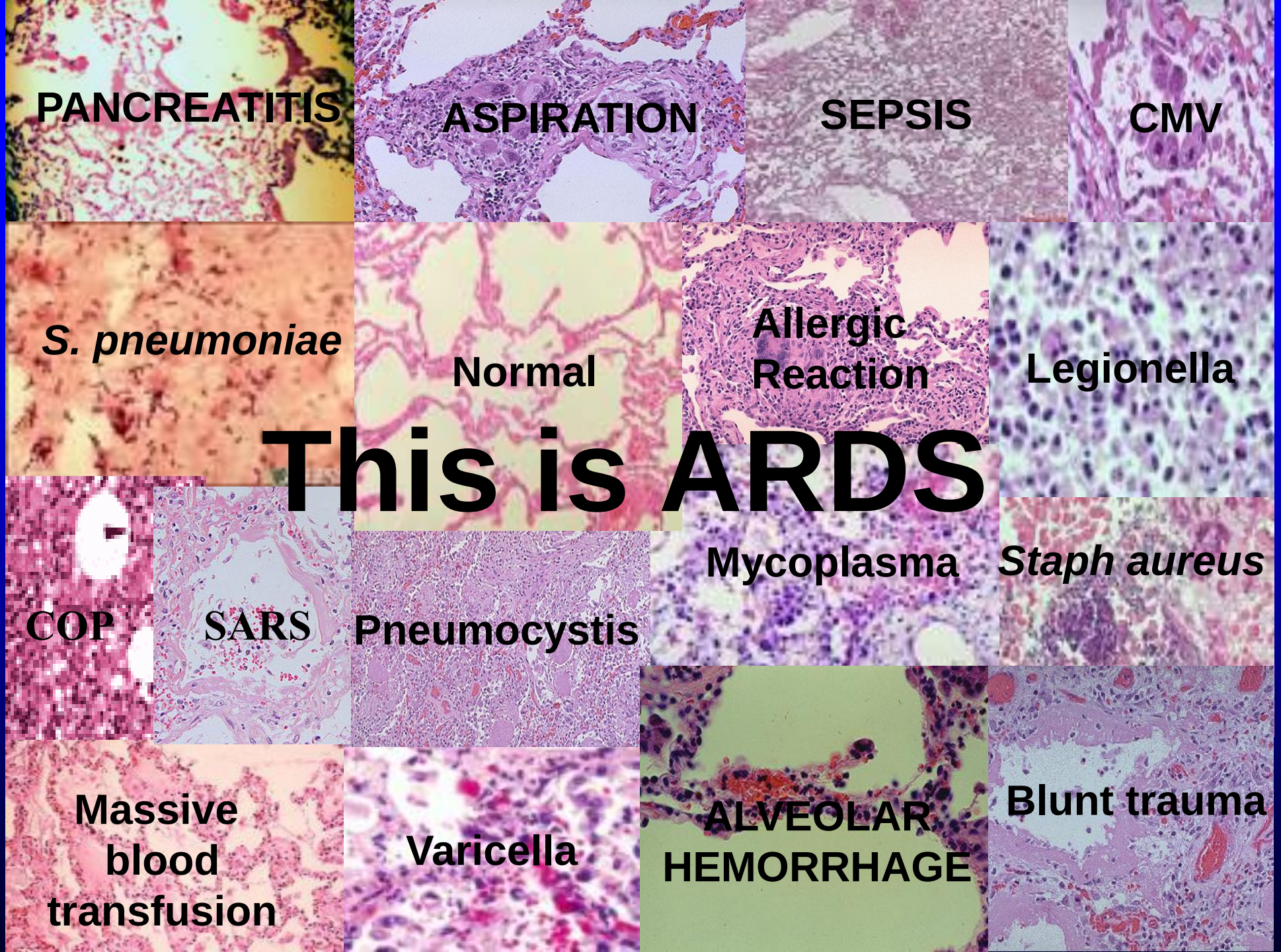
Matthay et al. AJRCMB 2005

35 Years of failed trials for ARDS

- nitric oxide
- surfactant/perflourocarbon
- corticosteroids
- prostaglandin E1
- pentoxyphylline/lysophylline
- ibuprofen
- n-acetylcysteine/procysteine
- anticytokine/antiendotoxin
- ketoconazole
- streptokinase
- neutrophil elastase inhibitor
- $sPLA_2$ Inhibitor
- rosuvastatin
- interferon beta

“Success in science is defined as moving from failure to failure with undiminished enthusiasm”

Winston Churchill


PANCREATITIS
ASPIRATION
SEPSIS
CMV
S. pneumoniae
Normal
Allergic Reaction
Legionella
This is ARDS
COP
SARS
Pneumocystis
Mycoplasma
Staph aureus
Massive blood transfusion
Varicella
ALVEOLAR HEMORRHAGE
Blunt trauma

Proposed ARDS Subphenotypes

- Severity of hypoxemia
  - More homogenous histology better response to prone
- Risk factor
  - Different biomarker profile and mortality (Sepsis >> Trauma)
- Direct vs Indirect
  - Different histology and biomarkers
- Focal vs Diffuse
  - Different biomarkers and response to ventilator Rx

Acute Respiratory Distress Syndrome Phenotypes

John P. Reilly, MD, MSCE[1] Carolyn S. Calfee, MD, MAS[2] Jason D. Christie, MD, MSCE[1]

Genetic defined endotypes	Endotypes of ARDS defined by genetic variability that alters ARDS risk, outcome, or response to treatment	• Distinct ARDS risk, outcome, or response to treatment	• Therapies targeting biology implicated by genetic variants
Biomarker defined endotypes	Endotypes of ARDS defined by biomarker measurements	• Distinct ARDS risk, outcome, or response to treatment	• Therapies targeting biology implicated by biomarker elevation
Hyperinflammatory versus uninflamed	Endotypes of ARDS determined from unbiased latent class analysis and cluster analysis	• Hyperinflammatory characterized by elevated plasma inflammatory biomarkers, and higher mortality	• Phenotypes responded differently to PEEP and fluid strategy • Survival benefit observed in response to simvastatin in hyperinflammatory phenotype

Semin Respir Crit Care Med 2019;40:19–30

MGH Molecular Epidemiology of ARDS (MEARDS)

- Only a minority of patients at risk for ARDS develop ARDS
- Evolutionary pressures (shock from bleeding or infection, dehydration, starvation) are mechanisms important to critical illness -> reasonable to assume modern genetic diversity alters risk
- Requirement for a catastrophe precludes family pedigree studies
- We compare at risk patients with and without ARDS

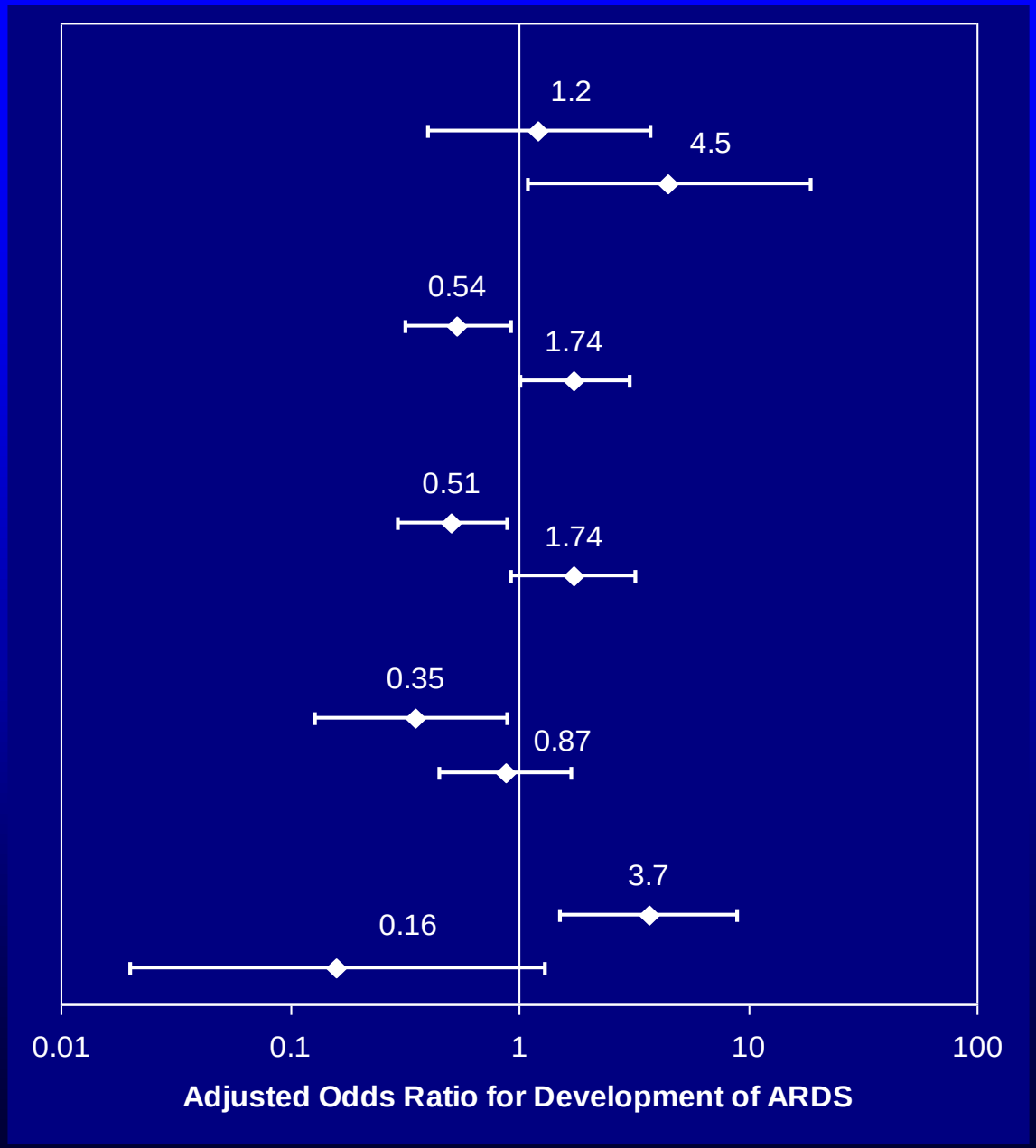
PI = David Christiani

MGH Molecular Epi Project: Selected Polymorphisms Investigated

- Variable number of tandem repeats in intron 4 of the *Surfactant Protein-B* gene
- *-308GA* promoter in the *TNF-α* gene
- *TNFB1/2 Nco*I restriction fragment length in the *TNF-β* gene
- *The -174GC* promoter of the *Interleukin-6* (*IL-6)* gene
- *The -1082GA* promoter of the *IL-10* gene.

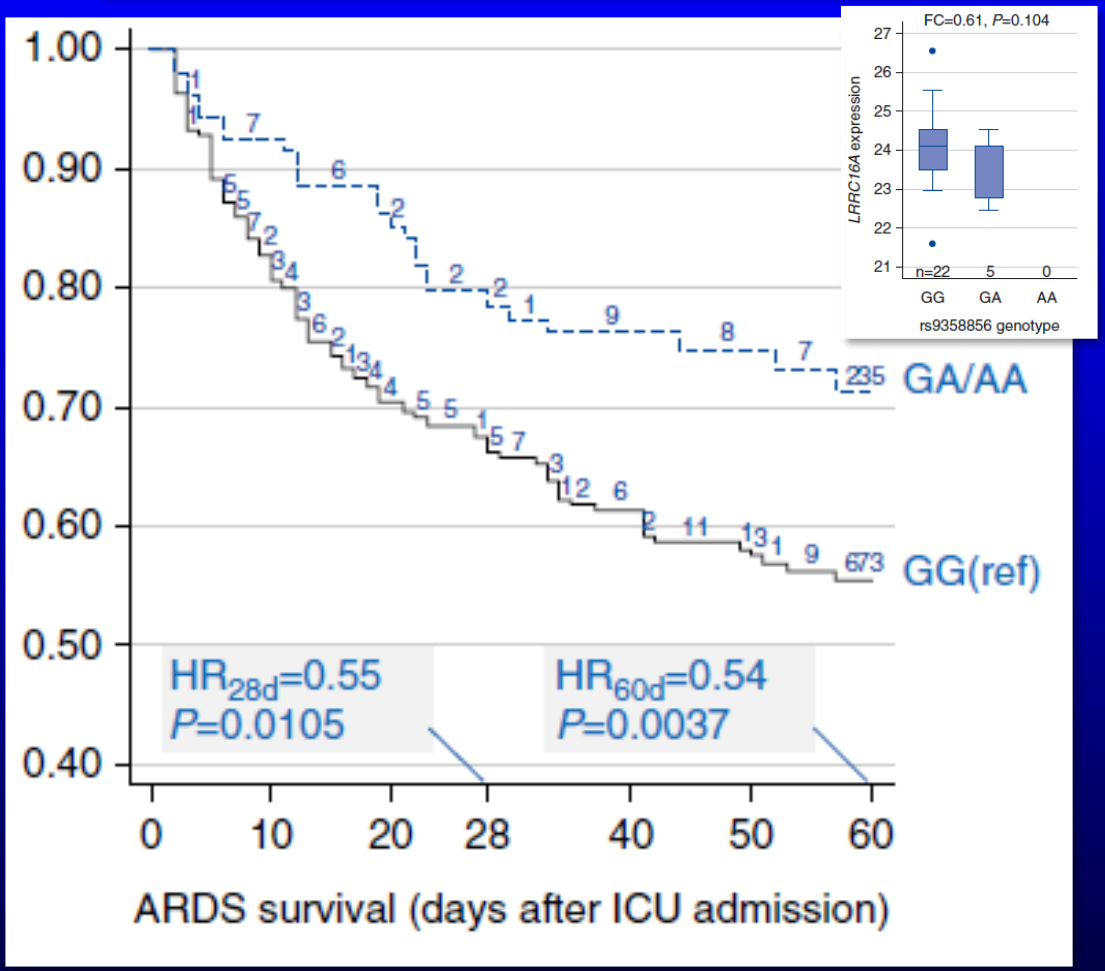
Development of ARDS Among Certain Clinical Subgroups

SP-B **(N=189)**	Men
	Women
-308A **(N=652)**	Direct Injury
	Indirect Injury
308A:TNFB1 **haplotype (N=652)**	Direct Injury
	Indirect Injury
CC IL-6 **(N=630)**	Age < 60
	Age ≥ 60
GG IL-10 **among subjects younger than 60 years (N=238)**	APACHE < 65
	APACHE ≥ 65



A Missense Genetic Variant in *LRRC16A/CARMIL1* Improves Acute Respiratory Distress Syndrome Survival by Attenuating Platelet Count Decline

Yongyue Wei[1,2,3], Paula Tejera[1], Zhaoxi Wang[1], Ruyang Zhang[1,2], Feng Chen[2,3], Li Su[1], Xihong Lin[4], Ednan K. Bajwa[5], B. Taylor Thompson[5], and David C. Christiani[1,3,5]



Mediation Analysis

- 20% of the effect of rs9358856 on improved survival is explained by an attenuation of platelet decline
- Provides additional support support for targeting platelets for the prevention or treatment of ARDS

American Journal of Respiratory and Critical Care Medicine Volume 195 Number 10 | May 15 2017

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

Carolyn S Calfee, Kevin Delucchi, Polly E Parsons, B Taylor Thompson, Lorraine B Ware, Michael A Matthay, and the NHLBI ARDS Network

Lancet Respir Med 2014
Published Online
May 20, 2014

- Latent classes identified by clinical variables and a panel of biomarkers
- Two class model = best fit for ARDS
- **Qualitative interaction of class assignment (but not APACHE III) and randomized treatment to:**
  - Higher PEEP (NEJM 2004)
  - Active de-resuscitation (aka “conservative fluid management”) (NEJM 2006)
  - Simvastatin (NEJM 2014)

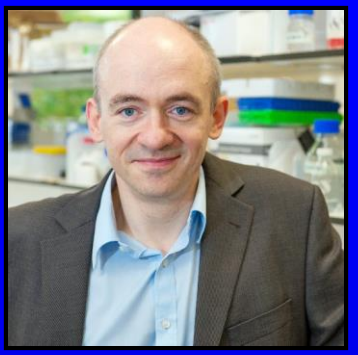
Famous, AJRCCM 2016
Calfee, Lancet Resp Med 2018

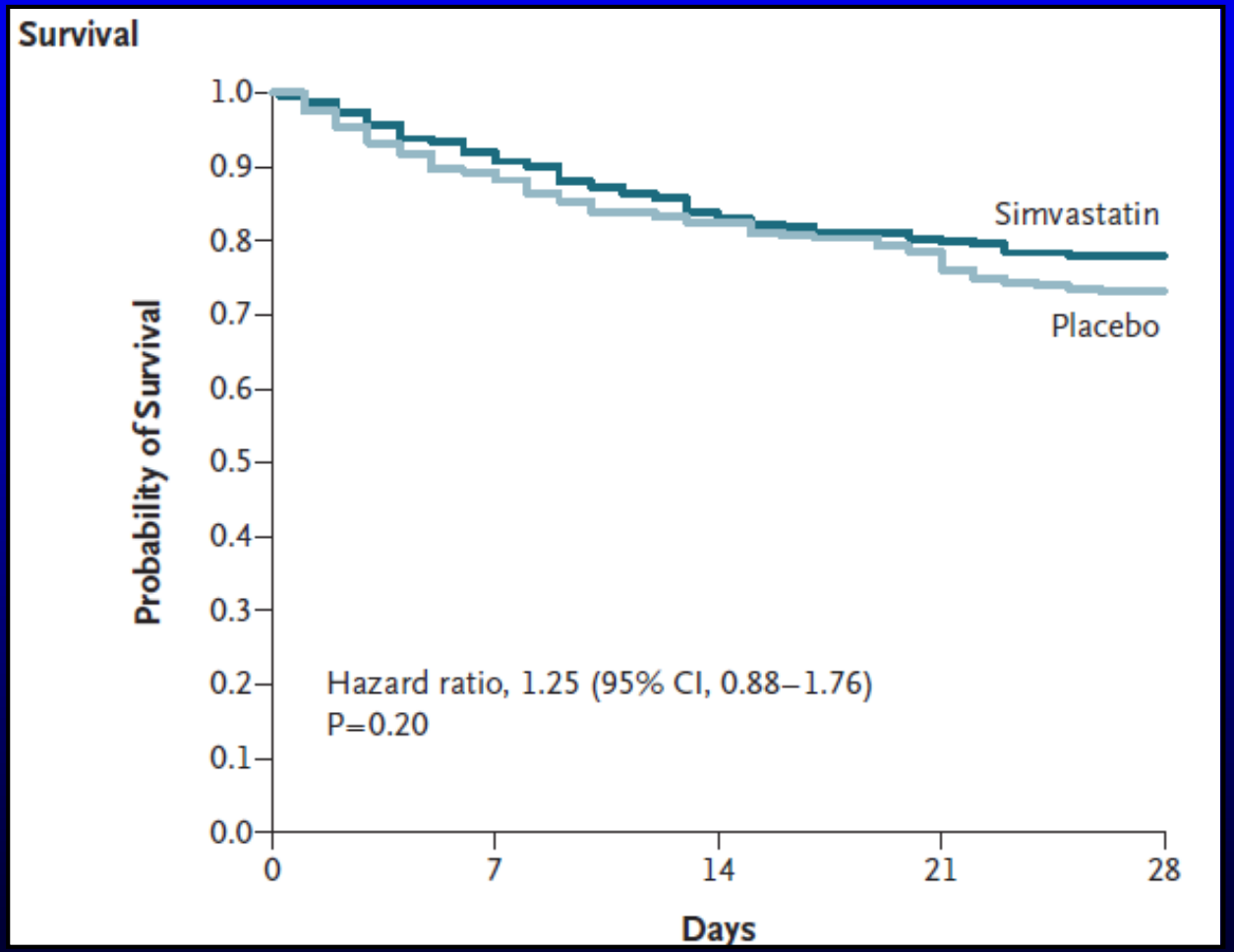
ORIGINAL ARTICLE

N Engl J Med 2014;371:1695-703.

Simvastatin in the Acute Respiratory Distress Syndrome

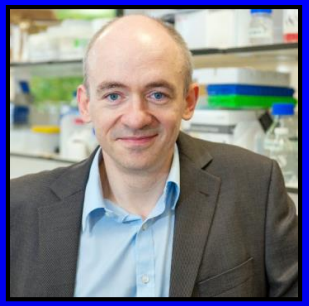
Daniel F. McAuley, M.D., John G. Laffey, M.D., Cecilia M. O'Kane, Ph.D.,

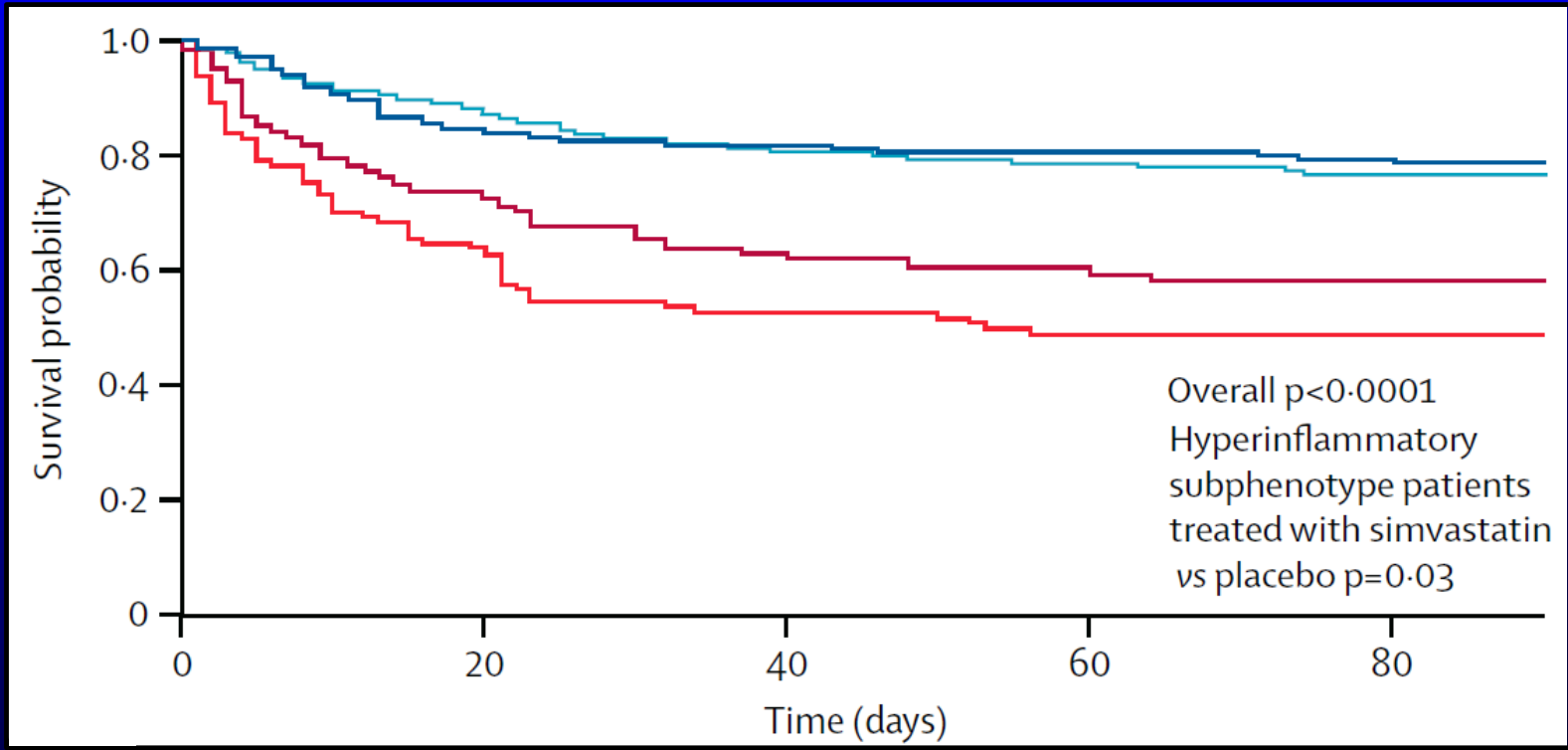




Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial

Carolyn S Calfee, Kevin L Delucchi, Pratik Sinha, Michael A Matthay, Jonathan Hackett, Manu Shankar-Hari, Cliona McDowell, John G Laffey, Cecilia M O'Kane, Daniel F McAuley, on behalf of the Irish Critical Care Trials Group





Lancet Resp Med 2018

ARDS Survivors One Year Later

- Near-normal lung size on lung function tests
- Mildly impaired gas diffusion into the lungs
- Mild oxygen desaturation with exercise in some
- Neuromuscular weakness than may interfere with activities of daily living for > 1 year

Ware *NEJM* 2000; Herridge *NEJM* 2003

Summary

- ARDS is a common problem in ICUs world wide with a high mortality, in part due to under recognition and under treatment (less than optimal lung protection)
- Subphenotypes within ARDS appear to have unique (though incompletely understood) biologic responses to injury and offer hope for targeted therapies and precision medicine approaches

Summary

- Survival following ARDS depends on the nature and severity of the injury, the resiliency and genetics of the patients, and the quality and finesse of the care they receive.
- A systems biology approach to the understanding of ARDS and MSOF will require consideration of these factors and may lead to a better understanding of syndrome heterogeneity

Thank you

thompson.taylor@mgh.harvard.edu

Extra Slides

Tidal Volume Strategies for ARDS

Traditional Approach: Large Breaths

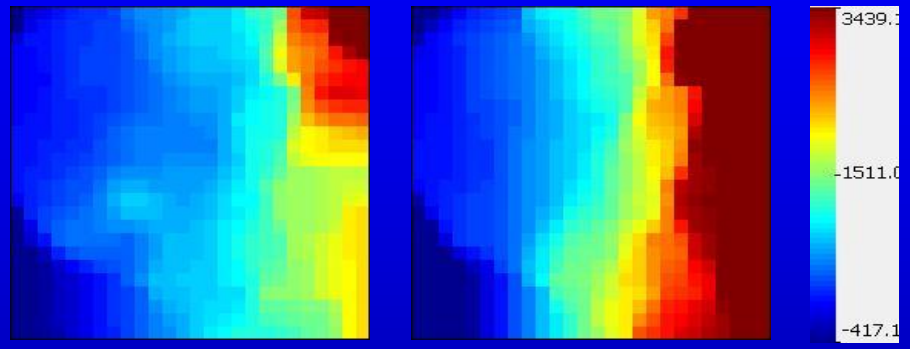
- High priority to traditional goals of acid-base balance and patient comfort.
- Lower priority to lung protection.

Low Stretch Approach: Normal Breath Size

- High priority to lung protection.
- Lower priority to traditional goals of acid-base balance and comfort.

Developing a Clinically Feasible Personalized Medicine Approach to Pediatric Septic Shock

Hector R. Wong[1,2], Natalie Z. Cvijanovich[3], Nick Anas[4], Geoffrey L. Allen[5], Neal J. Thomas[6],

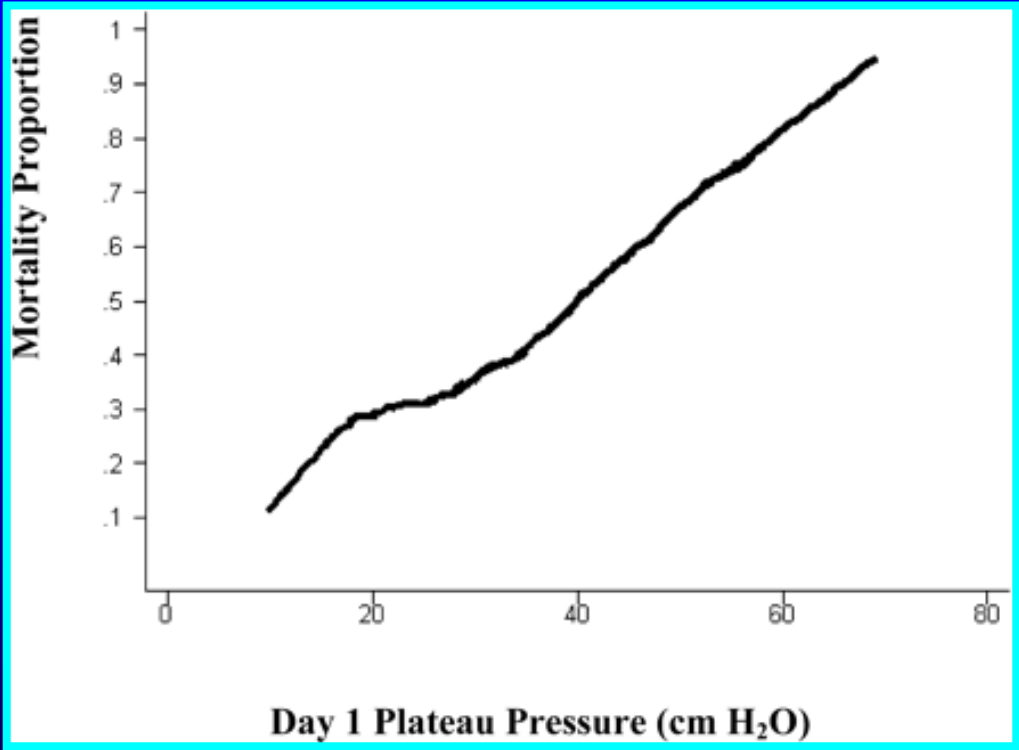


Subclass A **Subclass B**

- The genes that enable sub classification correspond to adaptive immunity and the glucocorticoid receptor signaling pathway (repressed in subclass A)
- The use of corticosteroids is independently associated with 4 times the risk of dying in subclass A.
- Subclasses also identified in ARDS

AJRCCM 2015; Pedi CCM 2019

Plateau Pressure and Mortality in ARDSnet: No evidence for a safe level of pressure



Hager *et al* *AJRCCM* 2005

Mechanisms of lung injury at low inspiratory airway pressures

- •Stretch of *injured* epithelium
- • Shear adjacent to flooded or atelectatic alveoli
- • Cyclic recruitment and collapse
- • Regional overdistension in dependent lung units due to vigorous inspiratory efforts (Pendeluft)

Perlman AJRCMB 2011; Oeckler AJPLCMB 2010, Beitler J Physiol 2013; Yoshida AJRCCM 2013

Acute Respiratory Distress Syndrome Phenotypes

John P. Reilly, MD, MSCE[1] Carolyn S. Calfee, MD, MAS[2] Jason D. Christie, MD, MSCE[1]

Phenotype	Description	Differences	Potential therapies
Hypoxia severity phenotypes	Berlin categories: Mild: $200 < PaO_2/FiO_2 < 300$ Mod: $100 < PaO_2/FiO_2 < 200$ Severe: $PaO_2/FiO_2 < 100$	• Severity of hypoxia • DAD more likely pathology in severe	• Prone positioning ($PaO_2/FiO_2 < 150$) • Cisatracurium ($PaO_2/FiO_2 < 150$)
ARDS by precipitating risk factor	Precipitating factors including: sepsis, trauma, pneumonia, aspiration, transfusion, pancreatitis	• Differences in ARDS risk, severity, and mortality	
Direct versus indirect lung injury	Direct: pneumonia, pulmonary contusion, aspiration Indirect: nonpulmonary sepsis, nonthoracic trauma, transfusions	• Epithelial vs. endothelial injury • Differences in mortality	• Epithelial vs. endothelial targeted therapies • Indirect more likely to respond to PEEP

Semin Respir Crit Care Med 2019;40:19–30

ALI/ARDS in the United States in 2000

Estimates

- 190,600 ALI/ARDS cases per year
- 74,500 deaths
- 3.6 million hospital days
- *Pneumonia and septic shock (eg severe sepsis)* as the ALI risk factor in ~80%

Rubenfeld et al *NEJM* 2005

Risk Factors for ARDS

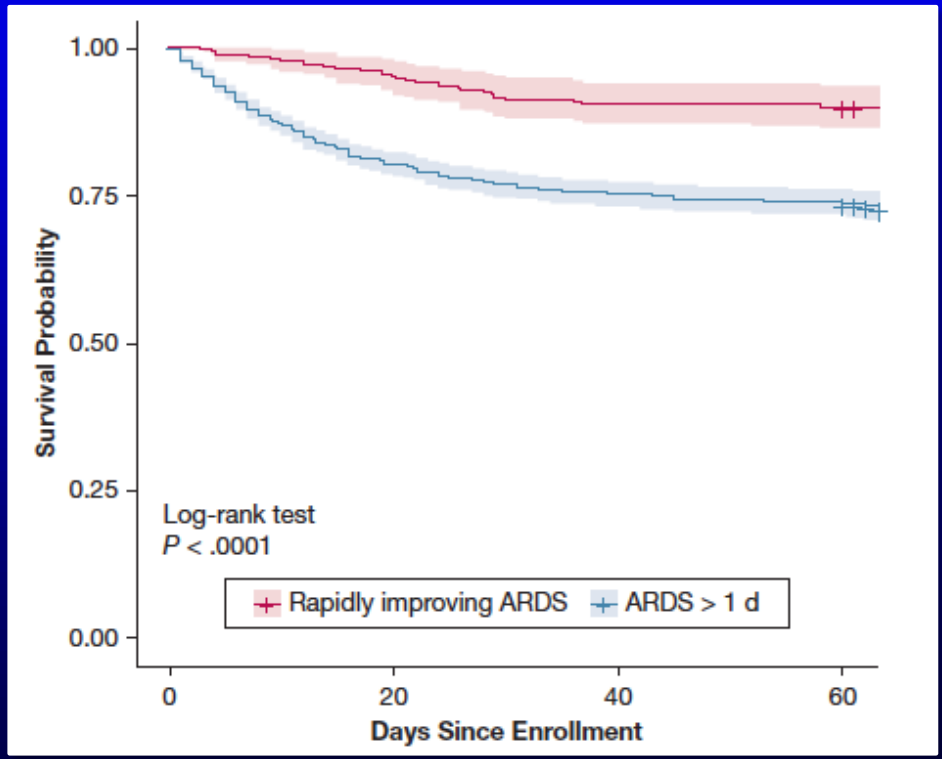
	Incidence of ARDS
• Sepsis	38%
• Aspiration	30-36%
• Transfusion (10u/6h)	24%
• DIC	22%
• Lung Contusion	17%
• Pneumonia in ICU	12%
• Fracture	5-8%

Pepe *Am J Surg* 1982; Fowler *Ann Int Med* 1983

Rapidly Improving ARDS in Therapeutic Randomized Controlled Trials

Edward J. Schenck, MD; Clara Oromendia, MS; Lisa K. Torres, MD; David A. Berlin, MD; Augustine M. K. Choi, MD; and Ilias I. Siempos, MD

- 10.5% (458/4,361) of participants in ARDSnet were vent free after one day
- Lower APACHE III, improving P/F, less likely to be on vasopressors,
- Steroids not a/w rapid improvement subtype



CHEST 2019

ARDS is a syndrome, not a diagnosis

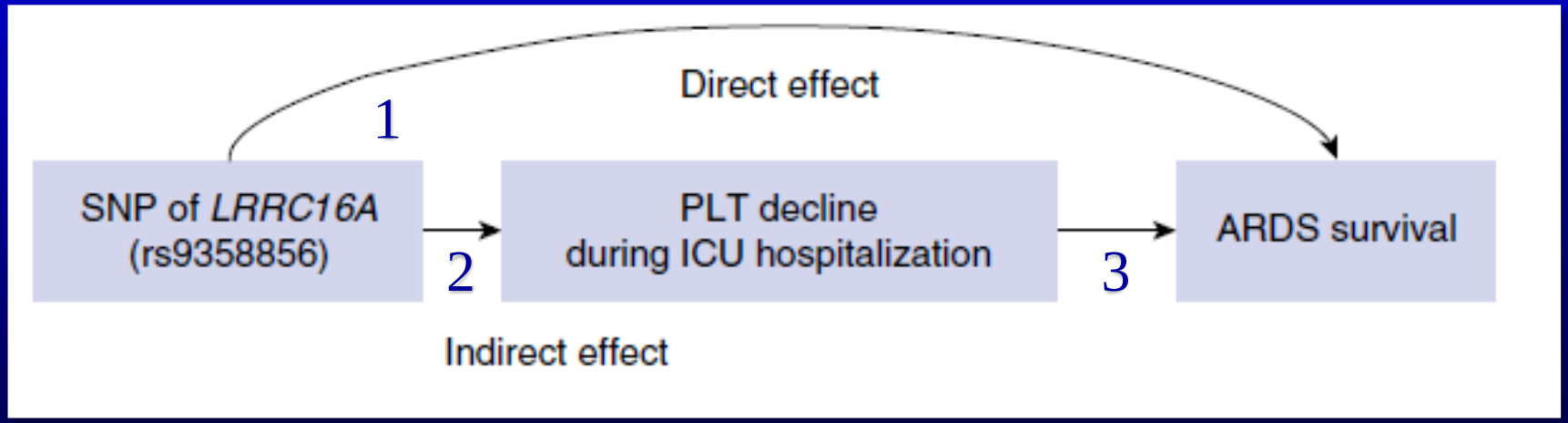
- Steroid responsive conditions may present as ARDS
  - Cryptogenic Organizing Pneumonia (COP)[1]
  - Acute Eosinophilic Pneumonia[2]
  - PCP complicating AIDS[3]

[1] Epler NEJM ‘85
[2] Allen NEJM ‘89, Buchheit ARRD ‘92
[3] Gagnon NEJM ‘90, Montaner, Ann Int Med ’90

A Missense Genetic Variant in *LRRC16A/CARMIL1* Improves Acute Respiratory Distress Syndrome Survival by Attenuating Platelet Count Decline

Yongyue Wei[1,2,3], Paula Tejera[1], Zhaoxi Wang[1], Ruyang Zhang[1,2], Feng Chen[2,3], Li Su[1], Xihong Lin[4], Ednan K. Bajwa[5], B. Taylor Thompson[5], and David C. Christiani[1,3,5]

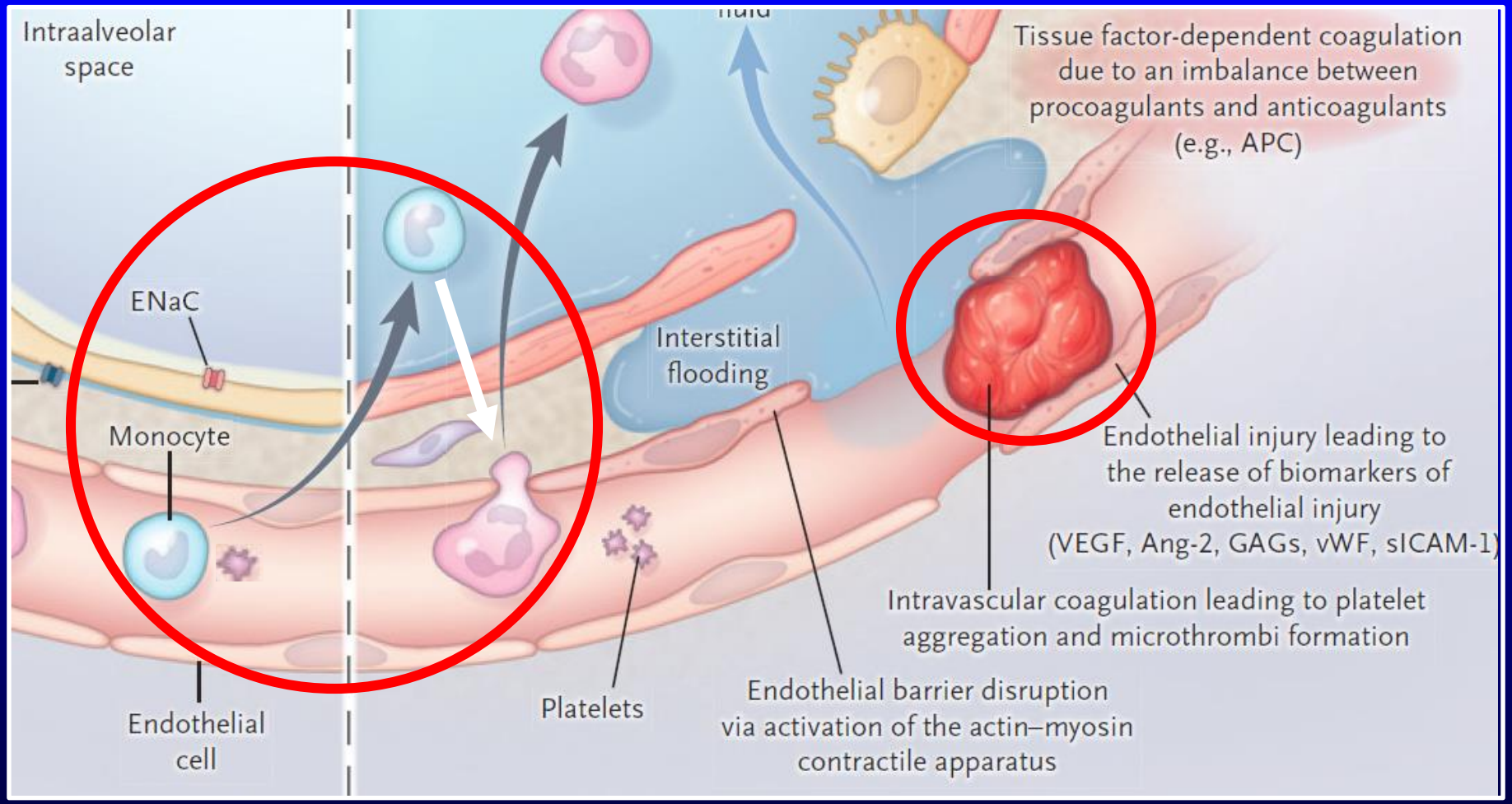
- Exome wide sequencing in established ARDS
- Prior work found LRRC16A heterozygotes had lower ARDS risk
- Explored LRRC16A genotype, platelet counts, and ARDS survival



Mediation Model

American Journal of Respiratory and Critical Care Medicine Volume 195 Number 10 | May 15 2017

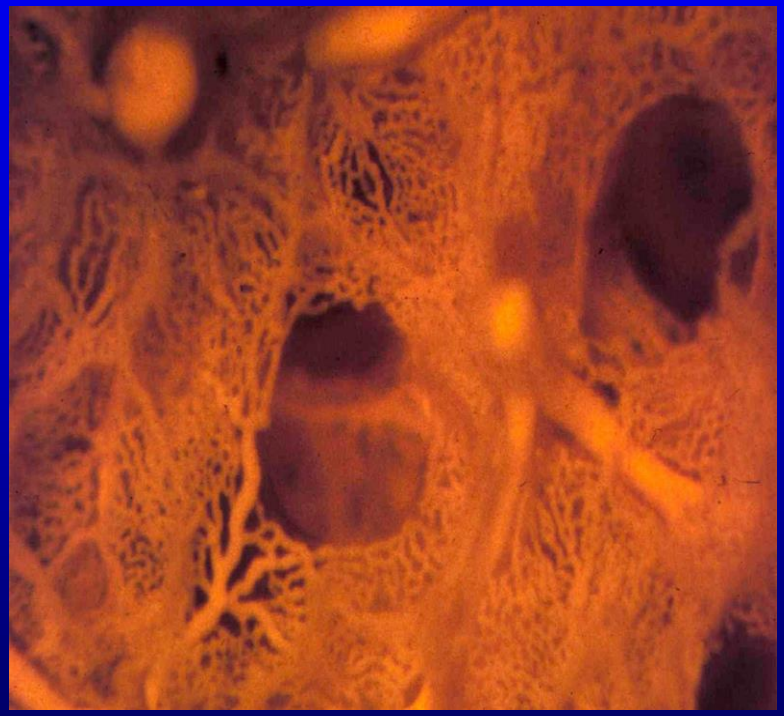
Platelet-monocyte interaction stimulates monocyte translocation and release of chemokines



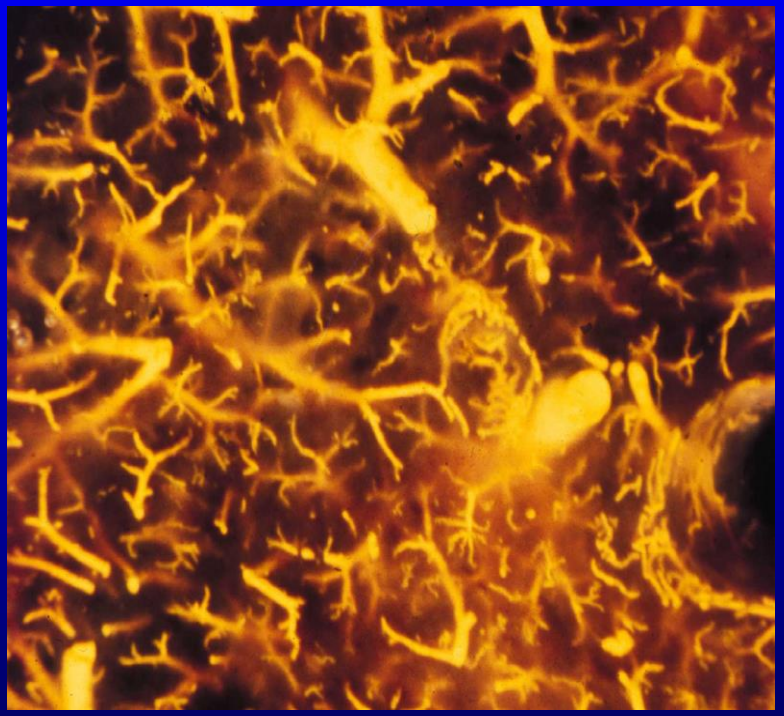
Modified from Thompson, NEJM 2017

Microvascular Obstruction and Remodeling in ARDS

Normal human lung capillaries



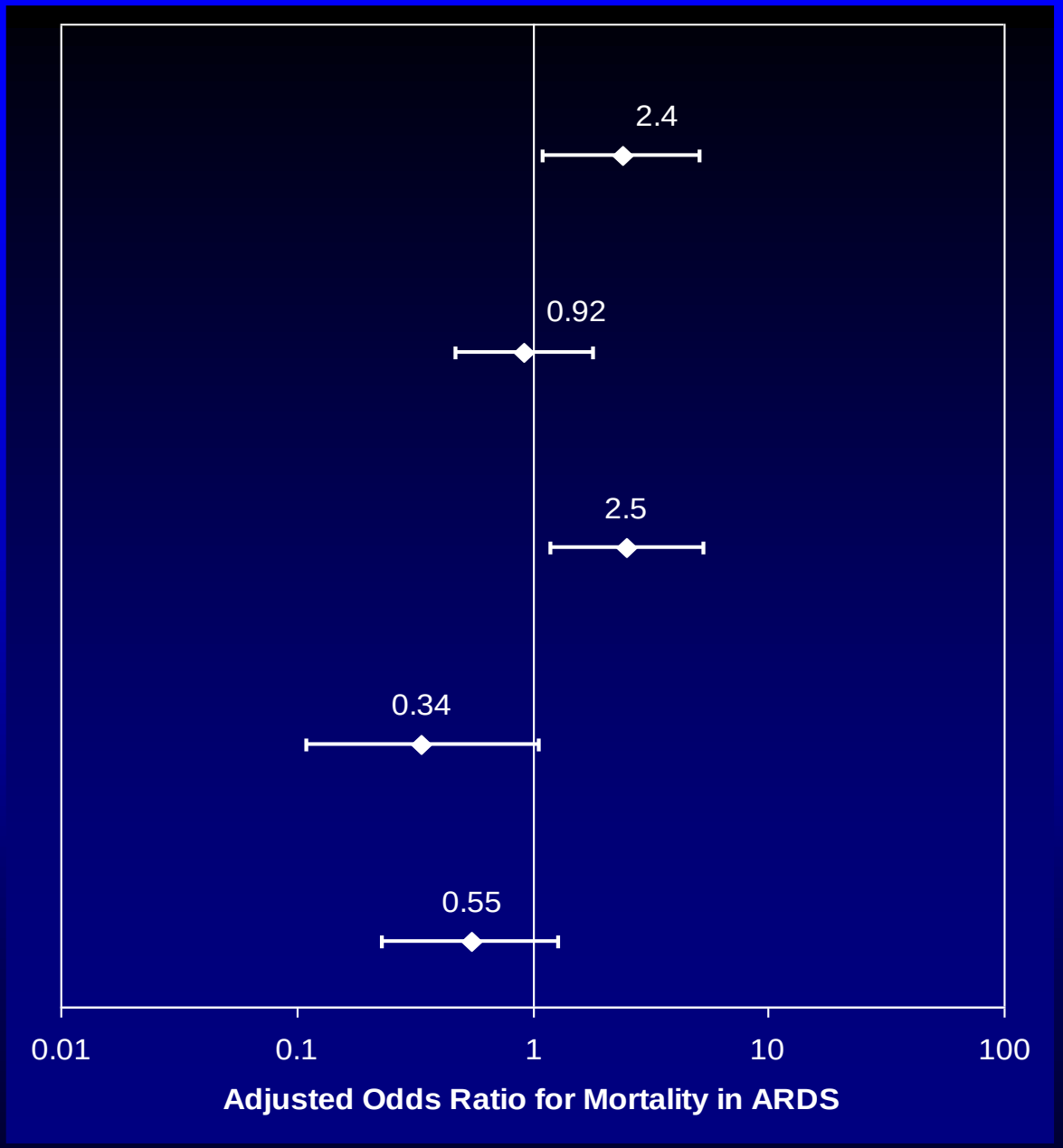
Lung capillaries p 14 d ARDS



Morphometric analysis -> Thrombosis, medial thickening, decreased vascular density of pre- and intra-acinar vessels

Zapol et al *Chest*, 1977; Snow et al *ARRD* 1982

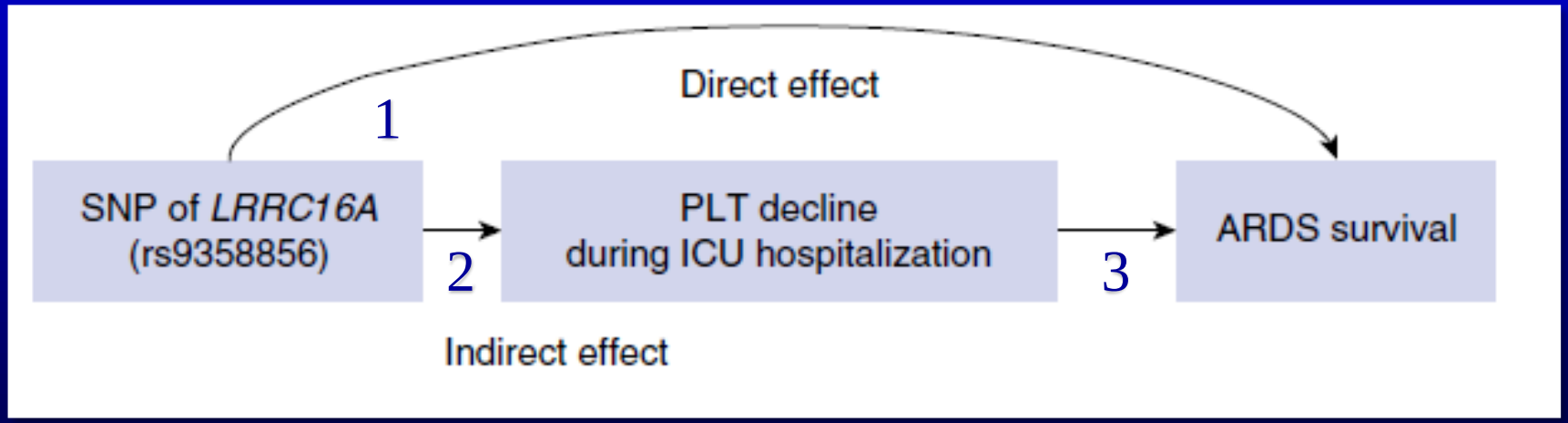
Mortality in ARDS



A Missense Genetic Variant in *LRRC16A/CARMIL1* Improves Acute Respiratory Distress Syndrome Survival by Attenuating Platelet Count Decline

Yongyue Wei[1,2,3], Paula Tejera[1], Zhaoxi Wang[1], Ruyang Zhang[1,2], Feng Chen[2,3], Li Su[1], Xihong Lin[4], Ednan K. Bajwa[5], B. Taylor Thompson[5], and David C. Christiani[1,3,5]

- Exome wide sequencing in established ARDS
- Prior work found LRRC16A heterozygotes had lower ARDS risk
- Explored LRRC16A genotype, platelet counts, and ARDS survival



Mediation Model

American Journal of Respiratory and Critical Care Medicine Volume 195 Number 10 | May 15 2017

Ventilator Induced Lung Injury: Conceptual Framework

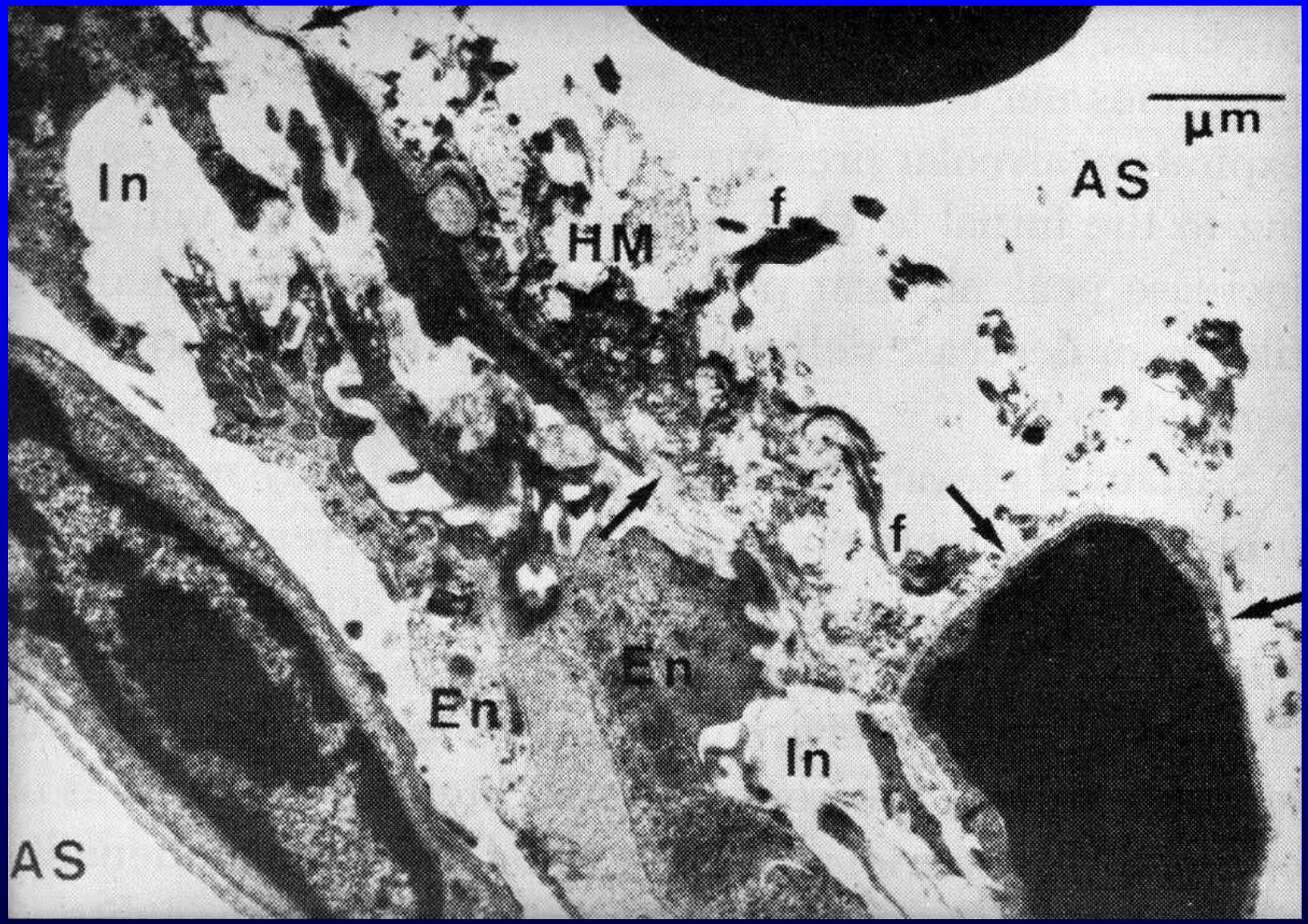
- Lung Injury from:
  - Overdistension/shear -> physical injury
  - mechanotransduction -> "biotrauma"

  } "volutrauma"

  - repetitive opening/closing
  - shear at open/collapsed lung interface

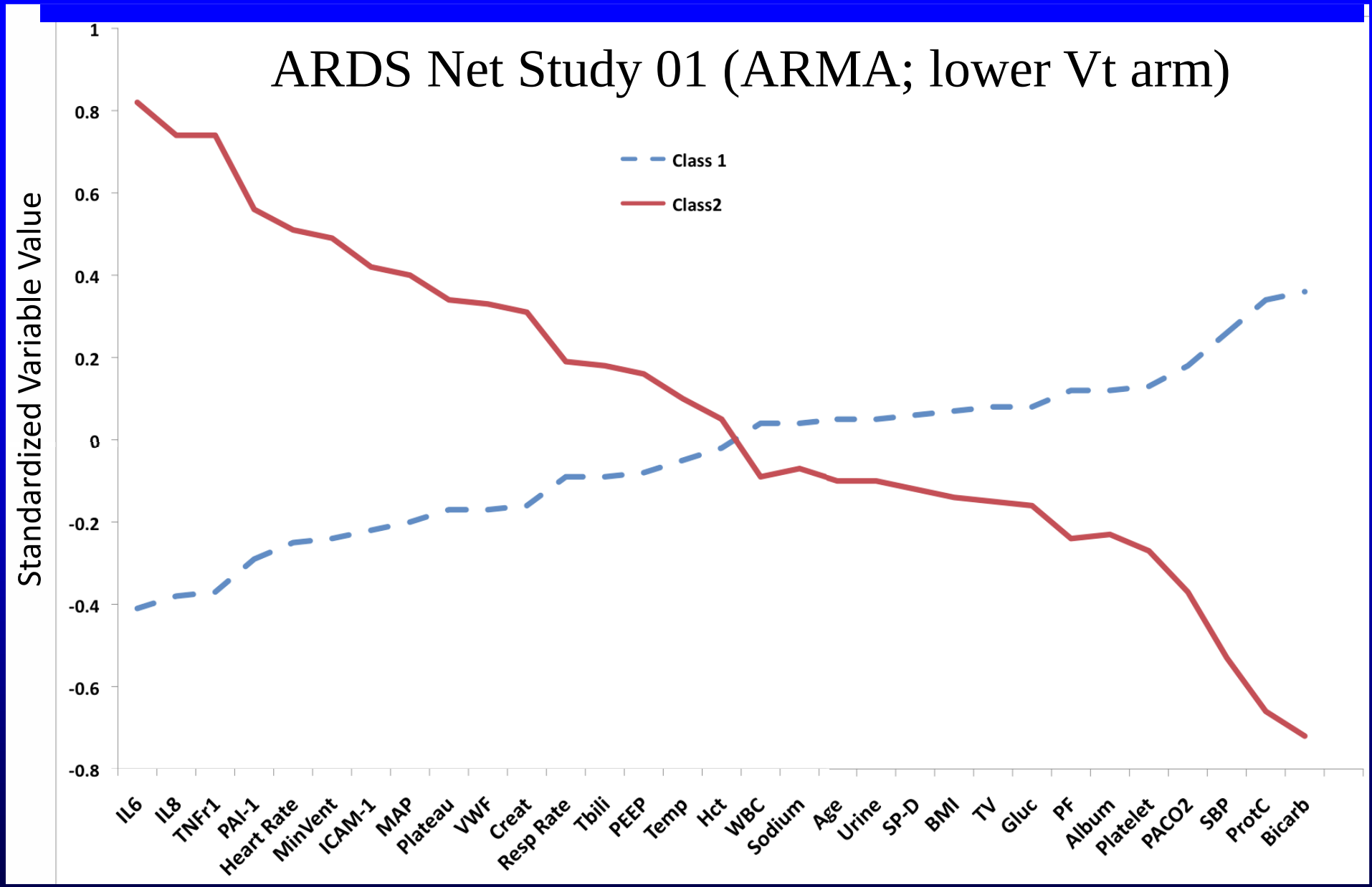
  } "atelectrauma"

- Systemic inflammation and death from:
  - systemic release of cytokines, endotoxin, bacteria, elastase


µm
In
HM
f
AS
f
En
En
In
AS

Results

	Bayesian Information Criterion	Entropy	Number of individuals assigned to each class or Subphenotype					p-value k vs k-1 classes
			1	2	3	4	5	
1 Class	93883.9	--	1000					--
2 Classes	92118.2	0.86	727	273				< 0.0001
3 Classes	91839.5	0.88	708	164	128			0.19
4 Classes	91519.8	0.82	434	351	159	56		0.66
5 Classes	91267.7	0.84	411	287	157	92	53	0.08


ARDS Net Study 01 (ARMA; lower Vt arm)
Standardized Variable Value
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
Class 1
Class2
IL6
IL8
TNFr1
PAI-1
Heart Rate
MinVent
ICAM-1
MAP
Plateau
VWF
Creat
Resp Rate
Tbili
PEEP
Temp
Hct
WBC
Sodium
Age
Urine
SP-D
BMI
TV
Gluc
PF
Album
Platelet
PACO2
SBP
ProtC
Bicarb